10. Harms Due to Opioids

Authors: Sarah J. Shoemaker-Hunt Pharm.D., Ph.D., Cori Sheedy Ph.D., and Brandy Wyant, M.P.H., M.S.W.

Reviewer: Scott Winiecki, M.D.

Introduction

Background

Prescription opioids are commonly used in the treatment of pain in the United States. In 2016, an estimated 20.4 percent of U.S. adults (50 million) had chronic pain.[1] Although opioids are a key treatment option in the management of acute, post-operative, procedural, and cancer pain, there is limited evidence of their efficacy for chronic pain.[2,3]

Importance of Harm Area

In the past 20 years, there has been a dramatic increase in opioid prescribing, peaking in 2012 with 255 million prescriptions, or a rate of 81.3 opioid prescriptions per 100 persons.[4] From 1999 to 2017, nearly 400,000 drug overdose deaths involved opioids (including prescription and illegal),[5] signaling three waves of an opioid epidemic. The first wave of the opioid overdose deaths began in 1999 with increased prescribing of opioids in the 1990s.[6] The second wave began in 2010 with the increase in heroin-related overdose deaths, and the third wave in 2013 with the increase in overdoses involving synthetic opioids (e.g., illicitly manufactured fentanyl). Accordingly, in the National Action Plan for Adverse Drug Event Prevention, opioids are one of three drug classes targeted.[7] In 2017, the Department of Health and Human Services declared the opioid epidemic a public health emergency.[8]

Methods for Selecting Patient Safety Practices

Given the importance of harms due to opioids, we identified potential patient safety practices (PSPs) for both primary care practice and other settings. PSPs that were not fully addressed in existing guidelines, systematic reviews, or standards were prioritized. The candidate safety practices were discussed with the Agency for Healthcare Research and Quality (AHRQ) for consideration and final selection.

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10.1 Patient Safety Practice 1: Opioid Stewardship

10.1.1 Practice Description

Key Findings:

- The majority of studies examined multicomponent opioid stewardship, which often consisted of guideline-recommended clinical interventions or care processes, as well as implementation strategies.
- Most studies examined the effect of opioid stewardship interventions on reducing the potential risks of opioids with judicious prescribing and guideline-concordant care.
- The overall strength of the evidence on opioid stewardship is low to moderate, with variation by outcome examined.
- The strength of the evidence for opioid stewardship producing significant reductions in opioid dosages was moderate.
- Two studies examined whether their opioid stewardship initiatives reduced overdoses; neither study observed significant reductions.

Opioid stewardship—similar to antibiotic stewardship—consists of a range of risk-reduction interventions or strategies, often used in combination, to prevent adverse consequences from prescription opioids, including misuse, abuse, and overdose.[1,2] The range of opioid stewardship interventions or strategies includes the following, several of which are recommended in the Centers for Disease Control and Prevention's *Guideline for Prescribing Opioids for Chronic Pain*:

- Conduct of an individualized assessment of risks and benefits of opioids, and the appropriateness of a tapering (tapering slowly to minimize withdrawal symptoms).[3]
- Avoid coprescribing opioids and benzodiazepines or other sedative hypnotics (as appropriate).
- Use of treatment agreements (also known as controlled substance agreements or pain contracts).
- Urine drug screening (UDS).
- Checking Prescription Drug Monitoring Programs (PDMPs).
- Pain and functional assessment.
- Registry of patients with chronic pain or patients on chronic opioid therapy (COT).
- Limiting number of days supply for acute pain opioid prescriptions.
- Pill counts to detect aberrant drug-related behavior.
- Referrals to nonpharmacologic treatment providers (e.g., physical therapy), pain management, behavioral health, or addiction specialists.
- Risk assessment.

Besides recommending these specific interventions, most opioid stewardship initiatives also include *implementation strategies* to actually change practice; these implementation strategies are not necessarily unique to opioid stewardship efforts.[4,5] The studies included in this review used a range of implementation strategies to change practice, including electronic health record (EHR) tools (e.g., clinical decision support, templates, alerts, integrated PDMP, autopopulated fields), dashboards for monitoring and/or audit and feedback, provider and staff education and training, academic detailing, committee or task force on opioids, telehealth, and nurse care management.

10.1.2 Methods

The question of interest for this review is: "What is the effect of opioid stewardship interventions on key process outcomes (e.g., PDMP, treatment agreement, UDS, referrals), intermediate and clinical outcomes (e.g., opioid dosage, opioid prescriptions, overdose), and unintended consequences (e.g., change in pain)?" The review's key findings are located in the box above.

Two databases (CINAHL® and MEDLINE®) were searched for articles published in the past 10 years using terms for opioids, the outcomes of interest (opioid abuse, overdose, death), and several terms for opioid stewardship and opioid stewardship strategies.

The initial search yielded 392 abstracts; an additional 16 studies were identified from authors' knowledge of the field, expert recommendation, and reference lists. After removing duplicates, records of 408 studies were screened, from which 24 studies were reviewed for full text. Fourteen individual studies and one systematic review met the inclusion criteria, as shown in the PRISMA flow diagram in Attachment.

Studies were included if they evaluated an opioid stewardship strategy or a multicomponent opioid stewardship initiative to address potential harms of opioids. Studies that examined only effective pain management approaches were excluded if they did not concurrently address potential opioid harms. Studies of naloxone (opioid overdose reversal drug) prescribing alone were excluded from this review due to their focus on tertiary prevention (overdose reversal) versus risk reduction with primary and secondary prevention strategies; no studies included in this review had naloxone prescribing as part of their initiatives.

Studies were included if they used experimental or quasi-experimental designs with pre/post, with or without a control group. If studies were observational or qualitative studies without tests of significance or had fewer than 50 patients, they were excluded.

Studies were excluded if the outcomes were not relevant to this review (e.g., focused only on clinician outcomes, e.g., knowledge or perceptions), if the article was out of scope, or if the report did not describe an intervention.

General methods for this report are described in the Methods section of the full report.

For this patient safety practice, a PRISMA flow diagram and evidence table, along with literature-search strategy and search-term details, are included in the report A through C appendixes.

10.1.3 Review of Evidence

The 14 single studies that met the inclusion criteria were characterized in terms of their setting, opioid stewardship strategies examined, study design, and outcomes. They are described in the Evidence Tables in Attachment.

Ten studies examined opioid stewardship interventions in primary care settings, of which three were in federally qualified health centers (FQHCs) or safety-net settings and two were in Veterans Administration (VA) clinics. One of the 10 studies in primary care settings examined a health system-wide opioid stewardship initiative, which included primary care practices, as well as emergency departments (EDs) and hospitals. Two studies examined opioid stewardship in EDs, one in a hospital outpatient surgery and the other in an urgent care setting.

The majority of studies examined multicomponent opioid stewardship interventions, which often consisted of guideline-recommended clinical interventions or care processes (e.g., use UDS, check PDMP), as well as implementation strategies (e.g., dashboards, audit and feedback), which are described in Section 9.1.1. There was variation in the level of detail provided in the descriptions of the various opioid stewardship initiatives. See Table 1 for an indication of the specific components of the opioid stewardship interventions reflected in the literature included in this review.

Table 1: Overview of Articles' Opioid Stewardship and Implementation Strategies, by Setting

Author, Year	Setting	Opioid Stewardship Interventions or Strategies	Implementation Strategies
Anderson et al., 2016[15]	• Primary care; Federally Qualified Health Center (FQHC)	• Treatment agreement • Urine drug screening (UDS) • Pain interference • Behavioral health visit • Project ECHO	• Education • Dashboard • Policy • Electronic Health Records (her) templates
Anderson et al., 2015[11]	• Primary care; FQHC	• Treatment agreement • Urine drug test/testing (UDT) • Document functional status • Behavioral health visit	• Dashboard
Dorflinger et al., 2014[18]	• Primary care; Veterans Affairs (VA)	• Treatment agreement • Shared decision making • Pain specialty care services • Use of nonpharmacologic treatments • Referrals	• EHR templates
Dublin et al., 2019[8]	• Primary care; integrated group practices	• Dose reduction • Risk stratification • Increased monitoring • Opioid care plans • UDS • Pain specialist consultation	• Education • Dashboard • Audit and feedback
Jacobs et al., 2016[19]	• Primary care; VA	• Pharmacist telephonic monthly assessment of medication use and aberrant drug-related behaviors at prescription renewal • Informed consent • UDT • Prescription Drug Monitoring Program (PDMP) • Electrocardiography monitoring	• EHR assessment and recommendations to provider
Liebschutz et al., 2017[6]	• Primary care; safety-net	• Nurse care management • Assessment of pain, addiction, misuse • UDTs • Pill counts • PDMPs • Electronic registry	• EHR tools • Education • Academic detailing • Electronic decision tools (intervention and control)
Von Korff et al., 2016[9]	• Primary care; integrated group practices	• Dose reduction • Risk stratification • Increased monitoring • Opioid care plans • UDS • Pain specialist consultation	• Education • Dashboard • Audit and feedback

Author, Year	Setting	Opioid Stewardship Interventions or Strategies	Implementation Strategies
Von Korff et al., 2019[10]	• Primary care; integrated group practices	• Dose reduction • Risk stratification • Increased monitoring • Opioid care plans • UDS • Pain specialist consultation	• Education • Dashboard • Audit and feedback
Weimer et al., 2016[17]	• Primary care	• Pain task force • Dose limitation • Initiation of taper for >120 morphine equivalents per day • Patient list of patients with high dosage	• Education • Policy
Weiner et al., 2019[16]	• Health system-wide	• Opioid Stewardship Committee • Prescribing, addiction, education task forces • Non-pharmacologic treatments • Referral for opioid use disorder (OUD) treatment • Naloxone	• Education • Patient education • EHR template • Integrated PDMP in EHR • Autopopulate patient discharge instructions • Connection to emergency department (ED) information exchange • Dashboard • Audit and feedback • Monitoring with opioid-related metrics
Kahler et al., 2017[12]	• ED	• Transfer "superusers" of ED to outpatient chronic pain program	• EHR alert of superusers
Neven et al., 2016[7]	• ED	• Citywide care coordination with EDs for patients' opioid-seeking behavior	• Information exchange across systems
Hartford et al., 2018[14]	• Hospital outpatient surgery	• Intra- and postoperative pain care bundle • Opioid reduction strategies	• Education • Patient education
Young et al., 2018[13]	• Urgent care	• Dose reduction • Increased monitoring	• Education • Guideline • Monitoring
Starrels et al. 2010[1] (systematic review, 11 studies)	• Pain specialists • Primary care	• Treatment agreement (10 studies) • UDT (8 studies)	• N/A

Fourteen single studies and one systematic review were included in this review. Six of the 14 studies had a control group: 2 studies were randomized controlled trials (RCTs),[6,7] 3 were interrupted time series with control groups,[89,10] and 1 was a one-way crossover intervention study with patients serving as their own control. Six pre/post intervention studies did not have a control or comparison group, and the remaining two studies were observational studies with tests of significance. The post-intervention time periods in these studies ranged from months to years.

The overall strength of the evidence on opioid stewardship was ranked low to moderate, with some variation by outcome examined.

The most clinically significant harms of opioids are opioid addiction or opioid use disorder (OUD), overdose, and death. Most studies did not examine the effect of opioid stewardship initiatives on OUD or overdose, although there were a few exceptions.[10] The majority of studies examined the effect of

opioid stewardship interventions on reducing the potential risks of opioids with judicious prescribing and guideline-concordant care (e.g., reduce inappropriate high opioid dosages; avoid coprescribing opioids and benzodiazepines; use UDS, treatment agreements).

The outcomes are presented by intermediate outcomes, process outcomes and utilization, overdose, and other outcomes.

10.1.3.1 Intermediate Outcomes

Most studies examined intermediate outcomes, including opioid prescribing, high opioid dosages and potential misuse.

Seven studies examined effects of opioid stewardship on prescribing any amounts of opioids. The evidence is low to moderate that opioid stewardship efforts decrease numbers of opioid prescriptions, the proportion of patients on long-term opioids, or days' supply.

Six of seven studies observed significant reductions in opioid prescribing either in pre/post studies or compared with control groups,[7,11-14] with the exception of Anderson et al. (2016), who observed no significant decline in opioid prescribing.[15]

Anderson et al. (2015) observed reductions in the proportion of patients on COT after their opioid stewardship intervention (from 3.4% to 3.1%; p=0.057).[11] Von Korff et al. (2016) found a significant decline in the proportion of patients receiving excess opioid days supplied (from 24.0% to 10.4% among COT patients in interventions and from 20.1% to 14.7% among COT patients in the control practices).[9]

Weiner et al. (2019) found a reduction in the number of unique patients with an opioid prescription each month (-52.6 patients; p<0.001).[16]

Hartford et al. examined a hospital outpatient surgery opioid stewardship initiative and found that only 78 of 172 (45%) patients in the post-intervention group filled their opioid prescription (p<0.001), with no significant difference in prescription renewals.[14]

Six studies examined the effect of their opioid stewardship interventions on opioid dosages, measured as morphine milligram equivalents (MMEs).[6,9,14,16-18] Four were in primary care settings,[6,9,17,18] one was health system-wide,[16] and one was in a hospital outpatient surgery.[14] The strength of the evidence for opioid stewardship initiatives producing significant reductions in opioid dosages was moderate.

While the opioid stewardship strategies varied and the post-intervention time periods ranged from months to years, the studies observed reductions in MMEs of varying magnitudes and measured in various ways. The following is a summary of the findings by the different measures of dosage used in the studies. Several studies also reported dosage in more than one way.

Mean daily MMEs decreased by 47 percent compared with control at 30 percent.[9] Weimer et al. reported that an average daily dose decreased by 64 mg (95% confidence interval [CI], 32 to 96]; p<0.001).[17]

In terms of dosage reduction, Liebschutz et al. found that intervention patients had a mean MME 6.6 mg lower than controls (p<0.001), and intervention patients were more likely than controls to have either a 10-percent MME dose reduction or opioid treatment discontinuation (adjusted odds ratio [AOR], 1.6).[6]

Studies examined high dosage by the proportion of patients on high dosages and observed a range of reductions in patients on high dosages. Von Korff et al. (2016) reported greater reductions in the intervention versus the control group (16.8% to 6.3%, a 63% reduction, vs. 20.6% to 13.6%, a 34% reduction).[9] Dorflinger et al. found that the proportion of patients receiving high-dose opioids decreased from 27.7 percent to 24.7 percent.[18]

In the health system-wide study, Weiner et al. (2019) found a significant decrease in mean MME per prescription (-0.4 MME per month, p<0.001) and prescriptions containing ≥90 MME also decreased (-48.1 prescriptions/month; p<0.001), which may or may not be statistically significant.[16]

In the study of the opioid stewardship initiative in general outpatient surgery, MMEs for prescriptions filled for the intervention group were significantly fewer than for the controls.[14]

Few studies included in this review examined misuse outcomes. One ED study found that the total number of unique controlled-substance prescribers at this specific health provider decreased from 11 to 7 (31% decrease, 95% CI, 23 to 38).[12] Another study in primary care found no difference in early refills in their intervention group compared with the control group.[6]

10.1.3.2 Process Measures and Utilization

The primary outcome targeted by most opioid stewardship initiatives was to improve use of recommended clinical interventions or care processes, or "guideline-concordant care." Five studies examined these various process outcomes.

In the randomized trial by Liebschutz et al., it was found that intervention patients were more likely than controls to receive guideline-concordant care (65.9% vs 37.8%; p<0.001; AOR, 6.0; 95% CI, 3.6 to 10.2).[6] Similarly, Jacobs et al. found significant improvements in guideline-concordant care after the pharmacist-led intervention in a VA setting.[19]

Five studies examined the effect of opioid stewardship initiatives on the use of annual UDS and observed significant increases.[6,15,18-20] In their systematic review, Starrels et al. (2010) found low to moderate evidence of the effectiveness of urine drug testing for reducing opioid misuse.[1]

One study (Jacobs et al.) found a significant increase in the use of a PDMP with opioid prescribing after implementation of a pharmacist-led risk assessment cliniced.[19]

Four studies examined the effect of opioid stewardship initiatives on the proportion of patients on COT with a treatment agreement and found significant improvements.[6,15,18,19] The systematic review by Starrels et al. (2010) found opioid misuse was modestly reduced after treatment agreements (with or without urine drug testing).[1]

Weiner et al. (2019) found that the number of prescriptions (+6.0 prescriptions/month; p<0.001) and prescribers (+0.4 providers/month; p<0.001) for the film version of buprenorphine/naloxone for OUD increased.[16]

Several opioid stewardship initiatives aimed to increase referrals to behavioral health and other specialists. Anderson et al. (2016) found significant increases in the percentage of patients with pain who had a visit with a behavioral health provider in their FQHC,[15] while Dorflinger et al. did not observe an increase.[18] Anderson et al. (2016) observed a significant increase in referral to a chiropractor,[15] and

Dorflinger et al., to physical therapy and pain management.[18] Anderson et al. (2016) also observed a significant decline in referrals to neurosurgery or orthopedic surgery and to pain specialists.[15]

The opioid stewardship initiative studied by Anderson et al. (2016) aimed to improve documentation, and significant increases were observed in the documentation of the presence of pain (64% to 82%; p=0.001), the source and/or cause of pain (62% to 74%; p=0.025), functional status (5% to 19%; p=.0.001), treatment plan (92% to 98%; p=0.002), and pain reassessment (17% to 39%; p=0.001).[15]

Two studies examined opioid stewardship initiatives in EDs and observed significant decreases in ED visits of 34 percent (from 14 to 4, a 58% decrease; 95% CI, 50 to 66)[12] and 58 percent (incidence rate ratio [IRR]=0.663; p<0.001; 95% CI, 0.569 to 0.775).[7]

10.1.3.3 Overdose

Two studies examined whether their opioid stewardship initiatives reduced overdoses. Neither study observed significant reductions.[10,16]

Von Korff et al. (2019) found that changes in overdose rates among patients did not differ significantly between intervention and control groups with the implementation of two different opioid stewardship initiatives (dose reduction and risk stratification/monitoring). Secondary analyses revealed that overdose rates decreased significantly (17% per year) with the dose reduction opioid stewardship initiative for patients on COT in intervention settings (relative annual change, 0.83; 95% CI, 0.70 to 0.99), but not in control settings (relative annual change, 0.98; 95% CI, 0.70 to 1.39). Von Korff et al. (2019) argued that the results are inconsistent given the differences observed in primary versus secondary analyses.[10]

While Weiner et al. (2019) observed a downward trend in overdoses, it was not statistically significant.[16]

10.1.3.4 Other Outcomes

Dorflinger et al. (2014) measured pain intensity over the 4-year study of a pain care and opioid stewardship model within the VA, and did not see differences from year to year.[18]

10.1.4 Implementation

Most opioid stewardship initiatives are multicomponent interventions, involving clinical interventions or care processes and often implementation strategies as well. The implementation strategies included education, policies, dashboards, audit and feedback, monitoring and metrics, health information exchange, and EHR tools. The EHR tools included an embedded PDMP, registry, alerts, autopopulation features, and templates.

The studies in this review examined multicomponent interventions and did not examine the differential effectiveness of different components.

10.1.4.1 Barriers and Facilitators

The included studies were not implementation or implementation-effectiveness designs that afforded a systematic evaluation of different implementation strategies' effectiveness.[21] The researchers of selected studies offered reflections and informal observations on facilitators and barriers to implementation of their opioid stewardship initiatives.

Anderson et al. (2015) fielded a survey of the participating primary care providers about their opioid dashboard. Respondents found the dashboard helpful for identifying patients on long-term opioids and gaps in services (85%), clinically useful (77%), and easy to use (69%).[11]

EHR tools were identified as key facilitators to opioid stewardship.[12,16,18] On the other hand, Dorflinger et al. also found EHRs limiting because of the challenges with capturing complementary health approaches (e.g., chiropractic).[18]

Weiner et al. (2019) reflected on several lessons learned. They found that it is critical to determine metrics and gain access to data at the beginning in order to guide the opioid stewardship effort. They also experienced a mismatch when primary care providers referred patients to pain specialists with the expectation that the pain physicians would prescribe opioids, whereas the specialists would only recommend opioid regimens and provide injections. Additionally, while their health system had increased access to substance use disorder treatment, their outpatient practices perceived there was inadequate access. Finally, they learned that many of these implementation challenges could be addressed by convening the various stakeholders to resolve the issues.[16]

Buy-in and administrative support were identified as key for two opioid stewardship initiatives, also.[7,12]

10.1.4.2 Resources To Assist With Implementation

- Centers for Disease Control and Prevention: Quality Improvement and Care Coordination: Implementing the CDC Guideline for Prescribing Opioids for Chronic Pain
- A Stakeholder-Driven Action Plan for Improving Pain Management, Opioid Use, and Opioid Use Disorder Treatment Through Patient-Centered Clinical Decision Support
- Six Building Blocks: A Team-Based Approach to Improving Opioid Management in Primary Care
- AHRQ: Clinical Decision Support (CDS) Connect Artifacts on Opioids and Pain Management

10.1.5 Gaps and Future Directions

This systematic review expands the evidence on opioid stewardship initiatives beyond what was known from previous reviews of specific opioid stewardship interventions or recommended strategies, but still points to several gaps and future directions for reducing the potential harms due to opioids:

- Seek out more detailed descriptions of the opioid stewardship initiatives to replicate the interventions in other practices and settings, as well as rigorously synthesize the evidence across studies.
- Improve the quality of future studies with control groups to account for secular trends, given the attention on the opioid epidemic and changing external environment, policies, regulations, and evidence.
- Examine the effect of coprescribing naloxone for patients on long-term opioid therapy on outcomes of interest.
- Study the effectiveness or benefits of different implementation strategies for changing practice in opioid stewardship efforts and in different settings.

- While the studies included in this review were not only in primary care settings, but also health system-wide, in EDs, and in an urgent care center, there is still a need to further understand the uniqueness and effectiveness of opioid stewardship efforts in different settings.
- Given that the latest waves in the epidemic's rise in overdoses are largely attributable to heroin and synthetic opioids, consider how best to identify and treat or refer patients using illicit opioids.

It should be noted that while most opioid stewardship efforts are aimed at preventing or reducing harms due to opioids with appropriate prescribing, the stewardship efforts could also result in unintended negative consequences, such as patients having poorly controlled pain, experiencing the negative consequences of forced tapers, or turning to illicit opioids.

References for Section 10.1

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10.2 Patient Safety Practice 2: Initiation of Medication-Assisted Treatment in Healthcare Settings

10.2.1 Practice Description

Medication-assisted treatment (MAT) is a proven method to treat OUDs. Effective MAT includes a combination of behavioral therapy and medications approved by the Food and Drug Administration (methadone, buprenorphine, and naltrexone). Individuals with OUD can safely take medications used in MAT as part of a long-term recovery plan.

This review focuses on initiation of MAT, as MAT's effectiveness in reducing illicit opioid use and overdose deaths has already been demonstrated in multiple randomized clinical trials.[1] The review's key findings are located in the box to the right.

Key Findings:

- MAT can be initiated and provided safely in a variety of healthcare settings.
- It has been most studied in primary care settings, hospitals, EDs, and community-based centers and clinics—for example, HIV/AIDS clinics.
- Initiation of MAT in the ED, primary care setting, or outpatient clinics may result in faster access to care and longer retention in or adherence to treatment.
- The majority of the studies found through the searches of the literature had sample sizes too small to detect differences between treatment groups—for example, RCTs with limited power to detect differences. Additionally, many of the studies' followup periods were relatively short—for example, less than 6 months.

Initiation of MAT can occur in primary care offices, EDs, hospitals, and community-based centers and clinics. The setting of MAT initiation might impact process and clinical outcomes, including engagement in and adherence to the patient's treatment and recovery plan. Initiation usually refers to the first prescription of a medication, as the psychosocial aspects of the treatment are not available in every setting (e.g., hospital) in which the prescriptions can be given. Therefore, this review focuses primarily on the medication component of MAT, as studies focused on treatment initiation are more limited in scope, with relatively short followup periods.

Several studies evaluated outcomes related to the maintenance phase of treatment. The maintenance phase occurs when a patient is doing well on a stable dose of MAT medication, without side effects, cravings, or problematic use.[2] Patients achieve the maintenance phase at different lengths of time following medication initiation. A patient may remain in the maintenance phase on the same dose of medication indefinitely or may choose to taper off of the medication.

10.2.2 Methods

The review is intended to answer two primary questions:

1. Where can initiation of the pharmacotherapy component of MAT occur?
2. Which outcomes of MAT initiation have been measured in various settings?

Two databases (CINAHL® and MEDLINE®) were searched for articles published in the past 10 years using terms for opioids, the outcomes of interest (opioid abuse, overdose, death), and several terms for MAT strategies. Detailed search terms are provided in the Appendix.

The initial search yielded 469 unique abstracts. All 469 citations were screened, from which 47 studies were reviewed for full text. Twenty-six individual studies met the inclusion criteria shown in the PRISMA flow diagram.

Studies were included if they used experimental or quasi-experimental designs with pre/post, with or without a control group. Most studies had small sample sizes and many were observational in nature.

Studies were excluded if the outcomes were not relevant to this review (e.g., focused only on clinician outcomes such as knowledge or perceptions), if the article was out of scope, or if the report did not describe an intervention.

General methods for this report are described in the Methods section of the full report.

For this patient safety practice, a PRISMA flow diagram and evidence table, along with literature-search strategy and search-term details, are included in the report A through C appendixes.

10.2.3 Review of Evidence

Reviewed and included studies examined initiation in a range of settings and combined with different psychosocial interventions provided in combination with MAT.

Nine of the included studies examined the feasibility, safety, and/or effectiveness of MAT initiated in primary care settings. One systematic review was included among these nine studies, which comprised 10 RCTs and 25 quasi-experimental designs.[3]

Ten studies explored outcomes associated with initiation of MAT in other outpatient settings. These included treatment programs specifically for substance abuse, a clinic to provide healthcare for homeless people, an HIV clinic, obstetric clinics, and FQHCs. One study examined outcomes among individuals introduced to buprenorphine while incarcerated.

Three studies, all originating from the same initiative at one facility, examined outcomes associated with initiation of buprenorphine and naloxone in the ED followed by 10-week followup in primary care. An additional four included studies were conducted in inpatient hospital settings.

Six studies examined the impact of the specific form of counseling or psychotherapy, as an independent variable, in various practice settings.

Three studies examined the use of shared medical appointments to provide MAT, in which several individuals who have OUD attend a longer medical appointment rather than a one-on-one appointment with a provider. The format includes all aspects of care that are covered in an individual appointment but allows more time for patient education and peer support.

A systematic review of 10 RCTs and 25 quasi-experimental designs in the primary care setting found that the most successful MAT programs involved clinical care managers—nurses or pharmacists—on the treatment team, used agreements that outlined conditions that the patient must meet to ensure continued treatment, or offered treatment induction in the patient's home.[3]

10.2.3.1 Clinical Outcome: Illicit Use of Opioids

Evidence suggests advantages to maintenance therapy as opposed to tapering MAT medications. Specifically, maintenance treatment was associated with less use of illicit opioids, as measured by urine drug tests (UDTs), as opposed to tapering off the medication after stabilization was achieved.

In an RCT of 113 patients at an urban primary care clinic, patients receiving a 3-week taper of buprenorphine reported more days per week of illicit opioid use (1.27 days) compared with those on

maintenance buprenorphine therapy (0.47 days). Patients being tapered also had fewer consecutive weeks of opioid abstinence, on average, compared with those on buprenorphine maintenance (2.70 vs 5.20 weeks). Participants in the taper groups were also less likely to complete the trial, and 16 of the 57 patients in the taper group reinitiated treatment after the trial due to relapse.[4]

Liebschutz et al. (2014) conducted an RCT of 139 hospitalized opioid-dependent patients in the general medical units of one urban safety-net hospital between 2009 and 2012. Patients were randomized to receive either transition to hospital-based outpatient buprenorphine treatment upon discharge or to receive a 5-day buprenorphine taper, which was continued at home if discharge occurred before finishing the taper. At 6-month followup, participants who received linkage to outpatient treatment were more likely to enter outpatient buprenorphine treatment (52 [72.2%] vs. 8 [11.9%]; p<0.001); were more likely to remain in treatment (12 [16.7%] vs. 2 [3.0%]; p=0.007); and were less likely to report illicit opioid use in the past month (IRR, 0.60; 95% CI, 0.46 to 0.73; p<0.01).[5]

In another RCT with three study groups, patients were randomized to receive either initiation of MAT in the ED; screening for OUD and referral to treatment; or screening, brief intervention, and referral.[6,7] Patients receiving MAT reported fewer days of illicit opioid use at 30 days and 2 months. However, no significant differences were found between the groups at 6-month followup.

A fourth RCT conducted at one outpatient substance use disorder treatment center found that clonidine as an adjunct to buprenorphine appeared to reduce craving, as evidenced by longer periods of abstinence during unstructured time—when cravings are more likely to arise—as compared with a placebo.[8]

In a hospital-based outpatient opioid treatment program, patients who received buprenorphine maintenance treatment had lower rates of positive UDTs for opioids at 20-month followup than patients who did not participate in the buprenorphine program.[9]

Results were generally mixed regarding the benefit to clinical outcomes of adding psychosocial interventions to MAT, which generally involved some form of individual or group psychotherapy using a modality such as cognitive behavioral therapy (CBT), Acceptance and Commitment Therapy (ACT), or motivational interviewing. In an RCT in which 141 patients receiving buprenorphine were randomized to receive physician management plus CBT versus physician management alone, both groups had a significant reduction in opioid use with treatment, with no additional advantage from adding CBT.[10] An RCT of 300 African-American participants receiving buprenorphine found that greater exposure to counseling was associated with negative outcomes in the form of greater days of heroin use, days of cocaine use, and days of criminal activity.[11] In an RCT of people seeking buprenorphine treatment, 49 participants were randomized to receive either standard-of-care health education or a distress tolerance intervention based on ACT, which aimed to reduce cravings. There was no statistically significant difference in the two groups' rates of opioid use at any of the three monthly followup points.[12]

10.2.3.2 Clinical Outcome: Retention in Treatment

Many studies used retention in treatment as a clinical outcome to assess MAT's effectiveness. Available evidence indicates that long-term buprenorphine maintenance in primary care may be feasible. In an observational study of 53 patients who initiated MAT in primary care, 38 percent continued to take buprenorphine after 2 years.[13]

Evidence further indicates that outcomes may be better when MAT is initiated upon first contact with the patient, as opposed to screening for OUD and providing a referral to MAT. In an RCT with three study groups, patients were randomized to receive either initiation of MAT in the ED; screening for OUD and referral to treatment; or screening, brief intervention, and referral. Patients who initiated MAT in the ED were more likely to be engaged in treatment at 30-day and 2-month followup than those in the other two groups.[6,7]

Like the evidence above indicating that initiation of MAT in the ED may be better than a referral, one RCT at an outpatient HIV clinic found that initiation of buprenorphine in the clinic resulted in faster access to care compared with referral to treatment.[14] Additionally, patients initiating MAT in the HIV clinic had fewer UDTs positive for opioids or cocaine and more visits with their primary care providers.

One included study examined 252 individuals being released from jail who had been treated with buprenorphine and naloxone while imprisoned. The outcome of interest was whether patients who continued MAT in a primary care setting were more likely to remain in treatment and abstinent from illicit opioids than those who received a referral for treatment in the community. No statistically significant differences were found between the two groups. This study did not support the hypothesis that direct linkage to care, as opposed to referral, offers a better chance of retention in care, yet it was observational with a relatively small sample size.[15]

A closely related outcome concerns whether patients who initiate MAT in the hospital are able to transition to longer term care following discharge. In a case series of 47 patients hospitalized for reasons other than treatment of opioid dependence at an urban medical center, patients were provided buprenorphine during their hospitalization if they met criteria for OUD in addition to the medical reason for the hospitalization. Twenty-two patients (46.8%) had initiated outpatient treatment between discharge and 2-month followup.[16] In another case series of 29 patients hospitalized at the same urban medical center with infective endocarditis related to intravenous drug use, patients were again provided buprenorphine during hospitalization.[17] Nine of these patients (31%) successfully initiated buprenorphine during their hospitalization, and nine patients (31%) accepted a referral to methadone maintenance following discharge. These studies did not show benefit from a followup with patients following referral.[17]

An RCT of 94 participants found that those who participated in a group-counseling CBT program were more likely to continue buprenorphine treatment than those receiving individual counseling.[18] Ober et al. (2018) found that, at an FQHC, having one session of behavioral therapy incorporating motivational interviewing and CBT improved the likelihood of engaging in MAT. However, the same study found that participants receiving the behavioral therapy intervention were more likely to report that they endorsed negative attitudes about themselves related to their substance use.[19] In a retrospective chart review of 356 patients, attending counseling was associated with completion of 6 months of buprenorphine treatment.[20]

Doorley et al. (2017) conducted a retrospective chart review of 77 opioid-dependent patients, over 60 percent of whom were currently homeless. Ninety-five percent of patients attended at least one shared medical appointment, and treatment retention at 12- and 24-week followup was 86 percent and 70 percent, respectively.[21]

10.2.3.3 Other Clinical Outcomes

Three included studies examined clinical outcomes other than those reviewed above—HIV risk behaviors, adverse events, and patient-reported outcomes. In an observational study of 166 patients receiving treatment with buprenorphine/naloxone in primary care, treatment was associated with a statistically significant reduction in overall HIV risk behaviors and drug-related behaviors in particular.[22]

Pade et al. (2012) assessed 143 patients with co-occurring chronic pain and opioid dependence at a clinic specifically for this population and found that the combination of buprenorphine and naloxone improved pain scores.[23]

Lee et al. (2009) assessed the safety and feasibility of induction to buprenorphine/naloxone at home, following assessment and education at the primary care provider's office. Of 103 patients in this observational study, no cases of severe precipitated withdrawal or adverse events were observed.[24] In a case series of 228 patients treated by two primary care providers over 4 years, only one patient experienced a rapid onset of withdrawal symptoms during buprenorphine induction.[25]

10.2.3.4 Cost Outcomes

Two cost-effectiveness studies suggest that maintenance therapy is a viable alternative to tapering from a cost perspective when quality-adjusted-life-years (QALYs) are considered. Schackman et al. (2011) examined the cost of providing long-term buprenorphine and naloxone for patients who had achieved stability on the regimen, with stability defined as 6 months in treatment. Their analysis was conducted using simulated data from hypothetical patients and concluded that the long-term use of these medications may be a cost-effective alternative to no maintenance but that further research is needed.[26] Additionally, Polsky et al. (2010) examined cost-effectiveness of detoxification using a 14-day taper of buprenorphine and naloxone, as compared with maintenance therapy, across six community outpatient treatment programs. Although treatment and medical costs for maintenance treatment were slightly higher than for detox, when analyzed at a threshold of $100,000 QALY, maintenance treatment was found to be a cost-effective alternative to detox when QALYs were taken into consideration, as the treatment resulted in better long-term health outcomes.[27]

In an RCT with three study groups, patients were randomized to receive either initiation of MAT in the ED; screening for OUD and referral to treatment; or screening, brief intervention, and referral. This RCT included a cost-effectiveness study using a subset of patients involved in the trial. Busch et al. (2017) found that the ED-initiated buprenorphine treatment was more cost-effective than either screening and referral or screening, brief intervention, and referral.[28]

10.2.4 Gaps and Future Directions

The majority of the studies found through the literature searches had sample sizes too small to detect differences between treatment groups, for example, RCTs with limited power to detect differences. Additionally, many of the studies' followup periods were relatively short, for example, less than 6 months.

Additionally, the majority of studies were focused on one component of MAT—the initiation of medications—in a few specific settings. Limited research exists on providing the initiation of MAT within the full definition of MAT and research that ties MAT to clinical outcomes. There is variance in the reported cost, clinical, and process outcomes, which makes it difficult to compare across studies.

Additionally, several studies within a specific setting were single-site studies, so there was limited variation of studies within a setting. More research is needed on the outcomes associated with the use of mobile technology, such as text messages, in delivering the psychosocial components of MAT.[3]

Research on initiating MAT in a variety of settings is critical for understanding the opportunity, capability, and outcomes associated with PSPs designed to reduce the impact and treat OUDs. As much of the previous research is limited in size and scope, future studies should incorporate defined, consistent outcomes in an expanded number of settings and with large sample sizes. Such studies would provide further insight into appropriate settings for initiating and sustaining MAT.

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Conclusion and Comment

The two PSPs addressed in this chapter—opioid stewardship and initiation of MAT in healthcare settings—aim to mitigate the potential harms of opioids, especially OUD, overdose, and death. Opioid stewardship can consist of a range of risk-reduction interventions or strategies (e.g., check PDMP, UDS, treatment agreement), often used in combination. The overall strength of the evidence on opioid stewardship varied from low to moderate by outcome. The evidence is moderately strong that opioid stewardship interventions can reduce opioid dosages (MMEs), which is an important intermediate outcome given high MMEs are associated with an increased risk of overdose.[1] The two studies that examined overdose did not find significant reductions.

MAT can be initiated and provided safely in a variety of healthcare settings. Initiation of MAT in the ED, primary care setting, or outpatient clinics may result in faster access to care and longer retention in or adherence to treatment. The majority of the studies in the review of MAT initiation had sample sizes too small to detect differences between treatment groups, and followup periods were relatively short (e.g., less than 6 months), limiting the strength of the evidence. MAT's effectiveness in reducing illicit opioid use and overdose deaths has already been demonstrated in multiple randomized clinical trials,[2] and effective MAT includes a combination of behavioral therapy and medications approved by the Food and Drug Administration (methadone, buprenorphine, and naltrexone). Research on initiating MAT in a variety is settings is critical for understanding the opportunity, capability, and outcomes associated with PSPs designed to reduce the impact of and treat OUDs. Such studies would provide further insight into appropriate settings for initiating and sustaining MAT.

References for Conclusion and Comment

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Appendix A. Harms Due to Opioids PRISMA Diagrams

Figure A.1: Opioids, Opioid Stewardship—Study Selection for Review

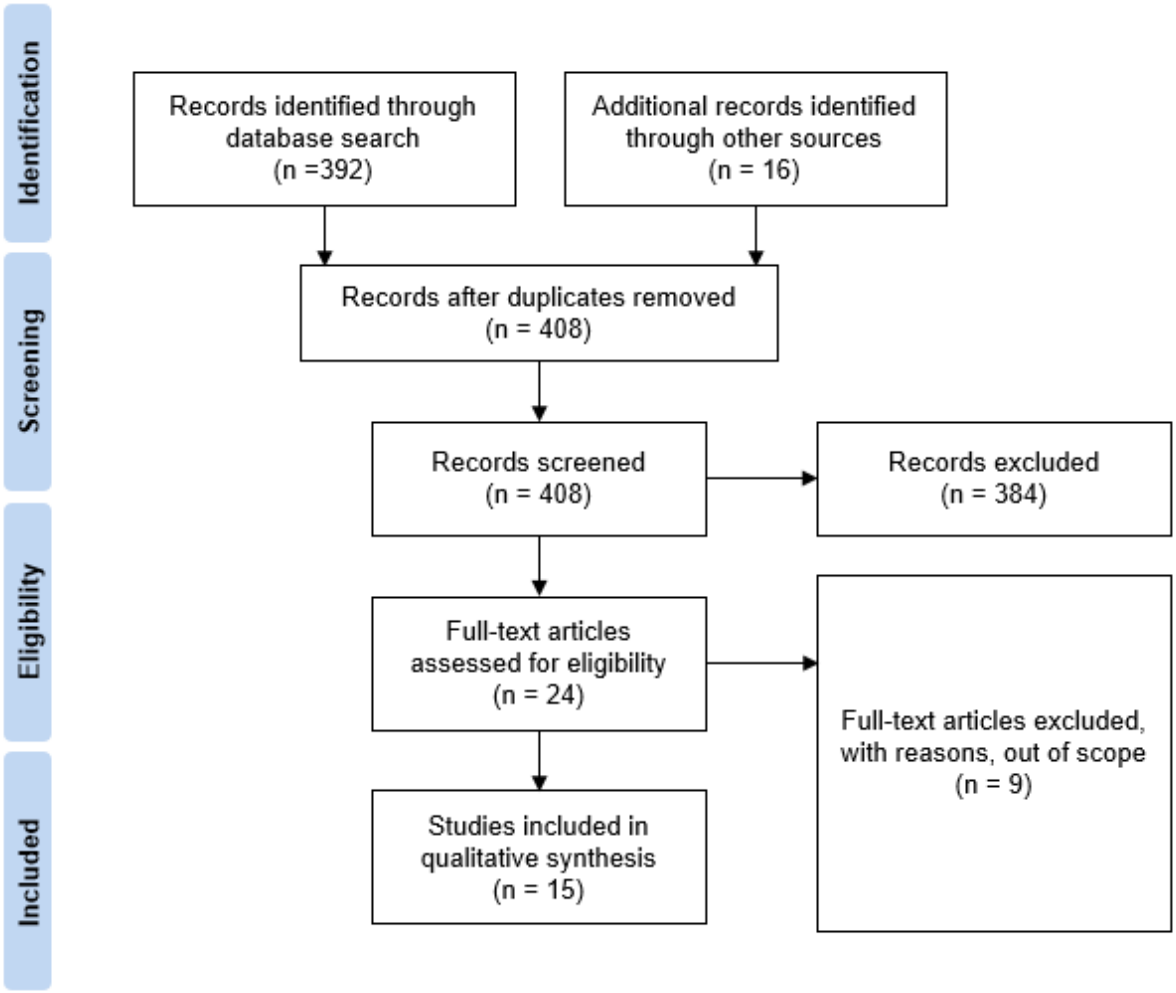

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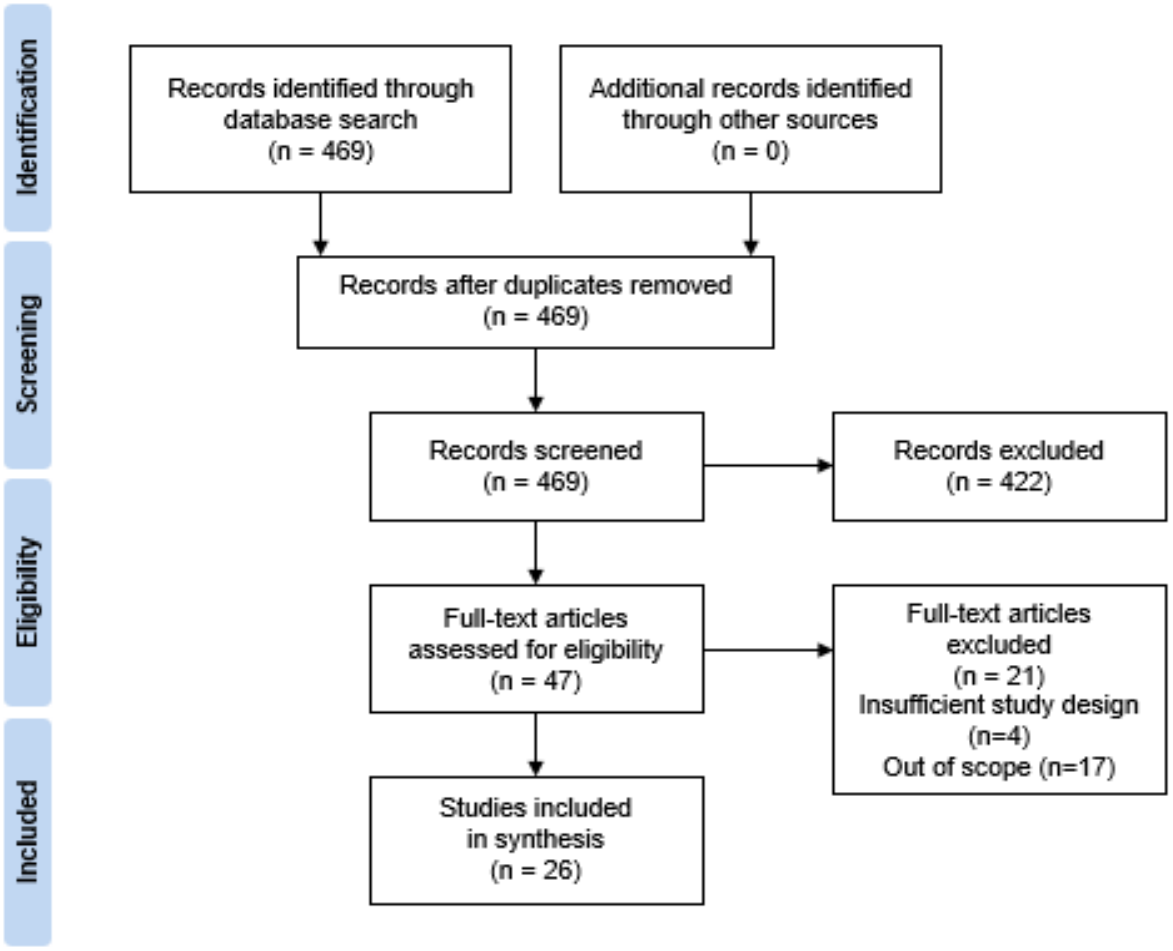
Figure A.2: Opioids, Medication-Assisted Treatment—Study Selection for Review



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Appendix B. Opioids Evidence Tables

Table B.1: Opioids, Opioid Stewardship–Systematic Reviews

Note: Full references are available in the Section 10.1 reference list.

Author, Year (Reference)	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings	Notes
Starrels et al., 2010[1]	• Treatment agreement • Urine drug test (UDT)	• Pain clinics • Primary care	All studies were observational and rated as poor to fair quality. In four studies with comparison groups, opioid misuse was modestly reduced (7% to 23%) after treatment agreements with or without UDT. In seven studies, the proportion of patients with opioid misuse after treatment agreements, UDT, or both varied widely (3% to 43%).	Not provided	None

Table B.2: Opioids, Opioid Stewardship–Single Studies

Note: Full references are available in the Section 10.1 reference list.

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
Anderson et al., 2016[15]	Stepped Care Model for Pain Management (SCM-PM): provider continuing medical education (CME) related to opioid prescribing; opioid dashboard for patients receiving chronic opioid therapy (COT) that listed whether the patient had a signed treatment agreement, had a urine drug screening (UDS) within the past 6 months, had completed a pain interference assessment questionnaire within the past 3 months, and made at least one behavioral	• Treatment agreement • UDS • Pain interference • Behavioral health visit • Project ECHO	• Education • Dashboard • Policy • Electronic health record (EHR) templates	Pre/post intervention; Provider and patient surveys (3,357 pre-intervention and 4,385 post-intervention) No control group	Multisite Federally qualified health center (FQHC) in Connecticut 25 providers Primary care; FQHC	During the baseline period, only 360 (34%) of the 1,309 patients receiving COT had a documented treatment agreement in the chart and 680 (64%) had had a urine drug test (UDT) in the preceding year. After implementation, 778 (61%) out of 1,230 patients receiving COT had a treatment agreement and 1,103 (87%) had had a UDT in the preceding year (both differences significant at $p<0.05$). Documentation of the presence of pain and the source and/or cause of pain increased significantly,	Not provided	Not provided	Moderate: no control group; one health system—not generalizable

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
	health visit in the past year; onsite specialty care; virtual access to pain specialists; EHR templates for chronic pain; and chronic pain and opioid prescribing policy.					from 64% to 82% (p=0.001) and from 62% to 74% (p=0.025), respectively. There were also significant improvements in documentation of functional status from 5% to 19% (p=0.001), in a documented treatment plan from 92% to 98% (p=0.002), and in documentation of pain reassessment from 17% to 39% (p=0.001). Providers' pain knowledge scores increased to an average of 11% from baseline; self-rated confidence in ability to manage pain also increased. Use of opioid treatment agreements and UDSs increased			

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
						significantly by 27.3% and 22.6%, respectively. Significant improvements were also noted in documentation of pain, pain treatment, and pain followup. Referrals to behavioral health providers for patients with pain increased by 5.96%. Results demonstrate statistically significant increases in the percentage of patients with pain who had a visit with an onsite behavioral health provider. Referrals to chiropractors also increased significantly for both groups, while there was a significant decline in referrals to neurosurgery or orthopedic			

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
						surgery and to pain specialists. There was no significant decline in opioid prescribing.			

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
Anderson et al., 2015[11]	Opioid dashboard to increase adherence to guidelines	• Treatment agreement • UDT • Document functional status • Behavioral health visit	• Dashboard	Outcomes evaluation with pre/post design provider survey post implementation. One multisite community health center serving over 140,000 medically underserved patients No control group	Multisite FQHC in CT Primary care; FQHC	Post implementation, there was an increased proportion of COT patients with: a signed opioid treatment agreement (49% to 63%, p<0.001), UDT (66% to 86%, p<0.001)), documented assessment of functional status (33% to 46%, p<0.001)), and at least one visit with behavioral health (24% to 28%, p<0.03). Percentage of adult patients who received opioid prescriptions decreased (13% to 12.5%, p=0.036). The percentage of patients receiving COT also declined (3.4% to 3.1%, =0.057) (Anderson, 2015).	Not provided	54% of primary care provider (PCP) respondents felt that the missed opportunities report was helpful. 85% of respondents reported that the dashboard helps them identify patients on chronic opioids, and gaps in services for patients. 54% reported dashboard helps them to plan care for these patients and 69% felt that it was easy to use the dashboard to help collaborate with team. 77% felt dashboard was clinically useful.	Moderate: no control group; one health system—not generalizable

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
Dorflinger et al., 2014[18]	SCM-PM—increase safe opioid prescribing practices and bolstering nonopioid, multimodal pain care	• Treatment agreement • Shared decision making • Pain specialty care services • Use of nonpharmacological treatments • Referrals	• EHR templates	Cross-sectional/ pre-post; 2,261 patients who received at least 90 consecutive days of opioids prescribed by a U.S. Department of Veterans Affairs (VA) PCP from July 2008 to June 2012 No control group	VA Connecticut Healthcare System—serves 178,144 patients Primary care; VA	Over the 4-year study period, the proportion of patients receiving high-dose opioids decreased from 27.7% to 24.7%. Use of opioid risk mitigation strategies increased significantly. The mean pain intensity rating did not differ from year to year over the 4-year study. Proportion of patients with an opioid treatment agreement increased from 27.9% to 81.1% ($p<0.0001$) and the percentage receiving a UDS increased from 52.5% to 79.6% ($p<0.0001$). Referrals to physical therapy, pain management, and chiropractic increased significantly ($p<0.05$), but	Not provided	Use of EHR note templates likely increased uptake. Challenges with EHR capturing complementary health approaches (e.g., chiropractic).	Not provided

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
						not for mental health. Use of topical analgesics increased ($p<0.05$) but not use of nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants / neuro, or anticonvulsants.			

Dublin et al., 2019[8]	Clinical leadership encouraging adherence to Washington (WA) state's 2007 COT guideline—periodic voluntary educational presentations and one mandatory CME course; Implementation of policy making PCPs responsible for overall management of COT patients; PCPs and medical directions received lists of their patients receiving high-dose COT; supervisory guidance for those PCPs with large numbers of patients on high-dose COT; financial incentives for physicians completing COT care plans	• Dose reduction • Risk stratification • Increased monitoring • Opioid care plans • UDS • Pain specialist consultation	• Education • Dashboard • Audit and feedback	Interrupted time series; 31,142 patients (22,673 intervention, 8,469 control) receiving COT from 2006 to 2014 Control group	26 group practice primary care clinics in WA state Primary care; Integrated group practices	Among 21,853 people receiving COT in the integrated group practice and 8,260 in contracted care, there were 2,679 injuries during followup. The baseline injury rate was 1.0% per calendar quarter in the integrated group practice and 0.9% in contracted care. Risk reduction initiatives did not decrease injury rates: Within the integrated group practice, the relative risk in the dose reduction period was 1.01 (95% confidence interval [CI], 0.95 to 1.07) and in the risk stratification and monitoring period, 0.99 (95% CI, 0.95 to 1.04). Injury trends did not differ between the two care settings.	Not provided	Not provided	Low-to-moderate: control of bias accounted for in analysis through comparing intervention and control groups; study took place within single health system and may not be generalizable
Jacobs et al., 2016[19]	Clinical pain pharmacist	• Pharmacist telephonic	• EHR assessment	Pilot/ implementation	Medical Practice	After the pilot, the proportion	Not provided	Not provided	Moderate: small sample;

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
	telephone-based risk assessment for COT renewals—two pharmacists provided monthly risk assessment for every patient requesting prescription renewal Pharmacist assessment of risk and VA guideline-concordant care	monthly assessment of medication use and aberrant drug-related behaviors at prescription renewal • Informed consent • UDT • Prescription drug monitoring program (PDMP) • EKG monitoring	and recommend-ations to provider	study; 148 patients served by 5 PCPs; patients receiving COT in primary care, excluding MAT for substance-use disorder (SUD) No control group	Primary Care Clinic at San Francisco VA Health Care System, serving 10,000 patients Primary care; VA	of patients meeting the universal precautions measures increased significantly. The proportion of patients with an updated opioid informed consent increased from 4.7% to 64.8% (p<0.0001), the proportion of patients with a completed UDT within 1 year increased from 62.8% to 79.7% (p=0.002), and the proportion of patients with a completed PDMP report within 1 year increased from 30.4% to 100% (p<0.0001). There was also a nonsignificant increase in EKG monitoring for patients on methadone (47.4% vs. 73.6%; P D .187).			no control group; implementation at one VA system with only 5 PCPs

Liebschutz et al., 2017[6]	Transforming Opioid Prescribing in Primary Care (TOPCARE): (1) nurse care management (assesses pain, addiction, misuse risk; prepares prescriptions; collects UDTs; conducts pill counts; checks PDMPs, assessing concerning patient issues; and collaborates with PCP), (2) electronic registry to facilitate population management, (3) one-on-one academic detailing, and (4) orientation and access to electronic decision tools through online platform (e.g., Opioid Risk Tool), and interactive tools to assist with UDT ordering and interpretation. Control clinicians only	• Nurse care management • Assess pain, addiction, misuse • UDTs • Pill counts • PDMPs • Electronic registry	• EHR tools • Education • Academic detailing • Electronic decision tools (INT and Control)	Cluster-randomized trial; 93 PCPs and 985 patients; patients receiving long-term opioid therapy; one health center served the homeless population; individual PCPs were randomized across four sites. Control group	Four safety-net primary care practices in Boston, MA Primary care; Safety net	At 1-year followup, intervention patients were more likely than controls to receive guideline-concordant care (65.9% vs 37.8%; p<0.001; adjusted odds ratio (AOR), 6.0; 95% CI, 3.6 to 10.2), to have a treatment agreement (53.8% vs. 6.0%, p<0.001, AOR, 11.9; 95% CI, 4.4 to 32.2), to have received at least one UDT (74.6% vs. 57.9%, p<0.001, AOR, 3.0; 95% CI, 1.8 to 5.0), and to have either a 10% morphine equivalent daily dose reduction or opioid treatment discontinuation (AOR 1.6). Intervention patients had a mean morphine equivalent daily dose 6.6 (1.6) mg lower than	Not provided	Not provided	Low: no data from outside the health system

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
	received fourth component.					controls (p<0.001). There was no difference between the two groups in early refills of opioids.			
Von Korff et al., 2016[9]	Clinical leadership encouraging adherence to WA state's 2007 COT guideline—periodic voluntary educational presentations and one mandatory CME course; Implementation of policy making PCPs responsible for overall management of COT patients; PCPs and medical directors received lists of their patients receiving high-dose COT; supervisory guidance for those PCPs with large numbers of	• Dose reduction • Risk stratification • Increased monitoring • Opioid care plans • UDS • Pain specialist consultation	• Education • Dashboard • Audit and feedback	Interrupted time series; 31,142 patients (22,673 intervention, 8,469 control) receiving COT from 2006 to 2014 Control group	26 group-practice primary care clinics in WA state Primary care: integrated group practices	From 2006 through June 2014, the percentage of patients on COT receiving ≥120 mg morphine equivalent dose decreased from 16.8% to 6.3% in the intervention clinics (a 63% reduction) versus 20.6% to 13.6% among patients on COT of control clinics (a 34% reduction). From the first quarter of 2006 to June 2014, the average daily MED decreased from 75.8 to 40.0 mg among all intervention clinic patients on COT (47% lower),	Not provided	Not provided	Low-to-moderate: control of bias accounted for in analysis through comparing overdose trends and other variables between intervention and control groups; study took place within single health system and may not be generalizable

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
	patients on high-dose COT; financial incentives for physicians completing COT care plans					compared with a decrease from 92.1 to 64.6 mg among patients on COT in the control clinics (30% lower). Among intervention clinic patients who used opioids regularly for 1 year, the percentage that received a UDT in a 1-year interval was >50% in 2011 through 2014, after being <20% in earlier years. In contrast, among control clinic patients who used opioids regularly for 1 year, the percentage that received a UDT within a 1-year interval ranged from 15.2% in 2011 to 21.4% in 2014.			
Von Korff et al., 2019[10]	Clinical leadership encouraging adherence to	• Dose reduction	• Education • Dashboard	Interrupted time series; 31,142 patients (22,673 intervention—	26 group practice primary care	Authors compared patients on COT in settings	Not provided	Not provided	Low-to-moderate: control of bias

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
	WA state's 2007 COT guideline—periodic voluntary educational presentations and one mandatory CME course; implementation of policy making PCPs responsible for overall management of COT patients; PCPs and medical directions received lists of their patients receiving high-dose COT; supervisory guidance for those PCPs with large numbers of patients on high-dose COT; financial incentives for physicians completing COT care plans	• Risk stratification • Increased monitoring • Opioid care plans • UDS • Pain specialist consultation	• Audit and feedback	integrated group practices, 8,469 control—contracted practices) receiving COT from 2006 to 2014 Control group	clinics in WA state Primary care; integrated group practices	that implemented a COT dose reduction initiative and then a COT risk stratification/ monitoring initiative to similar patients on COT from control settings. From 2006 to 2014, 31,142 patients on COT (22,673 intervention, 8,469 control) experienced 311 fatal or nonfatal opioid overdoses. In primary analyses, changes in opioid overdose rates among patients on COT did not differ significantly between intervention and control settings with the implementation of either dose reduction or risk stratification/ monitoring. In planned			accounted for in analysis through comparing intervention and control groups; study took place within single health system and may not be generalizable

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
						secondary analyses, overdose rates decreased significantly (17% per year) during the dose reduction initiative among patients on COT in intervention settings (relative annual change, 0.83; 95% CI, 0.70 to 0.99), but not in control settings (0.98. 95% CI, 0.70 to 1.39). We conclude that overdose rates among patients on COT were not decreased by risk stratification and monitoring initiatives. Results were inconsistent for COT dose reduction, with no significant difference between intervention and control settings (primary hypothesis test), but a			

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
						significant decrease in overdose rates within the intervention setting during dose reduction (secondary hypothesis test).			

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
Weimer et al., 2016[17]	Provider education and dose limitation policy (120 mg morphine milligram equivalents [MME]/day)	• Pain task force • Dose limitation • Initiate taper for >120 MEDs • Patient list of patients with high dosage	• Education • Policy	Retrospective cohort; 116 patients—41 tapered to safe dose following intervention, 71 not tapered; primary care patents prescribed opioids for more than 90 consecutive days No control group	One academic primary care clinic Primary care	Statistically significant change in MED per day during the post-intervention period. Among the 112 patients prescribed high-dose opioids, the average total MED declined from 263 to 199 mg MED in the post-intervention period (average change of 64 mg MED [95% CI, 32 to 96]; p<0.001). As shown in Figure 2, among the 41 TSD patients, the average dose declined from 207 to 85 mg MED (average change of 122 mg MED [95% CI,: 165 to 250]; p<0.001).	Not provided	Not provided	Moderate-to-high: single clinic—may not be generalizable; followup period limited to 8 months; no control group; did not control for other interventions or increased visibility of opioid epidemic that may have happened during the same time
Weiner et al., 2019[16]	Multicomponent program: inter-departmental Prescribing Task Force to develop safe prescribing	• Opioid Stewardship Committee • Prescribing, addiction,	• Education • Patient education • EHR template • Integrated PDMP in EHR	Cross-sectional/pre-post intervention; program began in Feb 2016 and data were	One health system in Boston, consisting of 160 ambulatory care clinics,	Schedule II opioid prescribing decreased from 8,941 prescriptions in July 2015 (the	Not provided	Determining metrics and gaining access to data was important to guide the effort.	Moderate: patients may have had prescription outside the system; no control; one

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
	guidelines for the health system; multidisciplinary Addiction Task Force, which proposed creation of a Bridge Clinic for patients with opioid use disorder (OUD) being discharged from hospital or emergency department (ED); provider education through Opioid Grand Rounds every 2 months; opioid take-back program advertised to patients; creation of curriculum on Clinical Opiate Withdrawal Scale for providers to access on demand; creation of opioid prescribing SmartForm in EHR to alert providers on best practices	education task forces • Nonpharma-cologic treatments • Referral for OUD treatment • Naloxone	• Autopopulate patient discharge instructions • Connection to ED information exchange • Dashboard • Audit and feedback • Monitoring with opioid-related metrics	gathered for July 2015 through April 2018; size of patient population for the health system not given in article No control group	15 primary care practices, and 2 hospitals Health system-wide	first year for which data are available) to 6,148 in April 2018 (-73.5 prescriptions per month; p<0.001). Mean MME per prescription (-0.4 MME per month; p<0.001). The number of unique patients receiving an opioid prescription each month also decreased, from 6,863 in July 2015 to 4,894 in April 2018, a 28.7% decrease (-52.6 patients per month; p<0.001). Prescriptions containing a total of ≥90 MME also decreased (-48.1 prescriptions/ month; p<0.001). The number of prescriptions (+ 6.0 prescriptions/m		Tensions between primary care and pain specialists because of mismatch of expectations of who was responsible for prescribing opioids and taking care of patients. Increased access to SUD, but outpatient practices believed had inadequate access. Helpful to convene stakeholders to address the challenges encountered.	health system—limited generalizability

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
	for prescribing opioids; integrate state PDMP into the EHR; join statewide ED information exchange to detect patients seeking opioids at multiple EDs; benchmarking reports for each provider's opioid prescribing, which lets them see how they compare with unidentified peers; autopopulating opioid education information in patients' discharge instructions; creation of internal opioid-related metrics					onth; p<0.001) and prescribers (+ 0.4 providers/month; p<0.001) for the film version of buprenorphine/ naloxone, indicated for treatment of OUD, increased. Overdose trend was downward, but not significant. The number of overdoses fluctuates markedly by month, and although the overall linear trend is downward, it does not reach statistical significance (-0.2 overdoses/ month; p=0.29).			

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
Kahler et al., 2017[12]	Protocol to transfer "superusers" from ED to outpatient chronic pain program—following referral to the program, an EMR alert would appear when patients arrived in ED	• Transfer "superusers" of ED to outpatient chronic pain	• EHR alert of superusers	Crossover patients served as their own controls in the year prior to referral to the chronic pain program; 243 patients with at least 6 visits/ year to the ED, with 1 visit primarily driven by opioid-seeking behavior; adults age 18–67, cancer and sickle cell disease excluded Control group (crossover)	One ED in Indianapolis, IN, serving 102,000 patients/year ED	ED visits decreased from 14 to 4 (58% decrease, 95% CI, 50 to 66). We also found statistically significant decreases for these patients' state PDMP opioid prescriptions (30% decrease, 95% CI, 24 to 37), total unique controlled-substance prescribers from 11 to 7 (31% decrease, 95% CI, 23 to 38), computed tomography imaging (2 to 0), radiographs (5 to 1), electro-cardiograms (12 to 4), and labs run (47 to 13).	Not provided	Administrative support is critical EHR alerts were key component	Moderate: no control group; national attention on opioid prescribing at the time of the intervention, which may have introduced confounding; no measure of MME; no control for whether improvements were due to passage of time
Neven et al., 2016[7]	City-wide care coordination program that provides real-time ED treatment plans through a case manager for patients at risk of obtaining	• Citywide care coordination with EDs for patients opioid-seeking behavior	• Information exchange across systems	Randomized controlled trial; 165 patients; patients with 5 or more ED visits in the previous 12 months, at least half of which were attributed	Three EDs in same metropolitan area of Spokane, WA—combined annual total of 112,000 visits	The intervention arm experienced a 34% decrease (incidence rate ratio = 0.66, p<0.001; 95% CI, 0.57 to 0.78) in ED visits and an 80%	Not provided	Providers reported being more empowered to say "no" in prescribing opioids.	Low to moderate: relatively small sample; did not assess for opioids prescribed outside the

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
	opioids for inappropriate use			to pain and/or drug-seeking behavior Control group	ED	decrease (OR=0.21, p=0.001) in the odds of receiving an opioid prescription from the ED relative to the control group. Declines of 43.7%, 53.1%, 52.9%, and 53.1% were observed in the treatment group for MMEs, controlled substance pills, prescriptions, and prescribers. At 1 year following study enrollment, patients receiving the intervention were 33% less likely to visit the ED compared with the control group, visited the ED fewer times on average than the control group, and received a smaller mean number of prescription at			ED or illicitly obtained

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
						discharge. There were 23 unique prescribers in the treatment group as compared with 40 in the control group over the study year. Number of pills dispensed and MME prescribed in the intervention group was nearly half that of the control group.			

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
Hartford et al., 2018[14]	"Pain care bundle"—promoting co-analgesia during surgery, reduced opioid prescriptions post-surgery (provider education), patient education around expectations for postoperative pain management	• Intra- and postoperative pain care bundle • Opioid reduction strategies	• Education • Patient education	Pre-post intervention; 224 patients (pre) to 192 (post); patients undergoing open hernia repair or laparoscopic cholecystectomy No control group	Three hospitals in Ontario that perform general outpatient surgery Hospital, outpatient surgery	The median total MMEs for prescriptions filled in the post-intervention group were significantly less (100; interquartile range 75 to 116 pre-intervention vs 50; interquartile range 50 to 50 post-intervention; p<0.001). Only 78 of 172 (45%) patients filled their opioid prescription in the post-intervention group (p<0.001), with no significant difference in prescription renewals (3.5% pre-intervention vs 2.6% post-intervention; p = 0.62).	Not provided	Division-wide buy-in from nurses, surgeons, and anesthesiologists was a strength	Low to-moderate: includes control group but differences between two groups are not compared; conducted at one health system and may not be generalizable.

Author, Year	Description of Patient Safety Practice	Opioid Stewardship Interventions or Strategies	Implementation Strategies	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
Young et al., 2018[13]	Provider education on CDC guideline; clinic guidelines implemented that required checking PDMP before prescribing and limiting all opioids to 7 days' supply.		• Education • Guideline • Monitoring	Cross-sectional/ pre-post intervention; clinic sees 2.75 patients per provider per hour; patients of all ages, pediatric through geriatric (95% adults); outcomes assessed via PDMP eight weeks before and after implementation. No control group	Four privately owned urgent care centers in Rhode Island, with a total of 14 providers Urgent care	Opioid prescribing before and after adoption of the guideline, and in this manner, a statistically significant ($P < 0.05$) decline in the rate of opioid prescribing was revealed. On average, 2.43 fewer opioid prescriptions were written, per provider, per week, in weeks five through eight after promulgation (5.21, SD =4.37) than in the eight weeks before promulgation (7.64, SD =7.73).	Not provided	Not provided	Moderate to high: no control; one health system—limited generalizability; short followup period; small sample size

Table B.3: Opioids, Medication-Assisted Treatment–Single Studies

Note: Full references are available in the Section 10.2 reference list.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
Busch et al., 2017[28]	Initiation of buprenorphine/ naloxone in the emergency department (ED) as compared to screening/referral/brief intervention only	Cost-effectiveness study; 244 patients (subset of larger randomized controlled trial [RCT] [D'Onofrio 2015], limited to those who completed 30-day follow-up; ED patients with a DSM-IV diagnosis of opioid dependence	Emergency department	At all positive willingness-to-pay values, ED-initiated buprenorphine treatment was more cost-effective than brief intervention or referral.	Not provided	Not provided	Low-to-moderate: single site—findings may not be generalizable	None
D'Onofrio et al., 2017[7]	Initiation of buprenorphine/ naloxone in the ED as compared to screening/ referral/brief intervention only	RCT with three arms: screening for opioid dependence and referral; screening, brief intervention, and referral; initiation of treatment in ED with 10-week follow-up in primary care; 290 patients (subset of larger RCT [D'Onofrio 2015]; opioid-dependent patients treated at an urban teaching hospital ED from 2009-2013	Emergency department	Six- and 12-month followup to 2015 RCT: a greater number of patients in the buprenorphine group were engaged in addiction treatment at two months [68/92 (74%), 95% confidence interval (CI) 65–83] compared with referral [42/79 (53%), 95% CI 42–64] and brief intervention [39/83 (47%), 95% CI 37–58; $p < 0.001$]. The differences were not significant at six months [51/92 (55%), 95% CI 45–65; 46/70 (66%) 95% CI 54–76; 43/76 (57%) 95% CI 45–67; p	Not provided	Not provided	Low-to-moderate: single site—findings may not be generalizable	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
				= 0.37] or 12 months [42/86 (49%) 95% CI 39–59; 37/73 (51%) 95% CI 39–62; 49/78 (63%) 95% CI 52–73; p = 0.16]. At two months, the buprenorphine group reported fewer days of illicit opioid use [1.1 (95% CI 0.6–1.6)] vs. referral [1.8 (95%CI 1.2–2.3)] and brief intervention [2.0 (95% CI 1.5–2.6), p = 0.04]. No significant differences in illicit opioid use were observed at six or 12 months. There were no significant differences in HIV risk or rates of opioid-negative urine results at any time.				
D'Onofrio et al., 2015[6]	Initiation of buprenorphine/ naloxone in the ED as compared to screening/ referral/brief intervention only	RCT with three arms: screening for opioid dependence and referral; screening, brief intervention, and referral; initiation of treatment in ED with 10-week follow up in primary care; 329 patients; opioid-dependent patients treated at an urban teaching	Emergency department	Seventy-eight percent of patients in the buprenorphine group (89 of 114 [95% CI, 70%-85%]) vs. 37% in the referral group (38 of 102 [95% CI, 28%-47%]) and 45% in the brief intervention group (50 of 111 [95% CI, 36%-54%]) were engaged in addiction treatment on the 30th day after randomization (P < .001). The buprenorphine group reduced the number of	Not provided	Not provided	Low-to-moderate: single site—findings may not be generalizable	At 30-day follow-up, rates of positive urine drug tests did not differ among the groups.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
		hospital ED from 2009-2013		days of illicit opioid use per week from 5.4 days (95% CI, 5.1-5.7) to 0.9 days (95% CI, 0.5-1.3) vs. a reduction from 5.4 days (95% CI, 5.1-5.7) to 2.3 days (95% CI, 1.7-3.0) in the referral group and from 5.6 days (95% CI, 5.3-5.9) to 2.4 days (95% CI, 1.8-3.0) in the brief intervention group (P < .001 for both time and intervention effects; P = .02 for the interaction effect). Eleven percent of patients in the buprenorphine group (95% CI, 6%-19%) used inpatient addiction treatment services, whereas 37% in the referral group (95% CI, 27%-48%) and 35% in the brief intervention group (95% CI, 25%-37%) used inpatient addiction treatment services (P < .001). Patients who received medication-assisted treatment (MAT) initiation while in the ED were less likely to use inpatient treatment for opioid use disorder (OUD) in the 30 days following the ED visit. This suggests that initiation of treatment in				

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
				the ED may result in more efficient use of resources.				
Doolittle & Becker, 2011[25]	Buprenorphine/ naloxone treatment	Case series; 228 patients with opioid use disorder over four-year period	Community practice with two primary care provider prescribers	One out of 228 experienced precipitated withdrawal during induction. Of the convenience subsample analyzed (n = 28), 82% (+/−10%) had negative urine drug tests for opioids; 92% (+/−11%) were negative for cocaine; 88% (+/−12%) were positive for buprenorphine. Authors concluded that treatment of OUD using buprenorphine in primary care was both feasible and safe.	Not provided	Not provided	Moderate: single site, no comparison group	None
Doorley et al., 2017[21]	Shared medical appointments for buprenorphine maintenance	Retrospective chart review; 77 opioid-dependent patients; 61% of patients currently homeless, 92% were unemployed, 81% had an Axis I psychiatric diagnosis, and 53% had recent polysubstance use	Clinic providing health care for homeless individuals in San Jose, CA	Of the 77 patients, 95% attended at least one shared medical appointment. Treatment retention at 12 and 24 weeks was 86% and 70%, respectively.	Not provided	Not provided	High: single site, no comparison group, small sample size	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
Fiellin et al., 2014[4]	Maintaining MAT indefinitely, as opposed to tapering following stabilization	RCT—participants randomized to either a three-week buprenorphine taper following six weeks of stabilization vs. ongoing buprenorphine maintenance therapy; 113 patients with prescription opioid dependence	One primary care clinic at a large, urban, academically-affiliated hospital in New Haven, CT	Patients in the taper group reported more days per week of illicit opioid use than those in the maintenance group once they were no longer receiving buprenorphine (mean use, 1.27 [95% CI, 0.60–1.94] vs. 0.47 [95% CI, 0.19–0.74] days). Patients in the taper group had fewer maximum consecutive weeks of opioid abstinence compared with those in the maintenance group (mean abstinence, 2.70 [95% CI, 1.72–3.75] vs. 5.20 [95% CI, 4.16–6.20] weeks). Patients in the taper group were less likely to complete the trial (6 of 57 [11%] vs. 37 of 56 [66%]; P < .001). Sixteen patients in the taper group reinitiated buprenorphine treatment after the taper owing to relapse.	Not provided	Not provided	Low-to-moderate: single site—findings may not be generalizable; patients were receiving nurse counseling during study period about their drug use, potentially overestimating effects.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
Fiellin et al., 2013[10]	Cognitive behavioral therapy (CBT)	RCT—Participants randomized to receive physician management or physician management plus 12 weeks of CBT; 141 adult patients with opioid dependence receiving buprenorphine, enrolled from 2006–2009	One primary care clinic at a large, urban, academically-affiliated hospital in New Haven, CT	Both groups experienced a significant reduction in opioid use during treatment, but the findings do not support addition of CBT to standard physician management for MAT treatment.	Not provided	Not provided	Low-to-moderate: single site—findings may not be generalizable	At 12 weeks follow-up post-treatment, the two groups did not significantly differ in frequency of illicit opioid use.
Fiellin et al., 2008[13]	Long-term treatment with buprenorphine/ naloxone in primary care: Results at 2–5 years	Observational (no control group); 53 opioid-dependent patients who had initiated MAT through a previous RCT	One primary care clinic at a large, urban, academically-affiliated hospital in the U.S.	Thirty-eight percent of enrolled subjects were retained for two years. Ninety-one percent of urine samples had no evidence of opioid use, and patient satisfaction was high. No serious adverse events related to treatment occurred. Authors summarize that this is a "moderate" level of retention two years after initiation of MAT in primary care.	Not provided	Not provided	High: single site, no comparison group, small sample size	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
Kowalczyk et al., 2017[8]	Clonidine as an adjunct to buprenorphine to decrease stress from craving	RCT—clonidine vs. placebo for 18 weeks of buprenorphine treatment; 118 participants seeking treatment for opioid dependence (108 included in this analysis due to 10 participants dropping out)	Outpatient substance-use disorder (SUD) treatment center in Baltimore, MD	Participants who received buprenorphine plus clonidine reported longer streaks of abstinence when they had unstructured time, as compared to the buprenorphine-only group. This indicates that addition of clonidine may help reduce cravings.	Not provided	Not provided	Low-to-moderate: single site—findings may not be generalizable	There was no statistically significant difference in average length of longest abstinence between the two groups.
Lagisetty et al., 2017[3]	MAT in primary care—buprenorphine or methadone	Systematic review; 35 included studies (10 RCTs and 25 quasi-experimental designs); included studies across eight countries	Adult outpatient primary care	Successful programs tended to integrate clinical teams with support staff such as nurses and pharmacists to serve as clinical care managers, utilize patient agreements, and offer treatment induction at the patient's home. More research is needed to determine the optimal level of provider training needed to provide behavioral counseling to this population.	Not provided	Not provided	Not provided	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
Lee et al., 2012[15]	Buprenorphine/ naloxone maintenance in primary care vs. community referral	Observational—patients induced to buprenorphine in jail vs. those seeking buprenorphine induction post-release; 252 patients from 2007–2008	Individuals released from jail—primary care maintenance vs. community referral	Treatment retention rates for post-release (37%) vs. community (30%) referrals were similar at 48 weeks. Rates of opioid positive urines and self-reported opioid misuse were also similar between groups. Post-release patients in primary care buprenorphine treatment had equal treatment retention and rates of opioid abstinence vs. community-referred patients.	Not provided	Not provided	Not provided	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
Lee et al., 2009[24]	Home buprenorphine/ naloxone induction, after prescription in primary care setting; the initial physician visit included assessment, education, induction telephone support instructions, an illustrated home induction pamphlet, and a one-week buprenorphine/ naloxone prescription. Patients initiated dosing off-site at a later time.	Pilot study (observational, no control group); 103 patients—predominantly heroin users (68%) but also prescription opioid misusers (18%) and methadone maintenance patients (14%).	Patient home/ primary care	At the end of week 1, 73% of patients were retained in treatment, 17% provided induction data but did not return to the clinic, and 11% were lost to follow-up with no induction data available. No cases of severe precipitated withdrawal and no serious adverse events were observed. Home buprenorphine induction was thus considered feasible and "appeared safe."	Not provided	Not provided	Low-to-moderate: small sample size, but this was feasibility not outcomes study	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
Liebschultz et al., 2014[5]	Linkage to hospital-based outpatient buprenorphine treatment following hospitalization; as compared to detoxification using buprenorphine taper	RCT; 139 patients; medically hospitalized opioid-dependent patients in general medical wards of one urban safety-net hospital between 2009–2012	Inpatient hospital	Participants who received linkage to buprenorphine treatment in primary care were more likely to enter outpatient buprenorphine treatment (52 [72.2%] vs. eight [11.9%], P < .001) as well as to stay in treatment at six-month follow-up (12 [16.7%] vs. two [3.0%], P = .007). Participants receiving the linkage intervention were also less likely to report illicit opioid use in the past month at six- month follow-up (incidence rate ratio, 0.60; 95% CI, 0.46-0.73; P < .01).	Not provided	Not provided	Moderate: small sample size; one study site—limited generalizability; underlying medical condition and severity of opioid dependence were not controlled for	Participants were expected to have lower rates of linkage to MAT compared to the general outpatient population of OUD patients, due to the medical illness that resulted in their hospitalization.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
Lucas et al., 2010[14]	Buprenorphine treatment in an HIV clinic, as opposed to referral to an OUD treatment program	RCT; 93 participants; HIV-infected, opioid-dependent patients	Outpatient HIV clinic in Baltimore, MD	Initiation of opioid agonist therapy was substantially more rapid in the clinic-based buprenorphine (BUP) group than in the referred-treatment arm: at two weeks, 84% (95% CI 72%–93%) in clinic-based BUP had initiated opioid agonist therapy compared to 11% (5%–24%) in referred-treatment ($p<0.001$). The average estimated percentages of opioid positive and cocaine positive urine drug tests were significantly lower in clinic-based BUP than referred-treatment (44% [32%–58%] vs. 65% [95% CI, 52%–76%] for opioids, $p=0.015$, and 51% [39%–61%] vs. 66% [54%–76%] for cocaine, $p=0.012$). Subjects in clinic-based BUP had significantly more visits with their primary HIV providers during the study than subjects in referred-treatment (median 3.5 [interquartile range (IQR) 2–4] vs. 3.0 [IQR 1–3] visits, respectively, $p=0.047$).	Not provided	Not provided	Low-to-moderate: small sample size; single center—limited generalizability; authors did assess for the effect of loss to follow up on the results.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
Miotto et al., 2012[18]	Buprenorphine therapy delivered in three distinct treatment settings: an opioid-treatment program (OTP) offering individual counseling; a group counseling program utilizing the manualized Matrix Model (MMM) of cognitive-behavioral treatment; and a private clinic setting mirroring standard medical management for buprenorphine treatment provided specifically at a psychiatrist's private practice (PCS).	Randomized trial: 94 participants—28 in OTP, 33 in PCS, and 33 in MMM; patients meeting opioid dependence criteria based on DSM-IIIR, recruited in the community through advertising.	Three settings: (1) a typical OTP is a structured clinical setting where the administration of methadone is observed, (2) a psychiatrist's private practice, and (3) a cognitive behavioral group therapy program, which had not offered physician services on-site in the past.	The proportion of participants who stayed in the study through Week 20 was significantly associated with treatment site (chi square= 6.12; p = 0.05) with the MMM site associated with the highest percentage of participants retained through week 20 (51.5%). For participants who remained in the study past nine weeks, OTP participants had a four times higher drop-out rate compared to MMM participants (p = 0.01) and a six times higher drop-out rate compared to PCS participants (p = 0.01).	Not provided	Initial education of the staff in all three settings about the utility of buprenorphine was crucial. This was particularly true at the MMM program where the staff advocated an abstinence approach to treatment. In addition to a shift in attitude, modifications of practice management were necessary, such as implementing a monitored induction protocol, on-site drug testing and random pill callback checks. The study staff all indicated that they would have made additional refinements in patient management practices had they not been confined by a research protocol.	Moderate: small sample size	No difference in opioid use by treatment site was found.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
Mitchell et al., 2013[11]	Intensive outpatient counseling vs. standard outpatient counseling for buprenorphine patients	Randomized trial; 300 participants; African American adults newly admitted to buprenorphine treatment from March 2010–March 2011	Two outpatient SUD clinics	Not provided	Controlling for number of days in treatment, greater counseling exposure was associated with significantly less improvement for three outcomes—days of heroin use, days of cocaine use, and days of criminal activity (all ps < .01).	Not provided	Moderate: no control; two sites—limited generalizability	There was no statistically significant difference between groups receiving standard counseling vs. intensive counseling, and there was no comparison group that received buprenorphine and no counseling.
Neumann et al., 2013[20]	Buprenorphine treatment	Retrospective cohort (chart review); 356 patients receiving buprenorphine for opioid addiction	Outpatient primary care	Of the 356 patients, 127 (35.7%) completed six-month buprenorphine treatment. Completion of treatment was associated with counseling attendance and having had a past injury.	Not provided	Not provided	Low-to-moderate: no comparison group; single center	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
Ober et al., 2018[19]	Behavioral therapy based on motivational interviewing and cognitive behavioral therapy; MAT in form of either injectable naltrexone or buprenorphine/ naloxone	Secondary analysis of RCT; 392 total RCT participants—23% received behavioral therapy and 13% received MAT; patients screening positive for substance use (either opioid abuse or alcohol abuse)	Federally qualified health center in Los Angeles, CA	Individuals who initiated behavioral therapy were more likely to have greater self-stigma (odds ratio [OR]=1.60, CI=1.06, 2.42), receive MAT (OR=5.52, CI=2.34, 12.98), and have received the study intervention of collaborative care management (OR=12.95, CI=5.91, 28.37). Individuals more likely to initiate MAT tend to be older age (OR=1.07, CI=1.03, 1.11), female gender (OR=3.05, CI=1.25, 7.46), having a diagnosis of heroin abuse or dependence (with or without alcohol abuse or dependence compared with have a diagnosis of alcohol dependence only (OR=3.03, CI=1.17, 7.86), and having received at least one session of BT (OR=6.42, CI=2.59,15.94),	Not provided	Not provided	Low-to-moderate: no comparison group; single center	Not sure whether the RCT results were ever published; the citation in the reference list has no title.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
Pade et al., 2012[23]	Buprenorphine/ naloxone in primary care (BUP/NLX)	Retrospective cohort (chart review); 143 patients induced with buprenorphine/ naloxone between 2009–2011	Co-occurring Disorders Clinic for patients with both chronic pain and opioid dependence (within outpatient primary care)	Sixty (65%) of those 93 patients were on BUP/NLX for more than six months, 19 (21%) were on BUP/NLX for greater than 12 months, and five (6%) for greater than 18 months. Pain scores showed a modest but statistically significant improvement on buprenorphine/ naloxone.	Not provided	Not provided	Moderate: no comparison group; single center; small sample size	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
Polsky et al., 2010[27]	Buprenorphine-naloxone detoxification (DETOX) vs. 12-week course of buprenorphine-naloxone (BUP)	Cost-effectiveness study based on randomized trial; 152 patients ages 15-21 years recruited from 2003–2006	Six community outpatient treatment programs	Treatment cost was $1,514 ($p<0.001$) higher for BUP relative to DETOX. One-year total direct medical cost was only $83 higher for BUP ($p=0.97$). The cost-effectiveness ratio of BUP relative to DETOX was $1,376 in terms of one-year direct medical cost per quality-adjusted life year (QALY) and $25,049 in terms of outpatient treatment program cost per QALY. The acceptability curve suggests that the cost-effectiveness ratio of BUP relative to DETOX has an 86% chance of being accepted as cost-effective for a threshold of $100,000 per QALY. Therefore, extended buprenorphine-naloxone treatment relative to brief detoxification was found to be cost effective.	Not provided	Not provided	Low-to-moderate: multisite but small sample	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
Polydorou et al., 2017[9]	Integration of buprenorphine maintenance treatment into an established hospital-based opioid treatment program	Case study; 735 opioid-dependent patients treated with buprenorphine from 2006–2013	Hospital-based outpatient opioid treatment program in New York City	During the initial 20 months of implementation, patients enrolled in OTP demonstrated lower rates of positive urine toxicology results for opioids compared with patients in primary care and outpatient psychiatry.	Not provided	Main barriers to implementation were regulations, clinical logistics of dispensing medications, internal cost and reimbursement issues, and professional and cultural resistance.	Moderate: single site but fairly large sample size; implementation themes were identified based on authors' personal experience	None
Schackman et al., 2011[26]	Long-term buprenorphine-naloxone treatment in primary care	Cost-effectiveness study; hypothetical data	Primary care	Office-based buprenorphine/naloxone for clinically-stable patients may be a cost-effective alternative to no maintenance treatment at a threshold of $100,000 QALY.	Not provided	Not provided	Unsure how to assess for a cost-effectiveness study with hypothetical data	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
Stein et al., 2015[12]	Distress tolerance (DT) intervention during buprenorphine initiation—behavioral exposure to opioid craving and skills training based in Acceptance and Commitment therapy (based on intervention developed for smokers, *Brown, 2008*).	RCT; 49 participants—24 assigned to DT intervention, 25 assigned to standard of care, which included health education; Individuals age 18–65 seeking buprenorphine treatment, excluding those requiring opioid treatment for chronic pain	Ambulatory care	Participants receiving the DT intervention had lower rates of opioid use at each of the three monthly follow-up points. At three months post-initiation of buprenorphine treatment, 72% of the health education participants were opioid positive compared with 62.5% of DT intervention participants. However, this difference was not statistically significant. No difference existed in drop-out rates between the two conditions.	Not provided	Buprenorphine initiators were targeted because they are at high risk for treatment drop-out and relapse.	Moderate: small sample size, possibility for selection bias as participants responded to study advertisements; study not blinded; no placebo control	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
Sullivan et al., 2008[22]	Buprenorphine/ naloxone treatment in primary care	Longitudinal; 166 opioid dependent patients receiving buprenorphine/ naloxone in primary care; outcomes assessed HIV risk behaviors at baseline, 12 weeks, and 24 weeks after treatment initiation	Primary care	Buprenorphine/naloxone treatment was associated with significant reductions in overall and drug-related AIDS/HIV Risk Inventory scores from baseline to 12 and 24 weeks. Intravenous drug use in the past three months was endorsed by 37%, 12%, and 7% of patients at baseline, 12 weeks, and 24 weeks, respectively; $p < 0.001$. Sex while you or your partner was "high" was endorsed by 64%, 13%, and 15% of patients at baseline, 12 weeks and 24 weeks, respectively; $p<0.001$. Inconsistent condom use during sex with a steady partner was high at baseline and did not change over time.	Not provided	Not provided	Not provided	None
Suzuki, 2016[17]	Initiation of buprenorphine during hospitalization	Case series; 29 patients; hospitalized with intravenous-drug-use related infective endocarditis	Inpatient; one urban medical center in Boston, MA	Overall, nine patients (31.0%) successfully initiated buprenorphine maintenance during the hospitalization, and nine (31.0%) accepted a referral to methadone maintenance following discharge. Eleven (37.9%) declined MAT altogether.	Not provided	Not provided	High: single site, no comparison group, small sample size	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (high, moderate, low)	Comments
Suzuki et al., 2015[16]	Initiation of buprenorphine during hospitalization	Case series; 47 patients; hospitalized for reasons other than treatment of opioid dependence	Inpatient; one urban medical center in Boston, MA	Twenty-two (46.8%) patients successfully initiated buprenorphine treatment within two months of discharge. Those patients obtaining a referral to a specific program were more successful in continuing treatment, but this difference did not reach statistical significance (59.1% vs. 39.1%, p = 0.18).	Not provided	Not provided	High: single site, no comparison group, small sample size	None

Appendix C. Harms Due to Opioids Search Terms

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis • Multicenter Study	Opioid Stewardship	((MH "Overdose" OR "Analgesics, Opioid") OR (AB “Drug Overdose*” OR “Opioid Abuse*" OR "Opioid Misuse" OR "Opioid Addiction" OR "Opioid*" OR "Prescription Drug Misuse" OR "Prescription Drug Overuse")) AND ((MH “Hospitals” OR “Inpatients” OR “Ambulatory Care Facilities” OR “Practitioner's Office” OR “Long-Term Care” OR “Palliative Care” OR “Subacute Care” OR “Rehabilitation Centers” OR “Residential Facilities” OR "Substance Use Rehabilitation Programs" OR MH “Transitional Care” OR “Primary Health Care” OR “Home Health Care” OR "Nursing Homes" OR "Emergency Service" OR "Dentists" OR "Ambulatory Care") OR (AB “Ambulatory Care” OR “Specialty Care” OR “Hospital*” OR “Long Term Care” OR "Long-Term Care" OR "Palliative Care" OR "Physicians' Office*" OR "Subacute Care" OR "Residential Facilit*" OR “Primary Care” OR "Transitional Care" OR "Rehabilitation Center*" OR "Primary Health Care" OR "Dentist" OR "Emergency Room" OR "Nursing Home" OR "Emergency Department")) AND ((MH "Decision Support Systems, Clinical" OR "Electronic Data Interchange" OR "Health Information Systems" OR "Prescription Drug Monitoring Programs" OR "Drug Monitoring") OR (AB “Stewardship” OR	((MH “Drug Overdose” OR “Opioid-Related Disorders” OR "Prescription Drug Overuse" OR "Prescription Drug Misuse" OR "Analgesics, Opioid") OR (AB “Drug Overdose*” OR “Opioid Abuse*" OR "Opioid Misuse" OR "Opioid Addiction" OR "Opioid*" OR "Prescription Drug Misuse" OR "Prescription Drug Overuse")) AND ((MH “Hospitals” OR “Inpatients” OR “Ambulatory Care Facilities” OR “Physicians' Offices” OR “Rehabilitation Centers” OR “Residential Facilities” OR "Substance Abuse Treatment Centers" OR “Transitional Care” OR “Primary Health Care” OR "Emergency Service, Hospital" OR "Ambulatory Care" OR "Patient Discharge") OR (AB “Ambulatory Care” OR “Specialty Care” OR “Hospital*” OR "Physicians' Office*" OR "Residential Facilit*" OR “Primary Care” OR "Transitional Care" OR "Rehabilitation Center*" OR "Primary Health Care" OR "Emergency Room" OR "Patient Discharge" OR "Emergency Department")) AND ((MH "Decision Support Systems, Clinical" OR "Health Information Exchange" OR "Health Information Systems" OR "Prescription Drug Monitoring Programs" OR "Drug Monitoring") OR (AB “Stewardship” OR

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Practice Guideline • Published Erratum • Randomized Controlled Trial • Review • Scientific Integrity Review • Technical Report • Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis • Practice Guidelines • Randomized Controlled Trial • Research Review		"Prescription Drug Monitoring Program" OR "Treatment Agreement" OR "Patient Contract" OR "Clinical Decision Support" OR "Health Information Technology" OR "Prescribing" OR "Monitoring" OR "Patient Registry" OR "Dashboard" OR "Feedback Approach")))	"Prescription Drug Monitoring Program" OR "Treatment Agreement" OR "Patient Contract" OR "Clinical Decision Support" OR "Health Information Technology" OR "Prescribing" OR "Monitoring" OR "Patient Registry" OR "Dashboard" OR "Feedback Approach")))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Systematic Review			
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis	Medication-Assisted Treatment	(((MH “Overdose”) OR (AB “Opioid Abuse*" OR "Opioid Misuse" OR "Opioid Addiction" OR "Prescription Drug Misuse" OR "Prescription Drug Overuse" OR "Opioid Use Disorder" OR "OUD" OR "Opioid-Use Disorder")) AND ((MH “Hospitals” OR “Inpatients” OR “Ambulatory Care Facilities” OR “Practitioner's Office” OR “Rehabilitation Centers” OR “Residential Facilities” OR "Substance Abuse Rehabilitation Programs" OR “Transitional Care” OR “Primary Health Care” OR "Emergency Service" OR "Ambulatory Care" OR "Patient Discharge") OR (AB “Ambulatory Care” OR “Specialty Care” OR “Hospital*” OR "Physicians' Office*" OR "Residential Facilit*" OR “Primary Care” OR "Transitional Care" OR "Rehabilitation Center*" OR "Primary Health Care" OR "Emergency Room" OR "Patient Discharge" OR "Emergency Department")) AND ((MH "Opiate Substitution Treatment") OR (AB "MAT" OR "Medication Assisted Treatment" OR "Medication-Assisted Treatment" OR "Medication-Assisted-Treatment" OR "Opiate Substitution Treatment" OR "Medication Assisted Treatment of Opioid"	(((MH “Opioid-Related Disorders” OR "Prescription Drug Overuse" OR "Prescription Drug Misuse") OR (AB “Opioid Abuse*" OR "Opioid Misuse" OR "Opioid Addiction" OR "Prescription Drug Misuse" OR "Prescription Drug Overuse" OR "Opioid Use Disorder" OR "OUD" OR "Opioid-Use Disorder")) AND ((MH “Hospitals” OR “Inpatients” OR “Ambulatory Care Facilities” OR “Practitioner's Office” OR “Rehabilitation Centers” OR “Residential Facilities” OR "Substance Abuse Rehabilitation Programs" OR “Transitional Care” OR “Primary Health Care” OR "Emergency Service" OR "Ambulatory Care" OR "Patient Discharge") OR (AB “Ambulatory Care” OR “Specialty Care” OR “Hospital*” OR "Physicians' Office*" OR "Residential Facilit*" OR “Primary Care” OR "Transitional Care" OR "Rehabilitation Center*" OR "Primary Health Care" OR "Emergency Room" OR "Patient Discharge" OR "Emergency Department")) AND ((MH "Opiate Substitution Treatment") OR (AB "MAT" OR "Medication Assisted Treatment" OR "Medication-Assisted Treatment" OR "Medication-Assisted-Treatment" OR "Opiate Substitution Treatment" OR

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Multicenter Study • Practice Guideline • Published Erratum • Randomized Controlled Trial • Review • Scientific Integrity Review • Technical Report • Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis • Practice Guidelines • Randomized Controlled Trial • Research Review		OR "Opiate Medication-Assisted Treatment" OR "Opiate Replacement Therapy" OR "Opioid Medication Assisted Treatment" OR "Opioid Replacement Therapy" OR "Opioid Substitution Therapy" OR "Opioid Substitution Treatment")))	"Medication Assisted Treatment of Opioid" OR "Opiate Medication-Assisted Treatment" OR "Opiate Replacement Therapy" OR "Opioid Medication Assisted Treatment" OR "Opioid Replacement Therapy" OR "Opioid Substitution Therapy" OR "Opioid Substitution Treatment")))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Systematic Review			

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