

## ***Technical Brief***

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# **Primary Care–Relevant Interventions to Prevent Opioid Use Disorder: Current Research and Evidence Gaps**

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# Key Informants

In designing the study questions and identifying evidence, the EPC consulted a panel of Key Informants who represent subject experts and end-users of research. Key Informant input informed key issues related to the topic. Key Informants were not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, the study questions, design, methodological approaches, and conclusions do not necessarily represent the views of individual Key Informants. Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end users, individuals with potential conflicts may be retained. AHRQ and the EPC work to balance, manage, or mitigate any conflicts of interest.

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# Chapter 1. Background

## Purpose

The misuse of and addiction to opioids—including prescription pain relievers and illicit opioids—is a serious national crisis that affects public health as well as social and economic well-being. Strategies to address the crisis include those focused on prevention and treatment of opioid misuse and use disorder, including education and counseling focused on primary prevention of opioid use, identifying and implementing effective pain management strategies, mitigating the risks associated with opioid use, accessing behavioral therapies and medications to treat opioid use disorder (OUD), and harm reduction strategies to minimize morbidity and mortality related to opioid use. While the U.S. Preventive Services Task Force (USPSTF) addresses both early detection and treatment of unhealthy drug use<sup>1</sup> as well as primary prevention of drug use among children, adolescents, and young adults<sup>2</sup> within its portfolio, questions remain about the evidence base surrounding other primary care–applicable OUD prevention strategies. The purpose of this report is to address two main objectives to inform the work of the USPSTF:

1. To describe the state of the evidence related to the primary prevention of OUD in persons not yet being prescribed opioids or using opioids.
2. To describe the efforts of other organizations relevant to the prevention of OUD in populations or settings that would be traditionally considered outside of the scope of the USPSTF (e.g., acute and chronic pain management).

## Definitions

Opioids are a class of natural (e.g., morphine), semisynthetic (e.g., heroin), and synthetic (e.g., fentanyl) drugs that act on one of the brain’s three main opioid receptor systems (mu, kappa, delta) and have analgesic, central nervous system depressant, and other effects.<sup>3</sup> The route of administration of opioids can be oral, sublingual, transdermal, or intravenous; nonmedical routes of administration also include intranasal or inhaled.

Problematic opioid use includes the *misuse of prescription opioids* or the *use of illicit opioids*. Misuse of prescription opioids refers to use of a prescription medication that is outside the manner and intent for which it was prescribed; this can include use without a prescription of one’s own; use in excess of the amounts, frequency, or duration than prescribed; use for effects other than analgesia (e.g., euphoria, as a sleep aid, to manage anxiety); diversion (sharing or selling medications to others); or use in any other way not directed by a doctor (e.g., concurrent use of alcohol or other recreational substances).<sup>4</sup> The terminology *nonmedical use of opioids* is no longer preferred, although it is still sometimes used synonymously with the misuse of prescribed opioids.<sup>4</sup> *Opioid use disorder* is defined in the Diagnostic and Statistical Manual, Fifth Edition (DSM-5) as a problematic pattern of opioid use leading to clinically significant impairment or distress. Prescription misuse is not a requisite step in the pathway to OUD, such that physiological dependence can (and does) occur in persons adherent to opioids as prescribed.

## Prevalence of Opioid Misuse and Opioid Use Disorder

In the United States, in 2018, 10.3 million persons age 12 years or older reported misusing opioids in the previous year, including 9.9 million people misusing prescription pain medications and 808,000 using heroin (**Figure 1**).<sup>5</sup> Misuse of prescription fentanyl products occurred in 0.1 percent of persons older than age 12 years; however, this estimate does not represent individuals who misused illicitly manufactured fentanyl. Dual use of prescription opioids and heroin occurred in 4.9 percent of individuals reporting opioid misuse. Rates of opioid misuse vary by age, with young adults ages 18 to 25 years having the highest rate.<sup>5</sup> While the overall rate of persons age 12 years or older who misused opioids in 2018 was lower than data from 2015 to 2017,<sup>5</sup> the proportion of individuals reporting dual use of heroin and prescription opioids has increased.<sup>6-8</sup> Prescription opioid misuse occurs more frequently among male patients and adults younger than age 40 years. In addition, previous or current substance misuse, history of mental health diagnoses, longer exposure to opioids, and being prescribed higher opioid doses have been associated with the development of misuse.<sup>9</sup>

In 2018, an estimated 2.0 million persons (0.7%) age 12 years or older in the United States had an OUD (**Table 1**), defined in the survey as those who met the DSM-IV criteria for either heroin dependence or abuse or prescription opioid dependence or abuse.<sup>5</sup> The incidence of developing OUD symptoms following an opioid prescription is not well known, with estimates ranging from 0.1 to 34 percent of patients depending on the methods of ascertainment (e.g., detailed evaluation vs. self-report questionnaires).<sup>10</sup>

## Opioid-Related Morbidity and Mortality

Opioid misuse and use disorder have many potential health consequences, including localized and systemic infections (e.g., cellulitis, endocarditis, HIV, hepatitis B and C), constipation hyperalgesia, accidents and injuries (e.g., motor vehicle collisions, falls/fractures), nonfatal overdose, and death (including but not limited to overdose).<sup>3,11</sup>

Drug overdose was reported to be among the leading causes of accidental death in the United States in 2018. In 2018 there were 46,802 opioid overdose deaths; 14,975 involved prescription opioids, including natural and semisynthetic opioids and methadone, 14,996 involved heroin, and 31,335 involved synthetic opioids (other than methadone).<sup>12</sup> From 2017 to 2018, opioid-involved death rates decreased 2.0 percent; including among females, persons ages 15 to 34 and 45 to 54, and non-Hispanic White persons. Rates increased during 2017 to 2018 among persons older than age 65 years, non-Hispanic Black persons, and Hispanic persons. Geographically, rates of overdose decreased in the Midwest and Southern regions while increasing in the Northeast and West.<sup>12</sup>

Although the steady increase in mortality rates for natural and semisynthetic opioids such as hydrocodone and oxycodone from 1999–2010 has begun to level off, the rapid increase in mortality rates associated with synthetic opioids like fentanyl has continued.<sup>13</sup> Rates of deaths involving synthetic opioids increased 10 percent from 2017 to 2018, likely driven by illicitly manufactured fentanyl.<sup>12</sup> Based on National Vital Statistic Systems data, in 2010, synthetic

opioids were involved in 14 percent of opioid-related deaths;<sup>14</sup> by 2017 this rate had increased to 45.2 percent.<sup>15</sup> During January to June 2018, in 25 states reporting opioid deaths, the most common category of opioid-involved deaths was from illicitly manufactured fentanyl (67.9%), followed by heroin (39.4%), prescription opioids (28.7%), and fentanyl analogs (20.0%). Of all opioid deaths, 62.6 percent co-occurred with at least one common nonopioid drug (including benzodiazepines, cocaine, and methamphetamine).<sup>16</sup>

Most opioid overdose deaths occur in persons ages 20 to 59 years. In addition, overdose deaths occur more frequently in men, White and American Indian/Alaska Native individuals, and individuals with indicators of low compared with high socioeconomic status (e.g., individuals who are disabled, widowed, unemployed, noncitizens, or have lower education levels).<sup>17</sup>

## **Epidemiology and Risk Factors for Opioid Use Disorder**

It is well understood that there is a strong genetic component to substance use disorders, and in most studies, family history of substance use disorder is the strongest risk factor after a personal history of substance use disorder.<sup>18, 19</sup>

While the prevalence of OUD varies by age, sex, race/ethnicity, income level, geographic area, and medical or mental health comorbidities, it is still unknown which of these factors are indeed causal (i.e., true risk factors) vs. risk markers. In addition, groups with a higher prevalence of OUD than the general population may vary somewhat depending on the opioid being used (e.g., heroin, prescription opioids, co-use of heroin and prescription opioids).<sup>6, 7, 20</sup>

## **Interventions to Prevent Opioid Use Disorder**

Interventions to prevent morbidity and mortality from OUD can target different populations. First, preventive intervention efforts may focus on persons not currently using opioids (including persons requiring pain management); its aim is to encourage avoidance or minimization of exposure to prescribed opioids (e.g., unnecessary short-term use, ineffective or unsafe long-term use) and avoidance of the nonmedical use of opioids altogether. These interventions can include public-, patient-, and clinician-focused education about opioids, education, and behavioral interventions to prevent illicit substance use and the initiation of unnecessary or ineffective prescription opioids, including optimization of nonpharmacologic and nonopioid pharmacologic treatment options for the management of acute and chronic pain. Second, preventive intervention efforts can focus on persons currently using opioids who do not have an identified OUD; these interventions can include the early detection of problematic opioid use or OUD (e.g., screening, monitoring practices in persons being prescribed opioids), management of problem use or screen-detected (e.g., mild to moderate) OUD (e.g., interventions to reduce or discontinue prescription opioids, brief interventions, drug treatment including behavioral therapy and medication assisted treatment), and judicious prescribing (risk mitigation in initiating, adjusting, monitoring, and tapering) in persons getting opioids for pain management. Third, preventive intervention efforts can focus on persons with established OUD and are aimed at the treatment of OUD (e.g., behavioral therapy, medication assisted treatment), preventing overdose or fatal

overdose (e.g., naloxone co-prescribing), and preventing other health consequences from OUD (e.g., needle exchanges). In this report, we focused on prevention efforts aimed at persons not currently using opioids as well as those who may use opioids but do not have an identified OUD and those who were considered applicable to primary care practice.

## National Response to the Opioid Crisis

On July 22, 2016, President Obama signed the Comprehensive Addiction and Recovery Act (CARA) into law, authorizing more than \$181 million to respond to the epidemic of opioid abuse,<sup>21</sup> and in October 2017 the Department of Health and Human Services (HHS) officially declared a national opioid emergency.<sup>22</sup> Over the past 5 years, numerous efforts have been undertaken by the federal government to coordinate activities related to addressing the opioid epidemic, deploying resources, and developing guidance for public health officials and care providers. Some major national efforts have included:

- HHS/Department of Defense (DOD)/Veterans Administration (VA) Pain Management Best Practices Inter-Agency Task Force: Proposes updates to best practices and issues recommendations that address gaps or inconsistencies for managing chronic and acute pain.<sup>23</sup>
- HHS five-point Opioid Strategy: Leverages HHS resources to address the following aims: improving access to prevention, treatment, and recovery services; improving availability of overdose reversing drugs; strengthening public health report data; increasing understanding of pain and addiction; and increasing evidence-based pain management practices.<sup>24</sup>
- National Institutes of Health (NIH) Helping to End Addiction Long-term (HEAL) initiative: Transagency effort to speed research related to the opioid crisis, including research on understanding, managing, and treating pain and improving treatment for opioid misuse and addiction. Hundreds of research projects have been funded that reflect the full spectrum of research from basic science to implementation research.<sup>25</sup>
- Food and Drug Administration (FDA): Includes comprehensive portfolio review;<sup>26</sup> risk evaluation and mitigation strategies (REMS);<sup>27, 28</sup> and plans to revise postmarketing requirements.<sup>26</sup>
- Health Resources and Services Administration: \$200 million funding to health centers and rural health organizations in every U.S. state and territory targeted to focus on the treatment, prevention, and awareness of opioid addiction.<sup>29</sup>
- National Academy of Medicine Action Collaborative on Countering the U.S. Opioid Epidemic: Includes more than 100 organizations across the United States working around four core priority areas: Health Professional Education and Training; Pain Management Guidelines and Evidence Standards; Prevention, Treatment, and Recovery Services; and Research, Data, and Metrics Needs.<sup>30</sup>

## Chapter 2. Methods Approach

This report integrates information obtained from searches of the published and grey literature with discussions with Key Informants related to four Guiding Questions (GQs). The findings related to each GQ are not presented in the order in which they are listed below given different foci. Information related to GQ1 was presented in the background section. Results for GQ2 and GQ4 are combined within the section titled “Interventions to Prevent Opioid Use Disorder” and are organized by intervention type; information regarding GQ1a (risk assessment tools) is also incorporated into this section. Information related to GQ3 (pain management guidance) is presented in a separate section titled “Guidance on Pain Management, Including Opioid Prescribing.”

### Guiding Questions

1. What are the main risk factors, including any social determinants, for developing an OUD and/or morbidity and mortality from opioid use?
  - a. What risk assessment tools are available to identify persons at high risk for prescription misuse or OUD?
2. What primary care–relevant interventions to prevent OUD have been studied?
  - a. What types of study designs and outcomes (both benefits and harms) have been used to evaluate these interventions?
  - b. What key evidence or knowledge gaps to prevent OUD in primary care exist?
3. What primary care–relevant evidence-based efforts on acute and chronic pain management exist or are currently underway?
  - a. What organizations have provided evidence-based guidelines around acute and chronic pain management and opioid prescribing, and what are their recommendations?
  - b. What are potential harms or unintended consequences related to implementation of pain management or opioid prescribing guidelines?
  - c. What critical areas in existing or ongoing guidance on acute and chronic pain management are not yet addressed, and what are the research needs to inform evidence-based opioid prescribing for the management of acute or chronic pain management?
4. What systems- or practice-level interventions to help implement prescribing practices or mitigation strategies around opioid prescribing have been studied?
  - a. What types of study designs and outcomes have been used to evaluate these interventions?

### Literature Searches

For GQs 1, 2, and 4, we conducted a systematic search of English-language literature published in the past decade (from 2009 to February 18, 2019). We worked with a research librarian to develop our search strategy and searched MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR), and PsycInfo. Additionally, we manually searched the websites of several federal and other national

funding organizations (e.g., Agency for Healthcare Research and Quality, NIH RePORTER, National Institute on Drug Abuse) as well as [clinicaltrials.gov](http://clinicaltrials.gov) to identify major ongoing studies specifically related to interventions to prevent OUD. Key Informants also suggested potential sources of information.

We conducted targeted searches of the websites of USPSTF partners, federal agencies, and professional societies in addition to discussions with Key Informants to identify current and ongoing evidence-based efforts and guidelines on acute and chronic pain management (GQ3).

## **Inclusion Criteria**

For GQ2 (primary care–relevant interventions to prevent OUD), we focused on studies of single- or multi-component interventions to prevent prescription misuse and OUD that were targeted to individual patients or clinicians. Such interventions included education and behavioral-based interventions focused on prevention of any illicit drug use or prescription drug misuse, reduction in opioid use, and safe storage and disposal practices. For GQ4 (systems- or practice-level interventions to help implement prescribing practices), we concentrated on research of strategies facilitating implementation of clinical prescribing guidelines or pain management protocols. For both GQ2 and GQ4, we included studies with any study designs reporting any outcome. We limited our scope to studies that included primary care–applicable interventions, including those taking place in primary care, emergency departments, surgical settings, hospitals, and healthcare systems. We did not include studies analyzing state- or national-level policies, implementation of Prescription Drug Monitoring Programs (PDMPs), preemptive prescribing of naloxone or naloxone distribution practices, other harm reduction strategies, or treatment of OUD. We did not include any studies recruiting patients with an established OUD but we did include studies among patients on chronic long-term opioid therapy.

The GQ3 scan was limited to identifying general pain management guidelines and did not review condition-specific treatment guidelines that may include aspects of pain management (e.g., sickle cell anemia).

## **Discussions With Key Informants**

We conducted semi-structured telephone interviews with five Key Informants to obtain additional insight on efforts related to guidance on acute and chronic pain management and interventions to prevent OUD. These Key Informants included representatives from the Centers for Disease Control and Prevention (CDC); National Academies of Sciences, Engineering, and Medicine (NASEM); and the Agency for Healthcare Research and Quality. Insight and information provided by the Key Informants was integrated with the evidence from the published and grey literature and incorporated throughout the report.

## Chapter 3. Findings

### Interventions to Prevent Opioid Use Disorder

Healthcare interventions to prevent the development of an OUD or to prevent morbidity and mortality from an OUD include efforts aimed at the avoidance of both illicit and prescription opioid use, early detection of problematic use or an OUD, management of problem use or risk mitigation strategies, treatment of OUD with behavioral therapy or medications, and harm reduction interventions. Such interventions can be delivered directly with patients or include provider education or systems-level policies and practices to facilitate such interventions.

Within this report, we focused on patient-, provider-, and systems-level interventions that addressed primary and secondary OUD prevention interventions that were applicable to primary care–delivered preventive services. We did not include evidence on broader strategies such as state-level policies (including the use of PDMPs), the use of abuse-deterrent formulations, insurance strategies, public safety and public health collaborations, or on harm reduction strategies. Furthermore, we did not review the evidence landscape on interventions to address social and environmental determinants that are known risk factors for the development of OUDs (e.g., providing access to education, sustainable work opportunities). Readers interested in the evidence on these strategies are directed to other systematic and narrative reviews, including recent reviews by Volkow (2018)<sup>31</sup> and Haegerich (2019).<sup>32</sup> Finally, a number of studies have evaluated interventions to optimize pain treatment, including opioid safety;<sup>33-35</sup> however, information on the effectiveness of pain management strategies and programs are outside the scope of this report.

#### Patient Education

Patient education interventions focus on individual-level strategies geared at preventing drug use initiation (universal prevention aimed at reducing the initiation of illicit opioids or exposure to diverted prescription opioids) and preventing misuse of prescribed opioid analgesics.

#### Universal Prevention Interventions

Early primary prevention strategies aim to prevent drug use among children, adolescents, and young adults before they ever try drugs (in the abstinence phase) or at the sporadic or limited use stages. General preventive counseling may be offered broadly to all young persons without knowing their history of drug use or may be delivered after establishing that they do not regularly use drugs. The USPSTF has a separate review<sup>36</sup> and recommendation<sup>37</sup> that address primary care–relevant interventions to prevent drug use in children, adolescents, and young adults. Consistent with the 2014 recommendation, in the 2020 recommendation, the USPSTF concluded that the current evidence was insufficient to assess the balance of benefits and harms of primary care–based behavioral counseling interventions to prevent or reduce illicit drug use, including nonmedical use of prescription drugs, in children, adolescents, and young adults.<sup>2</sup> Of the 29 included trials in that review, most interventions addressed general drug use prevention—

none of the included studies focused specifically on the avoidance of illicit opioids or misuse of prescription opioids.<sup>38</sup>

In addition to the studies identified in the review noted above, we identified one randomized clinical trial that evaluated a web-based program designed to prevent prescription drug misuse—including opioid analgesics—among women who work within a hospital setting (n=346).<sup>39</sup> Women randomized to the intervention group reported significantly higher self-efficacy related to medication adherence and managing medication problems and lower drug-related problem scores (CAGE score) at 4 weeks compared with a waitlist control group. However, no differences between groups were found on self-reported nonmedical use of any class of drug.<sup>39</sup> Given the specific population reported in this study (female hospital workers) it is unclear how these findings would translate to a more general adult population.<sup>39</sup>

### **Education on Safe Use, Storage, and Disposal of Opioids**

Another intervention strategy that could potentially prevent opioid misuse or the development of an OUD is patient education regarding the safe use of opioids and hazards of prescription opioid misuse, pain expectations, and ways to safely store and dispose of opioid analgesics. These interventions could occur among those patients prior to their receipt of an opioid prescription or among those with an existing prescription for an opioid. Several recent studies have evaluated the effectiveness of these types of interventions; however, the evidence base has numerous limitations that point to the need for further research in this area. In addition, it is unclear how this evidence base would apply to preventive services provided in primary care given the settings, populations, study designs, and outcomes employed in existing studies.

**Table 2** provides a summary of 13 studies published from 2009 to 2019 that we identified that evaluated a patient education intervention.<sup>40-52</sup> Of note, none of the studies took place in a primary care setting. All but one study were among preoperative or postoperative surgery patients or patients receiving an opioid analgesic prescription from an emergency department. One study was among patients receiving an opioid prescription from a dental clinic or pain or palliative care clinic. Very few studies limited inclusion to patients who were opioid naïve or those not currently using opioids. One study targeted patients undergoing surgery who were at high risk of persistent opioid use (a construct different than misuse or use disorder). Most of the patient education interventions consisted of short, printed handouts (e.g., one-page sheet, pamphlet) with or without verbal instructions or counseling to accompany the written advice. The content of most of the interventions included information on the indications and recommended dose, schedule, and indication for prescribed opioids and expectations for pain following their procedure or condition as well as opioid weaning, with or without also discussing safe storage and disposal practices. A few studies only focused on education around safe disposal methods or programs.

Within this evidence base, there is a lack of reporting on distal health outcomes such as measures of opioid misuse or the development of an OUD. Only two studies reported measures of opioid misuse or opioid-related problems.<sup>46, 47</sup> In one trial (n=200), patients in the intervention group were statistically significantly less likely to report driving in a car within 6 hours of taking an opioid compared with those in the control group; however, no differences were reported in safe

alcohol use while taking an opioid.<sup>46</sup> In the other small study of an interactive, web-based intervention (n=62), reductions in self-reported behavior change were observed from pre- to post-intervention.<sup>48</sup> At 1-month followup, patients were significantly less likely to report lending or borrowing opioids from others; taking more pills than prescribed; and saving unused pills. No other study reported measures of opioid-related problems or misuse (including an OUD) or other health outcomes.

In most cases, the primary outcome measure was patient-reported opioid use or disposal practices. In general, it appears that these interventions have the potential to decrease the amount of prescribed opioids without the unintended consequence of increasing patient pain (in those studies that reported pain as an outcome). The results were mixed, however, with regards to increasing proper disposal of unused pills, preventing opioid misuse, and preventing diversion.

## Screening for Unhealthy Drug Use

Screening for drug use in primary care can help to identify unhealthy drug use that requires intervention. The USPSTF has a separate review<sup>53</sup> and recommendation<sup>54</sup> on screening for drug use in primary care. An updated review concluded that several screening instruments with acceptable sensitivity and specificity could identify adults with problematic drug use, and that there was no direct evidence on the benefits and harms of screening for drug use.<sup>55</sup> Most included studies evaluated the accuracy of tools to detect *any* problematic drug use and did not focus on specific substances such as heroin or prescription opioids. In those studies that did report data related to opioid use, the sensitivity and specificity to detect unhealthy use or a use disorder of *heroin* was similar (>0.75 sensitivity and 1.00 specificity) to that seen for other specific drugs. The sensitivity estimates (<0.70) were generally lower and less precise for the detection of *prescription medication* problem use and disorders than for other classes of drugs, which may result from confusion about what constitutes nonmedical use.

## Provider Education

Educational interventions targeting providers may be an effective way to reduce the initiation, amount, or duration of patient opioid analgesic use; facilitate provider adherence to pain management- and opioid-related guidelines; and improve provider communication skills regarding pain management. Such interventions can include medical education, such as continuing medical education funded through the FDA REMS,<sup>56</sup> academic detailing, resident training, and general education. In recent years, several provider education interventions have been evaluated for their impact on providers' knowledge, confidence, and self-reported practice regarding opioid prescribing. Many of the tested interventions appear to be applicable to primary care settings and may provide insight on promising training strategies to improve pain care and reduce risks associated with opioid use.

**Table 3** provides a summary of 25 studies that we identified that evaluated a provider opioid education intervention.<sup>57-81</sup> Most of the research in this area examined providers' knowledge and efficacy related to opioid prescribing and self-reported prescribing behaviors before and immediately following educational training using pre-post study designs. Very few studies

employed randomized designs or included measures of opioid use, misuse, or patient-reported pain. The evidence targeted primary care providers in a variety of settings, including community-based health centers, federally qualified health centers, and Veteran’s Health Administration facilities or included statewide physician outreach or training of early career primary care providers. A few studies specifically targeted internal medicine or surgery residents and one study enrolled medical school faculty. Three studies targeted providers considered “high” opioid prescribers<sup>67</sup> or those who were mandated or referred by their state medical board, hospital board, or other authority due to opioid prescribing concerns.<sup>64, 73</sup>

The structure and content of the provider education programs was extremely varied and included very brief (5- to 20-minute) educational sessions, more lengthy didactic or interactive training (1 hour to 3 days) provided in person or online, and more intense weekly or biweekly virtual case-based educational sessions. Most of these more intense interventions are similar continuing medical education programs—some developed with REMS funding—including programs such as *SCOPE of Pain*,<sup>58</sup> *Project ECHO*,<sup>59</sup> and *SCAN-ECHO Pain Management*.<sup>60, 68</sup>

None of the studies reported on distal patient health outcomes or intermediate outcomes such as prolonged opioid use, opioid misuse or aberrant behaviors, or other health outcomes. Furthermore, only two studies reported the impact of provider education on patients’ self-reported pain.<sup>63, 69</sup> Two studies reported a decrease in opioid prescription–related deaths occurring in the state at the same time as the provider education intervention, although several other statewide efforts aimed at decreasing opioid-related deaths were implemented at the same time and could be responsible for these improvements.<sup>62, 74</sup>

The primary outcomes reported in most studies were measures of physician opioid-related knowledge, adherence to opioid prescribing guidelines, or changes in opioid prescribing practices. There was mixed evidence of the effects of interventions on providers’ self-reported or objectively measured adherence to opioid-related guidance and protocols, such as using formal risk assessment tools, using opioid agreements, using their state PDMPs, or using urine drug tests. Similarly, while some studies reported that provider education interventions were associated with decreases in rates of opioid prescriptions or lower doses per prescription, just as many studies found no differences in opioid prescriptions following the intervention. All studies that measured provider-reported knowledge, confidence, or intentions regarding safe opioid use and pain management reported significant improvements following the intervention; however, it is unclear to what extent these increases in knowledge affect patient care and health outcomes.

## **Risk Assessment**

Multiple risk assessment tools have been developed to help identify patients who may be at higher risk of substance abuse, misuse, or addiction. These tools may be applied prior to opioid prescribing and as regular reassessment of risk during long-term opioid use. The CDC indicated there is insufficient evidence to determine the utility of opioid risk screening tools and that evidence suggests it is very difficult for clinicians to predict whether benefits of opioids for chronic pain will outweigh risks of ongoing treatment for individual patients.<sup>82</sup> Other guidelines have indicated using a “risk stratified” approach when determining the benefits and harms of opioid prescribing.<sup>83, 84</sup>

Multiple tools (e.g., Screener and Opioid Assessment for Patients with Pain-Revised [SOAPP-R], Opioid Risk Tool [ORT]) have been developed to **predict opioid overdose, addiction, abuse, and misuse in patients being considered for opioid therapy**. These tools have demonstrated inconsistent estimates of test accuracy, and no studies have addressed the effectiveness of the use of risk prediction tools on OUD, abuse, misuse, or overdose.<sup>85</sup> Beyond patient- or provider-completed questionnaires, the use of natural language processing and machine learning may offer future automated opportunities for identifying patients at higher risk of developing an OUD.<sup>86-88</sup>

Risk assessment tools may also be used to **detect misuse among current opioid users**. A 2017 systematic review identified that the Current Opioid Misuse Measure (COMM) had the best performance for screening for current misuse.<sup>89</sup> The COMM is a 17-item questionnaire; therefore, some researchers have worked on developing briefer versions of the COMM,<sup>90</sup> or creating newer tools such as the 5-item Opioid Compliance Checklist (OCC),<sup>91</sup> which may offer simpler screening opportunities. Additional automated systems such as algorithms applied to prescription data,<sup>92</sup> predictive modeling of electronic health record data,<sup>93</sup> and natural language processing<sup>94-96</sup> have emerged as potential tools for the detection of current opioid misuse or drug aberrant behavior within large volumes of patient records.

Models have also been developed to predict the **risk of respiratory depression or overdose** among individuals prescribed opioids, although none are well validated. Detection of these individuals at high risk of overdose may help direct the coprescribing of naloxone or other risk mitigation methods (e.g., proactive monitoring). These models utilize data from within state PDMP programs,<sup>97</sup> administrative records,<sup>98-100</sup> and electronic health records.<sup>101, 102</sup>

## **Multilevel Interventions and Implementation of Opioid Prescribing Guidelines or Pain Management–Related Protocols**

The majority of evidence we identified were studies that evaluated the implementation and dissemination of clinical prescribing guidelines and pain management protocols (**Table 4**). Most of the interventions were multilevel quality improvement efforts that included system- or practice-wide changes and strategies to communicate with or train providers. All but two of these studies took place in the United States. The strategies and settings examined in these studies make the evidence highly applicable to a variety of healthcare settings within the United States, although few were specifically implemented in primary care settings.

The most studied strategy was implementation of a comprehensive directive or protocol related to pain management and opioid prescribing. The protocols addressed topics covered in national guidelines such as standardized documentation of patients' pain history and treatment plan, the use of PDMPs, specific protocols for opioid prescribing (including types of opioids, dosage, reductions, and discontinuation), referral to pain clinics, risk assessment, routine urine screening, and patient-provider agreements. Many of the interventions were facilitated through changes to the electronic medical records and clinician support tools. A few studies focused on the effectiveness of procedure- or condition-specific opioid prescribing protocols—including changes to the default number or dose of opioids listed in the electronic health record's physician order entry—in surgical centers or emergency departments. In most cases, the interventions were

designed to address patients receiving chronic opioid therapy. Some studies addressed acute pain needs, but none addressed protocols or policies specifically for those whom were opioid naïve.

Given the focus on quality improvement, the outcomes reported in this body of evidence largely focus on process improvement and compliance with the recommended protocol strategies. Outcome measures included number of urine drug screens ordered, number of signed opioid treatment agreements, documentation of chronic pain on the problem list, documentation of pain-related functional status, documentation of opioid risk assessments, referral to behavioral health providers, and provider satisfaction with the intervention. The evidence overwhelmingly showed that implementation of multilevel and system-level interventions can improve several of these quality improvement measures. It was less clear how they affect opioid prescribing—with some studies reporting beneficial decreases and others reporting no effect. Furthermore, this body of evidence is lacking data on patient health outcomes, including patient safety, aberrant behavior, and opioid misuse and abuse.

## **Guidance on Pain Management Including Opioid Prescribing**

In response to the growing opioid crisis in the United States, many professional societies, federal agencies, state and local governments, and healthcare organizations have issued guidelines related to pain management including opioid prescribing. In general, guidelines agree regarding recommended strategies for prevention and/or early identification of opioid prescription misuse, diversion, and OUD, including use of PDMPs, risk assessment prior to prescribing, regular assessment of risk during long-term opioid use, use of low-dose opioids, and patient-provider agreements. For a broader overview of existing guidance addressing acute pain management (including condition-specific management), readers may be directed to a 2019 NASEM report.<sup>147</sup>

The most impactful of these guidelines has been the 2016 CDC evidence-based guidelines for prescribing opioids in the management of chronic pain.<sup>148</sup> The CDC guideline included 12 recommendations addressing when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, followup, and discontinuation; and assessing risk and addressing harms of opioid use.<sup>148</sup>

The CDC guideline used evidence from an Effective Health Care Program review on the effectiveness, comparative effectiveness, and harms of opioid therapy; dosing strategies; and risk assessment and risk mitigation for patients with chronic pain.<sup>149</sup> Updated and supplemental reviews were conducted to address the effect of opioid therapy for acute pain on long-term opioid use, the effectiveness of nonpharmacologic and nonopioid pharmacologic treatments, clinician and patient values and preferences, and resource allocation.<sup>150, 151</sup> Based on these reviews, the CDC drafted the recommendations using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework and then conducted a multistep review process to obtain input from experts, stakeholders, and the public to help refine the recommendations.

Following the publication of the 2016 CDC guideline, there was widespread uptake of the recommendations by policy makers, including several state legislatures and Medicaid agencies.

However, in many cases the implementation of the guideline was inconsistent or beyond the scope of the original recommendations, as noted in a 2019 consensus panel report<sup>152</sup> as well as a perspective piece from the guideline authors.<sup>153</sup> Specifically, these groups noted misapplication surrounding hard limits related to recommended ceiling dosages or durations, abrupt tapering or cessation of patients on high doses, and application of the guidelines to populations outside the scope of the guidelines (e.g., cancer-related pain, acute sickle cell crisis). The CDC has stated that it is continuing to evaluate the impact of the guidance (including its unintended consequences) and is committed to updating the recommendations when new evidence becomes available.<sup>153</sup>

At a December 2019 meeting of the CDC's National Center for Injury Prevention and Control Board of Scientific Counselors, the CDC outlined considerations for updating the 2016 guidelines.<sup>154</sup> To identify whether evidence gaps are sufficiently addressed to warrant updates to expansion of the guideline, the CDC funded the Agency for Healthcare Research and Quality to conduct five systematic reviews on the effectiveness of opioid, nonopioid pharmacologic, and nonpharmacologic treatments for acute and chronic pain.<sup>85, 155-158</sup> The CDC stated that these new systematic reviews may allow updates to and/or expansion of the guideline, potentially including the following:

- Additional detail on nonpharmacologic and nonopioid pharmacologic therapies for chronic pain.
- Updated information on benefits and risks of nonpharmacologic, nonopioid pharmacologic, and opioid therapies for chronic pain.
- Expanded guidance on acute pain.
- Expanded guidance on opioid tapering.

In June 2020, the CDC sought comments from patients, patient family members/caregivers, and healthcare providers on the following topics: experiences managing pain, which might include the benefits, risks, and/or harms of pain management options; experiences choosing among the pain management options, including considering factors such as each option's accessibility, cost, benefits, and/or risks; and experiences getting information needed to make pain management decisions.<sup>159</sup> It is estimated that (if warranted by the available evidence) an update to the guideline would likely be available in 2022, with public comments solicited.<sup>160</sup>

In addition to the CDC, many other federal agencies and national professional societies have issued similar guidance. In 2017, the DoD/VA issued similar guidelines addressing the use of opioid therapy for chronic pain.<sup>161</sup> They noted that the guidance had substantial overlap with that of the CDC, with additional items particularly relevant to the VA populations. These additions include avoidance of long-term opioid therapy in patients younger than age 30 years due to risk of abuse/overdose, stronger language around avoiding concurrent benzodiazepine use, focus on suicide prevention, short-term reassessment for acute pain, and reassessment for treatment beyond 90 days. Additional chronic or acute pain management guidelines have been issued by the American Academy of Emergency Medicine,<sup>84</sup> American College of Obstetricians and Gynecologists,<sup>162</sup> American Society of Intervention Pain Physicians,<sup>83</sup> and the Canadian National Opioid Use Guideline Group.<sup>163</sup>

In December 2019 an ad hoc committee of the NASEM released a report commissioned by the FDA outlining a “framework to evaluate existing clinical practice guidelines for prescribing opioids for acute pain indications, recommend indications for which new evidence-based guidelines should be developed, and recommend a future research agenda to inform and enable specialty organizations to develop and disseminate evidence-based clinical practice guidelines for prescribing opioids to treat acute pain indications.”<sup>147</sup> The priority surgical procedures and medical conditions identified by the NASEM committee that would benefit from guidelines for opioid prescribing included cesarean delivery, total knee replacement, wisdom teeth removal, low back pain, sickle cell disease, migraines, and kidney stones. These conditions were selected based on their prevalence or frequency and the evidence for variation in current opioid prescribing practices.

The primary areas recommended by the NASEM report for future research include:

- Addressing the effect of nonopioid interventions for acute pain.
- Outcomes related to opioid prescribing in key populations (e.g., the elderly, persons with comorbidities).
- Impact of clinical setting on opioid prescribing strategies.
- Links between intermediate outcomes (e.g., number of unused pills, long-term opioid use) and health outcomes (e.g., pain, overdose, OUD).

## Chapter 4. Summary and Implications

The USPSTF has two topics in its portfolio related to preventing opioid misuse and OUD: one focused on [screening for unhealthy drug use among adolescents and adults](#) and another focused on [interventions to prevent drug use in children, adolescents, and young adults](#). Systematic reviews for both topics have recently been updated and each have recommendation statements posted. This project was conducted to describe the state of the evidence related to other interventions for the primary prevention of OUD and to describe what primary care–relevant evidence-based efforts are underway related to acute and chronic pain management.

We scanned the published and grey literature and conducted key informant interviews to better understand the scope of the evidence related to primary prevention of OUD and other national efforts in this area. We cast a wide net when describing evidence that might be applicable to primary care—including not only studies that took place in primary care settings or with primary care providers but also research in other healthcare settings and systems-level interventions. While the original intent was to focus on interventions that were truly on *primary* prevention—that is, focused on patients who were opioid naïve—all the evidence we identified was related to universal interventions (i.e., applied to unselected populations) or were interventions and policies for persons on long-term or chronic opioid therapy. Furthermore, beyond the evidence contained in the two current USPSTF reviews, all the evidence we found was specific to preventing risks from prescribed opioid analgesics. While some interventions focused on efforts to reduce diversion of prescription opioids (e.g., safe storage), none of the interventions focused on those who used diverted prescription opioids (a target that may be nearly impossible to focus on in research given that diversion is illegal). In addition, we did not identify any primary care–applicable studies that focused on preventing use of illicit opioids such as heroin or fentanyl.

A number of strategies have been evaluated to reduce the prescribed dosage, initiation, or duration of prescription opioid use and mitigate the risks related to opioid analgesic use. While the evidence is robust in volume, the rigor of the study designs used and the types of outcomes reported make it difficult to draw conclusions regarding the true impact that such interventions may have on important patient health outcomes. Almost all studies that reported changes in patient- or provider-reported knowledge, confidence, or intentions regarding safe opioid use reported significant improvements following the interventions. And, although some studies also reported significant reductions in self-reported opioid use or documented prescriptions, it is unclear to what extent these increases in knowledge or opioid use ultimately affects patient care and health outcomes. Importantly, we are lacking data on patient safety, aberrant behavior, opioid misuse and abuse, and key patient-reported outcomes such as functional status and quality of life. Given the study designs used in most of this evidence, other simultaneous interventions and legislation or policy mandates may have also contributed to these findings, and most evidence was based on patients’ or providers’ self-reports before and after the intervention and may be prone to reporting bias or confounding.

When introducing interventions that may deter prescribing opioids or in risk mitigation strategies that are perceived as threatening to patients (e.g., routine urine drug screens), there are potential unintended consequences (e.g., patients seeking drugs from other sources, doctor “shopping”).

The impact of these interventions on unintended consequences (apart from pain scores) was not reported.

In response to the growing opioid crisis, many professional societies, federal agencies, state and local governments, and healthcare organizations have issued guidelines related to pain management, including opioid prescribing. In general, these guidelines are consistent in their recommendations, including use of PDMPs, risk assessment prior to prescribing, regular assessment of risk during long-term opioid use, use of low-dose opioids, and patient-provider agreements. The most impactful of these guidelines has been the 2016 CDC evidence-based guidelines for prescribing opioids in the management of chronic pain.<sup>148</sup> An update to this guideline will likely be available in 2022.<sup>160</sup>

## **Evidence Gaps on Interventions to Prevent Opioid Use Disorder**

There are several areas for which more research is warranted to help fully understand the potential benefits and harms of primary care applicable interventions to prevent opioid misuse and opioid misuse disorder, including:

### **Risk Assessment:**

- Large observational studies examining the risk and protective factors associated with opioid misuse and OUD—for opioid use in general and by specific type of opioid.
- External validation studies of existing tools used to assess risk for opioid misuse in patients being considered for opioid therapy or for those who have initiated opioid therapy and transitioned to long-term therapy (alone and in conjunction with other risk mitigation strategies).

### **Intervention Effectiveness:**

- For the intervention effectiveness gaps below, application of more robust study designs to examine the impact of opioid misuse prevention interventions, including randomized clinical trials, prospective cohort studies, and time series analyses, and including longer-term followup and inclusion of patient-centered outcomes, including intermediate health outcomes such as measures of aberrant behaviors, and opioid misuse and distal health outcomes such as prevalence or incidence of OUD, pain, comorbid conditions, functional status, and quality of life:
  - Evaluation of patient-level education on the use (or safe use) of opioids (both illicit and medical/nonmedical use), pain expectations, and safe storage and disposal in primary care settings.
  - Comparative evaluation of clinical support tools and interventions to facilitate better communication between clinicians and patients about the risks and benefits of opioid therapy for acute and chronic pain.
  - Identification of which strategies are most effective at addressing prescription compared with illicit opioid misuse, acknowledging overlap in usage patterns.

- Replication of primary care–applicable interventions using these more rigorous designs, longer followup, and including important patient-centered outcomes.

## **Harms**

- Investigation of the potential unintended consequences of these interventions.

While we note these research needs, we also acknowledge the challenges associated with conducting these studies, including ethical issues (e.g., identifying and enrolling high-risk patients), difficulties establishing large samples given the low prevalence of opioid misuse identified in primary care settings, difficulties maintaining retention for longer-term followup, and challenges in identifying opioid misuse and diagnosing OUD, among others.

## **Ongoing Research**

There are several ongoing federally-supported research projects underway that may meet some of the evidence gaps noted above (**Table 5**). Consistent with the evidence summarized in this report, most of the ongoing research appears to focus on the misuse of prescription opioids, rather than on prevention or risk reduction related to illicit opioid use.

## **Conclusion**

Curtailling the opioid epidemic is a national priority and requires a multifaceted approach to address it. Primary care providers are among those at the front line in helping to prevent the misuse of prescribed opioids and use of illicit opioids, mitigate risks associated with opioid use, and identify opioid use that requires further assessment and treatment. Many interventions have been designed and tested in attempt to reduce prescribed opioid use. In general, these interventions have been shown to improve patients' and providers' knowledge and confidence regarding safe opioid use and to improve several process improvement outcomes across a variety of healthcare settings. The level of evidence, however, is generally low across all types of interventions and is limited by research designs at high risk of bias and a lack of reporting of important patient-centered outcomes.

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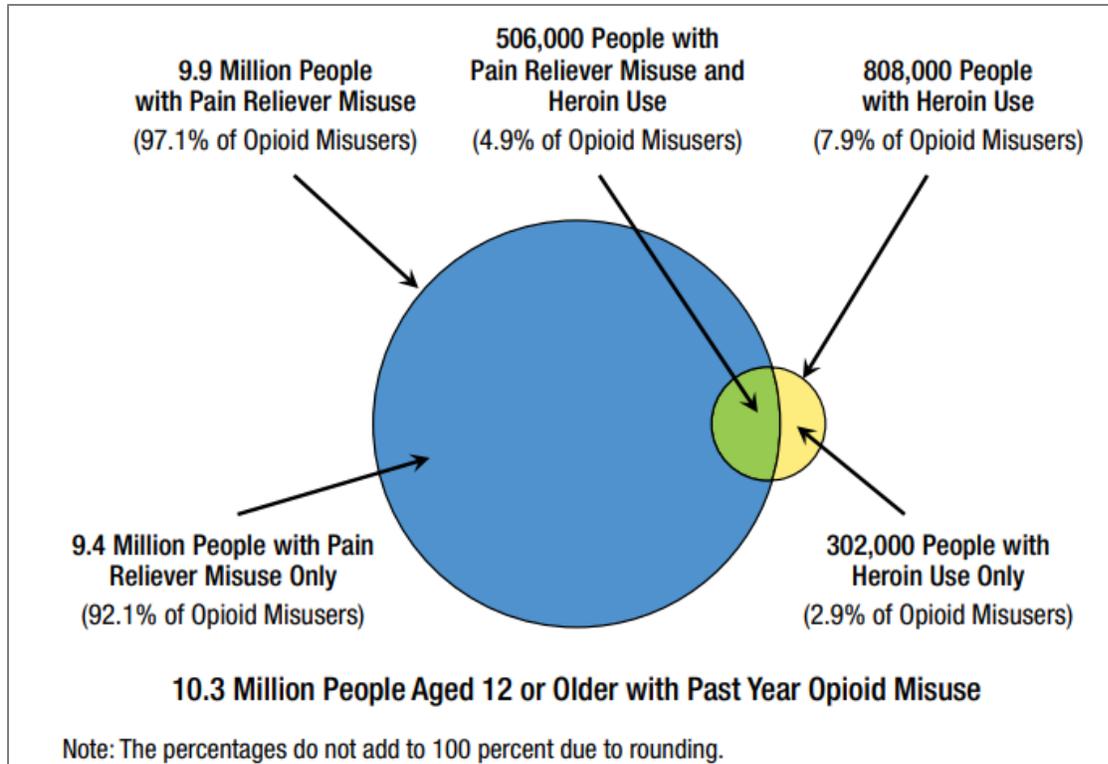
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**Figure 1. Past Year Opioid Misuse Among Persons Age 12 Years or Older: 2018<sup>5</sup>**



<sup>5</sup> Figure sourced from the Substance Abuse and Mental Health Services Administration report “Key Substance Use and Mental Health Indicators in the United States: Results From the 2018 National Survey on Drug Use and Health.”<sup>5</sup>

**Table 1. Past-Year Percentage of Opioid Misuse and Opioid Use Disorder, by Type of Opioid Used and Age, 2018 National Survey on Drug Use and Health (Rates for 2018)<sup>5</sup>**

Type of opioid used	Percentage			
	All (12 years or older)	Adolescents (12–17 years)	Young adults (18–25 years)	Adults (26 years or older)
Any opioid misuse	3.7	2.8	5.6	3.6
Opioid use disorder	0.7	0.4	0.9	0.7
Pain reliever misuse	3.6	2.8	5.5	3.4
Pain reliever use disorder	0.6	0.4	0.7	0.6
Heroin use	0.3	0.0	0.5	0.3
Heroin use disorder	0.2	0.0	0.3	0.2

**Table 2. Studies on Patient-Level Opioid Misuse Prevention Education Interventions**

Author, Year	Study Design	Setting	Population	Intervention	Intervention focus		Outcome measures				
					Safe opioid use and pain management	Safe storage and disposal	Opioid misuse	Opioid use	Pain	Opioid-related knowledge	Safe disposal or storage
Alter, 2017 <sup>40</sup> US	RCT	Orthopedic surgery center	Carpal tunnel release surgery patients (N=40)	Patient education handout and pre-operative counseling with surgeon	X			X*	X		
Cabo, 2019 <sup>41</sup> US	Before-after study	Urological surgery institution	Urological surgery patients (N=59)	Patient education handout		X		X*		X	X
Chakravarthy, 2018 <sup>42</sup> US	RCT	Emergency department	Emergency department patients (N=52)	Brief educational video	X	X				X	
de La Cruz, 2017 <sup>43</sup> US	Before-after study	Palliative care clinic	Cancer pain patients with current opioid prescription (N=600)	Patient education handout and personalized education and counseling	X	X					X
Hasak, 2018 <sup>44</sup> US	NRSI	Outpatient surgical clinic	Upper extremity/peripheral nerve surgery patients, without recent opioid use (N=258)	Patient education handout		X					X
Maughan, 2016 <sup>45</sup> US	RCT	Oral surgery practice	Oral surgery patients (N=58)	Patient education handout		X					X
McCarthy, 2015 <sup>46</sup> US	RCT	Emergency department	Emergency department patients, without opioid use in past 90 days (N=5,008)	Patient education handout with verbal review	X		X		X	X	
McCauley, 2013 <sup>47</sup> US	Before-after study	Chronic pain management clinic or dental clinic	Pain clinic and dental outpatients (N=62)	Brief interactive web-based patient education	X		X			X	

**Table 2. Studies on Patient-Level Opioid Misuse Prevention Education Interventions**

Author, Year	Country	Study Design	Setting	Population	Intervention	Intervention focus		Outcome measures					
						Safe opioid use and pain management	Safe storage and disposal	Opioid misuse	Opioid use	Pain	Opioid-related knowledge	Safe disposal or storage	
Rose, 2016 <sup>48</sup>	Canada	Before-after study	University hospital	Total hip or knee arthroplasty patients, without current use of ≥30 MME or history of opioid addiction (N=226)	Patient education handout	X	X		X*	X			X
Singh, 2018 <sup>49</sup>	Canada	RCT	Orthopedic department	Foot and ankle surgery patients, opioid naïve (N=561)	Patient education handout	X	X		X*	X			X
Smith, 2018 <sup>50</sup>	US	RCT	Mail/telephone	Arthroscopic rotator cuff repair patients at increased risk for persistent opioid use (N=561)	Patient education handout and pharmacist followup telephone call for refills	X			X†				
Syed, 2018 <sup>51</sup>	US	RCT	Orthopedic surgery center	Arthroscopic rotator cuff repair patients (N=140)	2-Minute narrative video and handout	X			X*	X			
Yajnik, 2019 <sup>52</sup>	US	Before-after study	VHA	Knee replacement surgery patients (N=40)	Patient education handout	X			X‡	X			

**Abbreviations:** MME = morphine milligram equivalents; NRSI = nonrandomized study of an intervention; RCT = randomized clinical trial; US = United States; VHA = Veterans Health Administration.

\*Patient-reported.

†Dispensed dosage.

‡Prescribed dosage.

**Table 3. Studies on Provider Education Interventions**

Author, year Country	Study design	Population	Intervention	Outcome measure		
				Opioid prescribing	Provider guideline adherence	Provider knowledge or beliefs
Alford, 2016 <sup>58</sup> US	Before-after study	Clinicians who manage patients with chronic pain (N=2,850)	3-Hour live or online REMS-compliant CME program ( <i>Scope of Pain</i> )		X*	X
Alford, 2016 <sup>57</sup> US	NRSI	Internal medicine residents (N=39)	1-Hour lecture +/- immediate or delayed objective structured clinical examination		X*	X
Anderson, 2017 <sup>59</sup> US	NRSI	PCPs in FQHCs (N=20)	48 Weekly 2-hour videoconference case-based learning sessions ( <i>Project ECHO Pain</i> )	X†	X†	X
Ball, 2018 <sup>60</sup> US	Before-after study	PCPs in community-based outpatient clinics and VHA facilities (N=25)	Case consultations plus weekly virtual training sessions ( <i>SCAN-ECHO</i> )			X
Chiu, 2019 <sup>61</sup> US	Before-after study	Surgery interns (N=31)	Single didactic educational presentation	X†		X
Cochella, 2011 <sup>62</sup> US	Post-test only	PCPs (N=366)	1-Hour educational presentation		X*	
Corson, 2011 <sup>63</sup> US	RCT	PCPs (N=42)	Two education sessions using case-based training with individualized feedback ( <i>SEACAP</i> )		X†	
Dewey, 2016 <sup>64</sup> US	Before-after study	PCPs mandated or self-referred to educational course (N=174)	3-Day in-person CME program with interactive learning sessions		X*	X
Donaldson, 2017 <sup>65</sup> Australia	Before-after study	Opioid prescribers in ED (N=30)	Brief (5-minute) one-on-one education intervention	X§		X
Donovan, 2016 <sup>66</sup> US	Before-after study	Medical school faculty (N=33)	Web-based CME training ( <i>COPE-REMS®</i> )			X
Fisher, 2012 <sup>67</sup> Canada	Before-after study	High opioid prescribers (N=30)	Provided three scholarly articles and individualized audit and feedback letter	X†		
Frank, 2015 <sup>68</sup> US	Before-after study	PCPs in VHA facilities (N=NR)	Case consultations plus weekly virtual training sessions ( <i>SCAN-ECHO-PM</i> )	X†		
Friesgaard, 2016 <sup>69</sup> Denmark	Before-after study	ED clinicians (N=67)	2-Hour e-learning session and subsequent simulation training	X†		X

**Table 3. Studies on Provider Education Interventions**

Author, year Country	Study design	Population	Intervention	Outcome measure		
				Opioid prescribing	Provider guideline adherence	Provider knowledge or beliefs
Gonzalez, 2012 <sup>70</sup> US	RCT	Prescribers of high-risk opioid patients (N=NR)	Personalized letter about prescribing practices and educational resources	X <sup>†</sup>		
Holliday, 2017 <sup>71</sup> Australia	Prospective cohort study	Early career GPs (N=NR)	90-Minute in-person educational program and electronic resources	X <sup>†</sup>		
Jamison, 2016 <sup>72</sup> US	NRSI	PCPs who manage patients with chronic pain (N=56)	Informational sessions, individual support, and monthly patient summaries			X
Kahan, 2013 <sup>73</sup> Canada	NRSI	PCPs mandated or self-referred to educational course (N=243)	2-Day in-person educational course followed by a telephone conference	X <sup>†</sup>		
Katzman, 2014 <sup>74</sup> US	Before-after study	PCPs (N=1,090)	5-Hour in-person CME course	X <sup>†</sup>		X
Langford, 2019 <sup>75</sup> US	Post-test only	PCPs (N=167)	20-Minute interactive education module			X
Larson, 2018 <sup>76</sup> US	Before-after study	PCPs in VHA facilities (N=68)	In-person individualized education (academic detailing) and provide patient-centered materials		X*	
Martello, 2018 <sup>77</sup> US	Before-after study	ED clinicians (N=11)	Text-based educational presentation regarding PDMP mandates	X <sup>†</sup>		X
McCracken, 2012 <sup>78</sup> UK	RCT	PCPs (N=81)	1-Day training incorporating Acceptance and Commitment Therapy	X*		X
Ruff, 2017 <sup>79</sup> US	Before-after study	Internal medicine residents (N=91)	2 Educational sessions (4.5-hours) incorporating education and debriefing of patient encounters			X
Srivastava, 2012 <sup>80</sup> US	Before-after study	PCPs (N=18)	Educational workshop followed by interactive video case conferences, clinical support system, and electronic resources			X
Sullivan, 2010 <sup>81</sup> US	RCT	Internal medicine residents (N=213)	Interactive web-based training (COPE)		X*	X

**Abbreviations:** CME = continuing medical education; COPE = Collaborative Opioid Prescribing Education; ECHO = Extension for Community Health Outcomes; ED = emergency department; FQHC = federally qualified health center; GP = general practitioner; NR = not reported; NRSI = nonrandomized study of an intervention; PCP = primary care provider; PDMP = prescription drug monitoring program; PM = pain management; RCT = randomized clinical trial; REMS = risk evaluation and mitigation strategy;

### Table 3. Studies on Provider Education Interventions

SEACAP = Study of the Effectiveness of a Collaborative Approach to Pain; SCAN = Specialty Care Access Network; UK = United Kingdom; US = United States; VHA = Veterans Health Administration

\*Provider-reported.

†Electronic records data/objectively documented.

‡Patient-reported.

**Table 4. Studies on Systems and Multilevel Interventions Focused on Implementation of Clinical Prescribing Guidelines and Protocols**

Author, Year Country	Study Design	Setting	Intervention
Anderson, 2015 <sup>103</sup> US	Before-after study	FQHC(s)	Clinician dashboard
Anderson, 2016 <sup>104</sup> US	Before-after study	FQHC(s)	Pain management education, resources, and protocols; clinician dashboard; telehealth consultation
Barber, 2017 <sup>105</sup> US	Interrupted time series study	VA hospital and clinics	Prescribing guidelines
Beaudoin, 2018 <sup>106</sup> US	Controlled before-after study	ED	Prescribing guidelines
Butler, 2013 <sup>107</sup> US	Before-after study	Pain clinic	PainCAS: Electronic assessment and tracking of pain patients
Canada, 2014 <sup>108</sup> US	Before-after study	Primary care clinic(s)	Education and implementation of standardized documentation and management of chronic pain patients using opioids; physician monetary incentives
Chen, 2016 <sup>109</sup> US	Before-after study	Primary care clinic(s)	Development and dissemination of chronic pain treatment guideline
Chiu, 2018 <sup>110</sup> US	Before-after study	Health system	Implementation and education around default prescribing dosage changes
del Portal, 2016 <sup>111</sup> US	Before-after study	ED	Development and dissemination of opioid prescribing guideline
Downes, 2018 <sup>112</sup> US	Before-after study	FQHC(s)	Implementation of chronic pain tool for patient management; SOAPP-R screening to guide opioid use decisions; prescribing guidance; tracking of physician guideline adherence
Earp, 2018 <sup>113</sup> US	Before-after study	Trauma center	Procedure-specific opioid prescribing protocol
Fox, 2013 <sup>114</sup> US	Before-after study	ED	Development of controlled substance guideline for ED for patients requesting refill, have multiple controlled substance prescriptions, or multiple ED visits
Garcia, 2016 <sup>115</sup> US	Interrupted time series study	Private insurer	Comprehensive opioid utilization program including patient-provider agreements, authorization of new opioid prescriptions, prescribing limits
Gugelmann, 2013 <sup>116</sup> US	Before-after study	ED	Multifaceted education program
Hartford, 2018 <sup>117</sup> UK	Pre-post	Tertiary care academic institution	The STOP Narcotics intervention including patient education; healthcare provider education; intraoperative multimodal analgesia and opioid reduction strategies; and postoperative multimodal analgesia and opioid reduction strategies
Holman, 2014 <sup>118</sup> US	Retrospective cohort	Orthopedic surgical department	Implementation of preoperative counseling and prescribing limits
Lee, 2019 <sup>119</sup> US	Interrupted time series study	Oncology surgical department	Mandatory provider education, procedure-specific prescribing guidelines, online training, standardized patient instructions
Liebschutz, 2017 <sup>120</sup> US	Cluster RCT	Primary care clinic(s)	TOPCARE: Nurse care management, electronic registry, academic detailing, electronic decision tools
Lin, 2017 <sup>121</sup> US	Before-after study	VA hospital and clinics	Dashboard of clinician adherence to guidelines and monitor prescribing variation, provider feedback
Losby, 2017 <sup>122</sup> US	Before-after study	Health system	Organization support, prescribing and dispensing policies, performance feedback, provider education, and decision support tools

**Table 4. Studies on Systems and Multilevel Interventions Focused on Implementation of Clinical Prescribing Guidelines and Protocols**

Author, Year Country	Study Design	Setting	Intervention
Mark, 2018 <sup>123</sup> US	Before-after study	Gynecologic oncology surgery center	Implementation of preoperative counseling and procedure-specific prescribing limits, patient evaluation prior to refills
Meisenberg, 2018 <sup>124</sup> US	Before-after study	County hospital	Physician education, prescribing reports, and academic detailing; patient/public awareness campaign; EMR tools for substance abuse referrals; development of multidisciplinary task force and prescribing practice guidance
Motov, 2018 <sup>125</sup> US	Before-after study	ED	Opioid reduction initiative and provider education
Nadeau, 2018 <sup>126</sup> US	Before-after study	Dental school	Implementation and education around opioid prescribing protocols, use of electronic prescribing tools
Osborn, 2017 <sup>127</sup> US	Before-after study	ED	Development and implementation of opioid prescribing guidelines, provider education, information on prescribing guidelines publicly posted
Osmundson, 2018 <sup>128</sup> US	RCT	Obstetrics-gynecology hospital department	Prescribing limits
Parchman, 2019 <sup>129</sup> US	Interrupted time series study	Primary care centers	Team-based redesign of opioid medication management (the Six Building Blocks), including clinician education
Pasquale, 2017 <sup>130</sup> US	Cluster RCT	Health system	Identification of patient with multiple prescribers, links to educational materials
Patel, 2018 <sup>131</sup> US	Retrospective cohort	VA hospital and clinics	Clinical decision support tools to guide physicians through pain and risk assessment and appropriateness of opioid de-escalation
Prabhu, 2018 <sup>132</sup> US	Before-after study	Hospital obstetric ward	Changes to default prescribing, patient counseling, patient handouts
Quanbeck, 2018 <sup>133</sup> US	NRT	Family medicine clinics	Audit and feedback, academic detailing, and external facilitation
Ringwalt, 2015 <sup>134</sup> US	RCT	ED	EMR prescribing reminders/notifications directed toward providers of patients who made multiple ED visits; letters sent to the patients and their community-based providers
Sauders, 2015 <sup>135</sup> US	NRSI	Health system	Education around appropriate prescribing, academic detailing
Schwartz, 2018 <sup>136</sup> AUS	Before-after study	ED	Change in default prescribing
Shah, 2015 <sup>137</sup> US	Before-after study	Primary care clinic(s)	Consolidation of providers offering controlled medications, implementation of stepwise treatment algorithm and patient-provider agreements
Stanek, 2015 <sup>138</sup> US	Before-after study	Hospital	Dissemination of prescribing guidelines, changes to default prescribing limits, patients provided with preoperative pain policy
Stepan, 2019 <sup>139</sup> US	Before-after study	Hospital	1-Hour physician education program, development and dissemination of opioid prescribing guidelines
Stepan, 2019 <sup>140</sup> US	Before-after study	Hospital orthopedic department	Mandatory provider education, development and implementation of specialty-specific prescribing guidelines
Sun, 2017 <sup>141</sup> US	Interrupted time series study	ED	Mandated opioid prescribing practices

**Table 4. Studies on Systems and Multilevel Interventions Focused on Implementation of Clinical Prescribing Guidelines and Protocols**

Author, Year Country	Study Design	Setting	Intervention
Von Korff, 2016 <sup>142</sup> US	Controlled before-after study (with interrupted time series analysis)	Health system	Dissemination of prescribing guidelines, educational presentations, academic detailing, development of minimum standards for monitoring and documenting opioid treatment, modifications to refill processes
Weimer, 2016 <sup>143</sup> US	Before-after study	Primary care clinic(s)	Implementation of opioid prescribing limit (dosage), physician training around clinical guidelines and patient communication
Weiner, 2017 <sup>144</sup> US	Interrupted time series study	ED	Implementation of statewide prescribing guidelines
Westanmo, 2015 <sup>145</sup> US	Before-after study	Hospital and outpatient clinics	Provider education, educational resources on opioid prescribing, pain education course for patients, monitoring of physician prescribing with provider reports
Wong, 2018 <sup>146</sup> US	Before-after study	Residency clinic	Implementation of EHR templates to standardize documentation of chronic pain management and patient followup; changes to refill procedures; random chart review for guideline adherence

**Abbreviations:** AUS = Australia; ED = emergency department; EMR = electronic medical record; FQHC = federally qualified health center; PainCAS = Pain Assessment Interview Network–Clinical Advisory System; RCT = randomized clinical trial; SOAPP-R = Screener and Opioid Assessment for Patients with Pain-Revised; TOPCARE = Transforming Opioid Prescribing in Primary Care; UK = United Kingdom; US = United States; VA = Veterans Affairs.

**Table 5. Ongoing Studies Related to the Prevention of Opioid Misuse**

Category	Trial ID	Title	Estimated completion date
Advice/coaching in individuals with existing high-risk behavior	<a href="#">NCT04218201</a>	The Subthreshold Opioid Use Disorder Prevention (STOP)	1/23
Pain/opioid education (general)	<a href="#">NCT04154384</a>	Life Pain Specialists (LPS)	9/22
	<a href="#">NCT03986866</a>	Video-Based, Patient-Focused Opioid Education	4/20
	<a href="#">NCT02674711</a>	Study of Opioid Use After Lumbar and Cervical Spine Surgery (SOULCS)	6/18*
	<a href="#">NCT03044522</a>	Use of a Nurse Pain Educator for Patients With Chronic Pain	11/17*
	<a href="#">NCT03586219</a>	Postoperative Opioid Consumption After Urogynecologic Surgery	6/20
	<a href="#">NCT03678870</a>	Discharge Opioid Education to Decrease Opioid Use After Cesarean	11/19*
	<a href="#">NCT02464410</a>	Primary Care Intervention to Reduce Prescription Opioid Overdoses (POST)	10/20
Disposal-specific education/aids	<a href="#">NCT03287622</a>	Evaluation of an Interactive Opioid Risk Education Program (STOMP) for Parents	4/19
	<a href="#">NCT03285061</a>	Excess Opioid Disposal Following Orthopedic Foot and Ankle Surgery	7/19*
Patient decision aids	<a href="#">NCT03012087</a>	Using m-Health Tools to Reduce the Misuse of Opioid Pain Relievers	4/17*
Behavioral “nudges” (e.g., provider comparisons)	<a href="#">NCT03537573</a>	Provider-Targeted Behavioral Interventions to Prevent Unsafe Opioid Prescribing for Acute Pain in Primary Care	2/21
	<a href="#">NCT03773484</a>	Application of Economics & Social Psychology to Improve Opioid Prescribing Safety (AESOPS): R21 Pilot Phase	8/19*
Provider education	<a href="#">ACTRN12617001160325</a>	Sydney Health Partners Emergency Department (SHaPED) trial	2/19*
	<a href="#">NCT03691948</a>	Reducing Prescription Opioid Misuse: ROPEs Pilot Trial	12/19
	<a href="#">NCT03629197</a>	Improving Communication About Pain and Opioids	1/20
Clinical decision support and collaborative care model	<a href="#">NCT03889418</a>	Opioid Treatment and Recovery Through a Safe Pain Management Program	6/22
	<a href="#">NCT03629197</a>	Improving Communication About Pain and Opioids	1/20
Changes to EMR defaults	<a href="#">NCT03377855</a>	Addressing Origins of the Opioid Epidemic by Improving Prescribing for Opioid-Naïve Patients	12/19
Prioritizing review of patients	<a href="#">ISRCTN16012111</a>	Evaluation of a Veterans Health Administration tool and policy to reduce patients’ risk of adverse events from opioid prescriptions	12/18*

\*No results published.

Abbreviation: EMR = electronic medical record.