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Prevention, Diagnosis, and Management of Opioids, Opioid Misuse and Opioid Use Disorder in Older Adults

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new healthcare technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

This EPC evidence report is a Technical Brief. A Technical Brief is a rapid report, typically on an emerging medical technology, strategy or intervention. It provides an overview of key issues related to the intervention—for example, current indications, relevant patient populations and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Although Technical Briefs generally focus on interventions for which there are limited published data and too few completed protocol-driven studies to support definitive conclusions, the decision to request a Technical Brief is not solely based on the availability of clinical studies. The goals of the Technical Brief are to provide an early objective description of the state of the science, a potential framework for assessing the applications and implications of the intervention, a summary of ongoing research, and information on future research needs. In particular, through the Technical Brief, AHRQ hopes to gain insight on the appropriate conceptual framework and critical issues that will inform future research.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality.

If you have comments on this Technical Brief, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Peer Reviewers

Prior to publication of the final technical brief report, the EPC sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

The list of Peer Reviewers follows: To be included in the final report.

Prevention, Diagnosis, and Management of Opioids, Opioid Misuse, and Opioid Use Disorder in Older Adults

Structured Abstract

Background. Opioid-related harms are increasing among older adults. Until we better understand the factors contributing to this trend, we will be unable to design and implement effective interventions to optimally manage opioid use and its potential harms among older adults.

Objectives. To provide a framework for understanding how to reduce adverse outcomes of opioid use among older adults and to describe the evidence available for different factors associated with and interventions to reduce adverse outcomes related to opioid use in this population.

Approach. With input from a diverse panel of content experts and other stakeholders, we developed a conceptual framework and evidence map to characterize empirical studies of factors associated with opioid-related outcomes and interventions to reduce opioid-related harms in older adults. We identified relevant literature among older adults (age ≥60 years) for an evidence map by systematically searching PubMed, PsycINFO, and CINAHL for studies published in English between 2000 and August 30, 2019.

Findings. We identified 5402 citations, from which we identified 35 studies with multivariable models of factors associated with opioid-related adverse outcomes and 14 studies of interventions in older adults. Half (17/35) of the multivariable analysis studies evaluated factors associated with long-term opioid use. Prior or early postoperative opioid use, or greater amounts of prescribed opioids (high number of opioid prescriptions or higher opioid dose), were consistently (100% agreement) and strongly (measure of association ≥2.0) associated with long-term opioid use. Back pain, depression, tobacco use, fibromyalgia, and concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) also had consistent, but weaker, associations with long-term opioid use. Low income and benzodiazepine use were mostly associated (>75% agreement) with long-term opioid use. However, studies were mostly consistent that alcohol abuse and healthcare utilization were *not* associated with long-term opioid use. Gender, age among older adults, black race, and dementia were variably associated (<75% agreement) with long-term opioid use.

Six studies examined factors associated with opioid-related disorders. Alcohol misuse and gender were variably associated with opioid misuse (examined by 3 studies each).

All other evaluations of specific associated factors and outcomes of interest were evaluated by only one or two studies each. These included analyses of opioid use disorder, high-risk obtainment of prescription opioids, procuring multiple opioid prescribers, mental health outcomes, physical health outcomes, all-cause hospitalization, opioid-related hospitalization, nonopioid-specific hospitalization, emergency department visits, opioid overdose, all-cause death, opioid-related death, and nonopioid-related death.

The evidence on interventions directed at older adults is sparse. Of the 14 studies of opioid-related interventions in older adults, six examined screening tools to predict opioid-related harms, but none of these tools was tested in clinical practice to assess real-world results. Two studies

found that prescription drug monitoring programs are associated with less opioid use in communities. Other studied interventions include multidisciplinary pain education for patients, an educational pamphlet for patients, provision of patient information and pain management training for clinicians, a bundle of educational modalities for clinicians, a nationally-mandated tamper-resistant opioid formulation, and motivational interview training for nursing students. Each intervention was evaluated by only a single observational study except for one of the clinician education studies which was evaluated by a randomized controlled trial.

Conclusions. The evidence base that is directly applicable to older adults who are prescribed opioids or have opioid-related disorders is limited. Fundamental research is necessary to determine which factors may predict opioid-related harms. Studies to date have identified numerous possible factors associated with long-term opioid use, but analyses of other opioid-related outcomes in older adults are relatively sparse. Research is also needed to identify interventions to reduce opioid prescribing where harms outweigh benefits, reduce opioid-related harms and disorders, and treat existing misuse or opioid use disorder among older adults.

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MAIN POINTS

- We developed a Conceptual Framework outlining the stages of care for older adults who require or use opioids, and factors that have an impact on management decisions and patient outcomes (see Figure). The framework prioritizes three potential targets to determine factors associated with and interventions for: 1) reducing opioid prescriptions where harms outweigh benefits, 2) preventing opioid misuse and opioid use disorder (OUD), and 3) reducing other opioid-related harms.
- 35 studies assessed factors independently associated with opioid-related outcomes among older adults (≥60 years).
    - While the 35 studies reported multivariable analyses, none of the analyzed models was designed or evaluated as a screening or prediction tool.
    - 17 multivariable studies evaluated **long-term opioid use**, which may sometimes be a high-risk behavior, but is not necessarily evidence of problematic opioid use.
        - All 8 studies that looked at prior or early postoperative opioid use found mostly strong associations (e.g., relative risk [RR] >2.0) with long-term opioid use.
        - All 6 studies that examined greater amounts of prescribed opioids (higher number of opioid prescriptions or higher opioid dose) found mostly strong associations with long-term opioid use.
        - Other factors with consistent (100% agreement), but largely weak associations (e.g., RR <2.0, but statistically significant), included back pain, depression, tobacco use, fibromyalgia, and concomitant NSAID use.
        - Studies were *mostly consistent* (≥75% agreement) that having a low income and benzodiazepine use were each associated with long-term opioid use, but the associations were mostly weak.
        - In contrast, studies were *mostly consistent* that alcohol abuse and healthcare utilization were *not* associated with long-term opioid use.
        - Studies had *variable findings* (<75% agreement) regarding the associations with gender, age (within older adults), black race, and dementia.
    - Across 6 studies evaluating opioid-related disorders, including OUD and opioid misuse, 3 studies each had *variable* findings regarding the associations of alcohol misuse and of gender with **opioid misuse**.
    - All other evaluations of specific factors and outcomes of interest were evaluated by only one or two studies each. These included factors associated with **opioid**

use disorder, **high-risk obtainment of prescription opioids**, **procuring multiple opioid prescribers**, **mental health outcomes**, **physical health outcomes**, **all-cause hospitalization**, **opioid-related hospitalization**, **nonopioid-specific hospitalization**, **emergency department visits**, **opioid overdose**, **all-cause death**, **opioid-related death**, and **nonopioid-related death**.

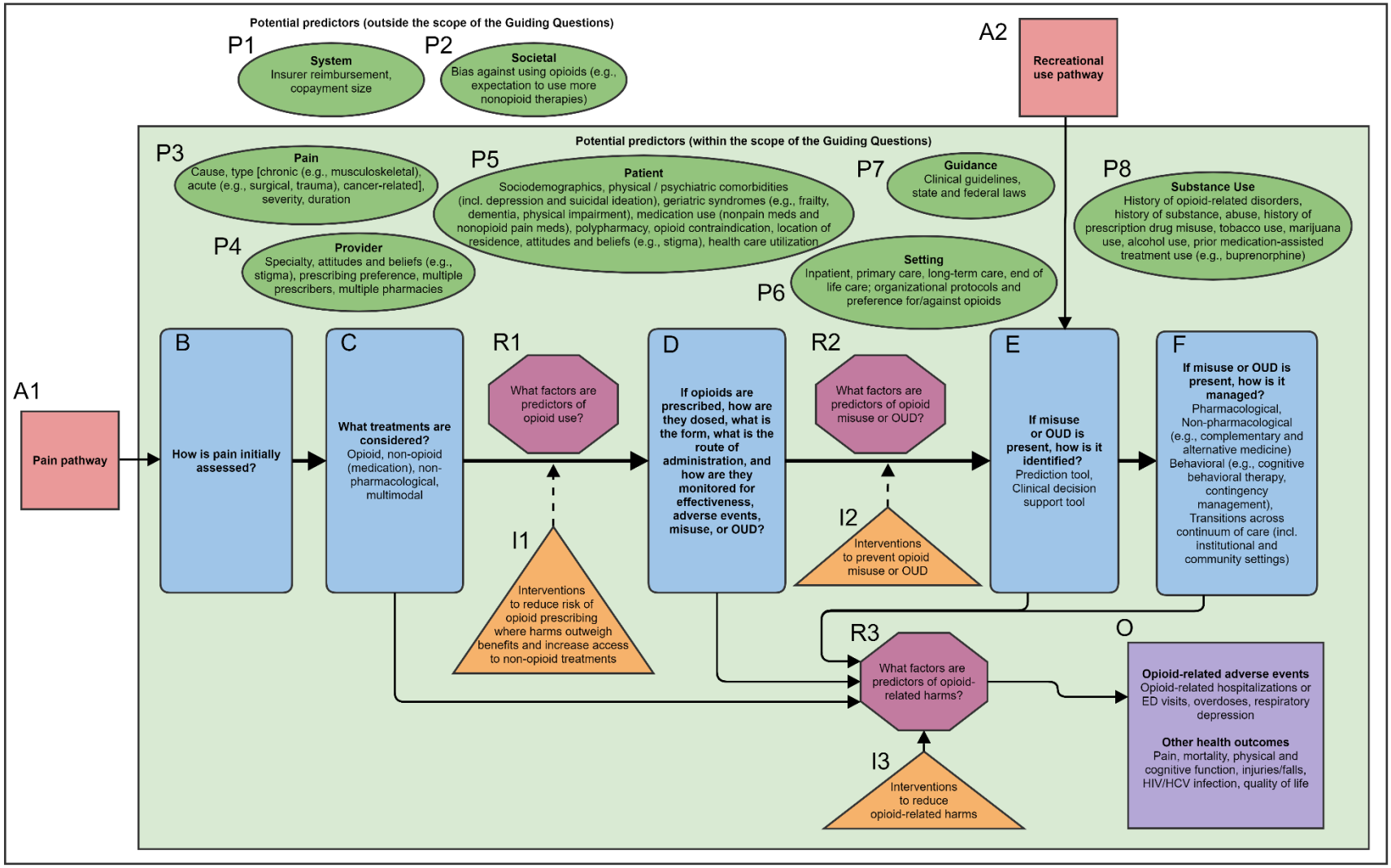
- 14 studies addressed interventions related to opioid use and opioid-related disorders in older adults.
    - Only 1 study was a randomized trial. Each intervention was evaluated by only 1, or rarely, 2 studies.
    - The most-studied interventions were **screening tools to predict opioid-related harms** but none of these tools has been tested in clinical practice to assess real-world results.
    - 2 studies found that **prescription drug monitoring programs** have been associated with less opioid use (at the State level).
    - Other studied interventions include included **multidisciplinary pain education for patients**, an **educational pamphlet for patients**, **provision of patient information and pain management training for clinicians**, a **bundle of educational modalities for clinicians**, **clinician education**, a nationally-mandated **tamper-resistant opioid formulation**, and **motivational interview training for nursing students**. Each intervention was evaluated by only a single observational study except for one of the clinician education studies which was evaluated by a randomized controlled trial.
    - Among studies that had the goal of reducing overall opioid prescriptions or use, none specifically assessed "appropriate" reduction of opioid prescriptions or use (e.g., when the risks of opioid use outweigh the benefits).
- Future research is needed to establish the strongest factors associated with important clinical outcomes related to opioid use in older adults and to identify interventions to improve primary prevention (reducing unnecessary opioid use), secondary prevention (reducing opioid-related harms), and treatment of existing opioid misuse or OUD.

BACKGROUND and PURPOSE

Opioid-related hospitalizations, emergency department (ED) visits, and deaths are increasing among older adults even as rates of nonopioid-related hospitalizations and ED visits are decreasing. Older adults make up a growing share of the US population and are at a greater risk of opioid exposure due to higher incidences of pain and comorbidities that result in pain. Older adults are more likely than younger adults to experience adverse drug reactions and opioid misuse is an increasing source of opioid-related harms among older adults. To address these issues, we need a better understanding of the factors driving opioid-related harms in older adults and the evidence-based interventions to reduce those harms.

This Technical Brief provides a conceptual framework that diagrams the process of care to identify areas of risk and opportunities for intervention, and describes the relevant evidence base. The framework and evidence map will support the Agency for Healthcare Research and Quality (AHRQ) and other agencies' development of an evidence-based research agenda to answer the most important questions regarding prevention, diagnosis, health outcomes, and management of opioid use, misuse, and opioid-related disorders among older adults.

Figure. Conceptual Framework



See legend in full report.

METHODS

We developed a Conceptual Framework based on existing frameworks and discussion with 15 Federal and nonfederal stakeholders (see Figure). The Conceptual Framework identifies key questions regarding factors potentially associated with Opioid-related outcomes (featured in the octagons) and relevant interventions (featured in the triangles). Using the Conceptual Framework as a guide, we conducted a literature search of relevant studies published between January 2000 and August 30, 2019. The review was conducted in accordance with the AHRQ EPC Program Methods Guidance for Technical Briefs.

RESULTS

The Conceptual Framework outlines the stages of care for older adults related to opioid use as well as the factors that impact management decisions and patient outcomes. These include assessment of pain, selection of pain treatment, choice of opioid regimen, assessment for opioid misuse or opioid use disorder (OUD), and management of misuse or OUD (featured in Rectangles B to F). Multiple potential patient, provider, health system, and societal factors (in the 8 ovals) may influence risks of adverse outcomes and the effect of interventions to reduce the adverse outcomes (Box O). The framework includes factors associated with interventions to 1) reduce opioid prescriptions where harms outweigh benefits 2) prevent opioid misuse and OUD and 3) reduce other opioid-related harms.

Regarding factors related to opioid use and harms in older adults (≥60 years), we focused on the 35 studies that reported multivariable analyses, to best identify independent factors associated with the outcomes of interest. Seventeen of these studies addressed long-term opioid use (categorized into Octagon R1). Eight studies that addressed opioid misuse or OUD (related to Octagon R2) examined two sets of outcomes: opioid misuse (6 studies) and having multiple opioid prescribers (2 studies). The 13 studies that addressed opioid-related harms (Octagon R3) had four sets of outcomes: mental or physical harms (4 studies), hospitalizations or ED visits (4 studies), opioid overdose (3 studies), and death (5 studies).

Seventeen multivariable models evaluated a large range of factors potentially associated with long-term opioid use among older adults. Eight studies that examined opioid use prior to surgery or injury (or early use after surgery) and 6 studies that examined greater amount of opioid use (more prescriptions or higher dose) were **consistent** (in full agreement) that these factors are associated with long-term opioid use, with mostly strong associations (e.g., RR ≥2.0).Other consistent associations, but with largely weak associations (RR <2.0, but statistically significant), were found with back pain (4 studies, 2 with strong associations), depression (10 studies, all weak associations), tobacco use (4 studies, 1 with a strong association), fibromyalgia (3 studies, all weak associations), and concomitant NSAID use (3 studies, all weak associations).

Studies were **mostly consistent** (≥75% agreement) that low income (5 of 6 studies) and benzodiazepine use (4 of 5 studies) were associated with long-term opioid use, but these associations were mostly weak. Studies were also mostly consistent that alcohol abuse (4 of 5 studies) and healthcare utilization (3 of 4 studies) were *not* associated with long-term opioid use; however, one of these studies found a strong association between "any hospitalization" and long-term use.

Factors with **variable** findings (<75% agreement) of association (evaluated by at least 3 studies) included gender (6 of 14 studies found weak associations with female gender; 2 found associations with male gender, one strong), "substance abuse" (8 of 12 studies found mostly weak associations), age among older adults (6 of 10 studies found mostly weak associations with younger age among older adults; 1 found a weak association with older age), black race (3 each, among 8 studies, found weak associations with increased and with decreased likelihood), and dementia (2 each, among 5 studies found associations with increased and with decreased likelihood).

Only 14 studies addressed interventions to appropriately reduce opioid prescriptions, reduce opioid-related harms, or identify or treat opioid-related disorders and only one was a randomized controlled trial. Seven studies evaluated interventions to reduce opioid prescribing (depicted in Triangle I1); although none specifically focused on or attempted to account for whether harms outweighed benefits. One of these interventions was also designed to prevent opioid misuse or OUD (Triangle I2) by minimizing activities that may lead to opioid misuse. Six additional studies evaluated screening tools to identify people at increased risk of opioid-related disorders (also Triangle I2). One study addressed an intervention to manage (and thus reduce) opioid misuse in older adults (Rectangle F and Triangle I3 in the Framework). No study specifically addressed reducing harms among older adults appropriately using opioids (Rectangle D). The studies provide some evidence that various screening tools and interventions may be effective to reduce opioid use, reduce the risk of opioid misuse, and manage opioid misuse among older adults. Two studies found that prescription drug monitoring programs were associated with less opioid use (at the State level), but, overall, there has been little replication of evaluations of interventions and none of the screening tools have been tested in routine clinical practice to assess the real-world results of their use.

LIMITATIONS

Our literature search does not include studies published prior to 2000 and did not include all potentially relevant literature databases. In accordance with guidance for AHRQ Technical Briefs, we did not fully assess each eligible study, including detailed assessments that would be required for evaluation of methodological quality, generalizability, and strength and conclusions of the evidence base.

CONCLUSIONS

The evidence base that is directly applicable to older adults who are prescribed or use opioids or who have opioid-related disorders is relatively sparse. Fundamental research is necessary to determine which factors may predict opioid-related harms. Studies to date suggest that the amount of prescribed opioids (or dose), prior or early use of opioids, musculoskeletal pain, and history of abuse of other substances are potentially important factors. Research is also needed to identify interventions to reduce opioid prescribing where harms outweigh benefits, reduce opioid-related harms and disorders, and treat existing misuse or OUD among older adults. Future research should emphasize the adaptation of existing interventions for use in older adults, but the development, validation, and evaluation of new interventions tailored to the needs of older adults will likely also be necessary to manage opioid misuse and OUD in older adults.

Introduction

Background

Between 2010 and 2015, opioid-related hospitalizations among adults aged 65 years and older increased by 34 percent, from 199.3 to 267.6 per 100,000 individuals, while nonopioid-related hospitalizations decreased by 17 percent.[1] Over that same period, opioid related emergency department (ED) visits among older adults increased by 74 percent.[1] Although younger age cohorts suffered larger absolute increases in opioid-related mortality between 2001 and 2016, opioid-related mortality also increased among adults between the ages of 55 to 64 and those that are 65 and older.[2] In addition, nonmedical prescription opioid use among individuals aged 65 years and older has doubled, from 0.4 percent in 2002 to 0.8 percent in 2014.[3] These data raise concerns regarding the current approaches to pain management with opioids, and prevention, diagnosis, and management of opioid misuse and opioid use disorder (OUD) among older adults.

Older adults are a growing population

The U.S. and global population of older adults is increasing, further creating a critical need to understand opioid use among older adults. The U.S. population aged 65 years and older is forecast to increase from 48 million people in 2015 to 88 million people in 2050.[4] The combination of the growing population of older Americans and the increasing rates of opioid-related harms in this population will likely result in even larger increases in the absolute numbers of opioid-related hospitalizations, ED visits, and mortality among older adults.

The challenge of pain management in older adults

Older adults are more likely than younger adults to be exposed to opioids due to their high incidence of pain and need for acute and chronic pain treatment for conditions such as diabetic neuropathy, large joint osteoarthritis, fractures, and cancer. In older adults, compared with younger individuals, episodes of acute pain are more likely to transition to chronic pain due to biological changes in the nervous system, contributing to their experiencing severe or persistent pain.[5-7] Older adults may also have accumulated psychological (or emotional) trauma, resulting in anxiety and depression; loss of loved ones or other important individuals; an erosion of social roles; and occurrence of disability, all of which may increase the probability that an older adult uses opioids as a treatment for emotional and physical pain.[3] For these reasons, and more, pain management in older adults is particularly challenging.

Opioid treatment is often indicated for older adults

Opioid medications[A] are commonly used to treat pain; however their use at higher doses and concurrently with benzodiazepines is associated with increased risk of opioid-related harms, including overdoses.[8-12] Furthermore, the effectiveness of long-term opioid therapy is unclear.[13-15] For some older adults, opioid use is an appropriate option. For example, many older adults are unable to tolerate nonopioid analgesics (e.g., nonsteroidal anti-inflammatory drugs) due to impaired liver or kidney function, hypertension,[16-18] other cardiac risks,[19-25] concomitant anticoagulant therapy in atrial fibrillation or after stroke, risk of gastrointestinal bleeding,[26-29] or other conditions.[30] Nonpharmacologic treatments, such as exercise or cognitive behavioral therapy, may

[A] See *Definition of Terms* section at the end of the Introduction.

be difficult for older adults to access. Since untreated pain has been associated with many negative consequences, including depression, anxiety, functional impairment, slow rehabilitation, decreased socialization, sleep and appetite disturbances, and greater healthcare utilization, opioids have an important role in the management of pain for many older adults.[31] Opioid use may be particularly necessary for short-term acute pain after surgery or other procedures. Appropriate use of opioids under clinicians' supervision may provide many older adults with necessary pain relief, allowing them to remain active, independent, engaged in necessary therapy (e.g., rehabilitation or physiotherapy), and able to maintain a higher quality of life.

Older adults are at higher risk of adverse events even with appropriate opioid use

Empirically, older adults are significantly more likely to experience adverse drug reactions than younger adults,[32, 33] and are at increased risk of opioid-related falls and fractures,[34-37] hospitalizations, ED visits, and death,[38] even when using opioids as directed and intended by the prescriber. The frequency of opioid-related hospitalizations and ED visits appears to vary geographically, presumably because of geographic differences in patients' characteristics and access to healthcare and other services and structures.[1]

Age-related physiological changes (e.g. in metabolism and body composition), drug-condition interactions, and polypharmacy (resulting in drug-drug interactions) all increase older adults' risk of opioid adverse effects, even when opioids are used as intended. Polypharmacy is highly prevalent in older adults and increases the risk of adverse drug-drug interactions. For example, combining opioids and benzodiazepines can result in respiratory depression and death.

Opioids may exacerbate pre-existing conditions such as cognitive impairment, compromised respiration, hypogonadism, osteoporosis, frailty (or diminished physical reserve), and other substance (e.g., alcohol) use disorders.[39-42] Reciprocally, unrecognized cognitive decline or dementia may lead to unintentional deviations from a prescribed opioid regimen, and accidental poisoning or overdose. These risks may be exacerbated by the high frequency at which older adults see multiple providers and specialists, who often do not coordinate their care and prescribe interacting or duplicative medications.[43, 44] Clinician use of state prescription drug monitoring programs (PDMP) provides information on a patient's prescription history for controlled medications and may promote safer prescribing practices. However, it is unclear whether PDMP programs have an effect on opioid use in older adults.

Misuse of opioids may also be responsible for opioid adverse events in older adults

It is unclear to what extent medical opioid use (as prescribed) versus nonmedical opioid use or misuse accounts for the increases in opioid-related harms over the past decade among older adults. Media coverage and research has focused almost entirely on opioid misuse among younger individuals due to their higher prevalence of misuse.[1, 2, 45] It is plausible that many older adults misuse prescribed opioids by taking them in greater amounts, more often, or for longer than they were directed to by a prescriber, or even resort to illicit opioids to alleviate untreated or undertreated pain, increasing the risk of overdose.[46] Additionally, some older adults may attempt suicide via self-poisoning; suicide mortality appears to be increasing among older adults[47] and social isolation, depression, chronic pain, disability, and loss of functioning are all factors associated with suicide that are prevalent among older adults.[47]

As with younger individuals, opioid misuse may transition to OUD. Regardless of age, individuals may become physically dependent on opioids (i.e., the body adjusts its normal functioning around regular opioid use) and continue taking them to avoid uncomfortable withdrawal symptoms.[48, 49] Long-term opioid use—use of opioids on most days for longer than 3 months—

may predispose individuals to developing OUD; although, this connection has not been established in younger or older adults. Once OUD develops in an older adult, its symptoms may resemble those of common geriatric syndromes like cognitive impairment, Alzheimer disease and related dementias, delirium, and depression.[50] The similarities between the symptoms of OUD and other geriatric syndromes hinders and likely delays or precludes the identification of OUD among older adults.

Considering all of the aforementioned information, a better understanding of the current approaches to prevention, diagnosis, and management of opioids, opioid misuse, and OUD among older adults and the supporting evidence is necessary.

Overview of the Technical Brief

This Technical Brief comprises a conceptual framework and a focused evidence map of the current evidence base with the goal of understanding the issues that are driving the current rise in opioid-related morbidity and mortality in older adults, and what evidence is needed to support effective interventions to prevent and manage harms from opioids in this population. The framework and evidence map will allow the Agency for Healthcare Research and Quality (AHRQ) and other agencies to design an evidence-based research agenda to answer the most important questions regarding prevention, diagnosis, and management of opioid use, misuse, and OUD among older adults. The ultimate goals are to accelerate practice change and improve outcomes in older adults. This brief focuses on care management rather than societal or high-level system issues that are outside provider or health-system control.[51]

Definition of Terms

Opioid medications: All natural, synthetic, and semisynthetic substances that have effects similar to morphine, specifically those approved by the U.S. Food and Drug Administration (FDA) as medications (e.g., oxycodone).

Medical opioid use: Use of an opioid for a condition or a disease (an indication) for which reasonable scientific evidence supports that an opioid is an effective treatment.

Recreational opioid use: Use of an opioid for its psychoactive effects in the absence of a condition or a disease (an indication) that reasonable scientific evidence supports that an opioid is an effective treatment.

Multimodal Stepped Pain Therapy: A pain treatment approach that sequentially 1) combines medications from different pharmacologic classes and/or 2) combines pharmacologic and nonpharmacologic therapies or multiple nonpharmacologic therapies.

Prescribers: Healthcare professionals from any discipline who have the legal authority to prescribe opioids and other medications.

Long-term opioid use: Opioid use on most days for more than 3 months. Long-term use is defined regardless of the clinical appropriateness of the duration of opioid use.[15]

Opioid-related disorders: For the purpose of this report, any problematic opioid use, including OUD and opioid misuse, defined next.

Opioid use disorder (OUD): The diagnosis of problematic use of opioids as, for example, defined by DSM-V (Diagnostic and Statistical Manual of Mental Disorders) criteria.[52] OUD is the clinical term for opioid addiction. OUD is typically characterized by loss of control of opioid

use, risky opioid use, impaired social functioning, tolerance, and withdrawal. Tolerance and withdrawal do not contribute toward a diagnosis of OUD when individuals are using opioids appropriately and under medical supervision. Diagnosis of OUD is made when a person uses opioids and experiences 2 or more of 11 symptoms in a 12-month period.

Opioid misuse: A problematic pattern of opioid use, distinct from OUD. Opioid misuse is not a clinical diagnosis. It is the use of opioids in any way (other than OUD) that is different than as directed by a prescriber (e.g., at higher doses, more frequently, or for longer duration than prescribed; for a reason other than indicated; without one's own prescription) or the use of any opioid in a manner, situation, amount, or frequency that can cause harm to self or others.[53]

Methods

We address three overarching research questions ("Guiding Questions") related to opioids in older adults:

1. What are the most important factors driving the increase in opioid-related hospitalizations and ED visits for older adults and what interventions are needed to reduce the risk of opioid-related adverse events, opioid misuse, and OUD in older adults without compromising pain control or quality of life?
2. Among older patients taking opioids, what factors are most strongly associated with harms from opioids (adverse events, misuse, or opioid use disorder)?
3. What interventions have been studied to help providers…
    a. reduce opioid prescription where harms outweigh benefits in older adults without compromising pain control or quality of life (e.g., shared decision-making)?
    b. reduce the risk of adverse events, misuse or opioid use disorder in older adults for whom opioids are appropriate?
    c. identify and treat opioid misuse or opioid use disorder in older adults?

In addition, we address the question of what research is necessary to develop interventions that improve the management of opioids and reduce the risk of opioid-related harms in older adults. The original detailed Guiding Questions developed by AHRQ in consultation with other federal agencies can be found in Appendix B together with further details about the methods.

To address the issues raised by the Guiding Questions, we developed a conceptual framework informed by stakeholder (Key Informant) discussions and generated an evidence map of the existing evidence base. The conceptual framework and evidence map summarize the evidence in a way that allows stakeholders to readily identify the next steps for research on opioid use and misuse in older adults. Here we give an overview of the methods; details can be found in the Appendices.

Development of Conceptual Framework

Initial Development

A draft conceptual framework was developed to address Guiding Question 1 based on existing prior conceptual frameworks and systems maps, including those developed by Wakeland and colleagues,[54, 55] the U.S. Department of Health and Human Services Pain Management Best

Practices Inter-Agency Task Force Report,[56] and the National Academies of Sciences Engineering and Medicine report "Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use".[57] Existing frameworks and systems maps from other conditions not directly related to pain were considered to help inform alternative structures and formats for the framework.[58, 59]

Key Informants and Discussions

We formed a 15-member panel comprising six individuals employed by federal agencies and nine individuals employed by nonfederal entities. These individuals included experts in the care of older adults, experts in pain treatment and opioid use, nationally and internationally recognized researchers, policy makers, and internationally recognized advocates for older adults with pain. We had discussions with the 15 Key Informants to help us revise the conceptual framework. We solicited the panel's input in three teleconferences and over email until we deemed that we had sufficiently discussed all of the most relevant themes. The interactions with the Key Informant Panel were facilitated by the EPC and included several structured prompts based on all Guiding Questions. The Key informants were asked about the draft Conceptual Framework and to identify peer-reviewed publications or other relevant literature related to the topics of interest. In Appendix C we provide an overview of our discussions with Key Informants that helped to shape the Conceptual Framework and to evaluate the evidence base. Appendix C also includes specific themes identified during the discussions.

Evidence Map

We conducted a literature search to find articles primarily addressing Guiding Question 2 (factors associated with harms from opioids in older adults) and Guiding Question 3 (interventions that either appropriately reduce opioid prescribing and risk of harms, or identify and treat misuse and OUD in older adults). We primarily sought studies that pertain to the likelihood of opioid use, preventing opioid misuse and OUD and reducing opioid-related harms (relating to the three Octagons and Triangles in the Conceptual Framework (Figure 1).

The evidence map enumerates and describes the primary studies that directly address relevant questions pertaining to the management of opioid use and misuse in older adults. It forms a citation list and database for any future systematic review on the topic. We did not summarize study findings or assess their methodological quality. The literature search is described in Appendix A. Appendix B describes processes for abstract screening and further details about our methods to create an evidence map from full-text articles.

Based on discussions with the Key Informants and the variable definitions of "older adults" across studies, we focused on studies that included adults aged 60 and over. We restricted to studies conducted in high-income countries and excluded studies of older adults who were terminally ill, in hospice, or in similar situations where opioid harms, misuse, or OUD are of lesser concern. All factors associated with opioid misuse, harm, or OUD were considered and included, as were all interventions used to predict future opioid use, manage opioid use, or prevent opioid-related harms, including misuse and OUD. Any outcome (person-, provider-, and system-level) was eligible for inclusion. All primary study designs, as well as systematic reviews and clinical practice guidelines, were eligible for inclusion.

We searched PubMed, PsycINFO, and CINAHL, using terms related to older age or aging, crossed with terms on opioid use, opioid-related disorders, opioid misuse, and opioid-related adverse events. We did not include search terms for (and thus avoided excluding articles based on)

interventions, outcomes, or study designs. We limited results to studies published in English, between the years 2000 and August 30, 2019, inclusive. To screen the evidence base, we used the online software Abstrackr, which uses machine learning algorithms to predict and sort citations based on likely relevance; using these algorithms, we stopped screening when the remaining prediction values suggested no further relevant citations would be identified.

We also searched ClinicalTrials.gov and PROSPERO to identify unpublished studies, ongoing studies, and unpublished systematic reviews. All potentially eligible citations were retrieved and screened in full text for eligibility by a single reviewer, after a training period to ensure consistency between all reviewers. Each eligible study was extracted for a limited set of elements on the population, the association variables (factors) or intervention, intent of interventions, examined outcomes, and study design features. All data was extracted in a predefined electronic form.

We provide a high-level summary of the body of evidence that evaluated putative factors that predict adverse outcomes related to opioids in older adults. The summary focuses on only multivariable analyses within clearly specified cohorts of older adults since these studies are more likely to reliably identify independent variables (factors) than studies performing univariable analyses of a single variable in each model. We then organized the data from the studies by factor and opioid related outcome. The measure of association estimates from these multivariable analyses were each categorized according to the direction of the association and by following schema:

- **Strong association**: a *statistically significant* association between a (categorical) factor and higher (or lower) risk of the outcome with a measure of association ≥2.0 (or ≤0.5); e.g., relative risk (RR) or odds ratio (OR).
- **Weak association**: a *statistically significant* association between a (categorical) factor and higher (or lower) risk of the outcome with a measure of association between 0.5 and 2.0
- **Statistically significant association**: for evaluations of continuous factors (e.g., age, per year) for which we could not estimate a standardized measure of association where the association was statistically significant (we did not classify these associations as strong or weak)
- **No statistically significant association**: for factors without a statistically significant association, regardless of magnitude of measure of association

In partial determination of the strength of the body of evidence, we assessed whether findings were consistent across studies. We found no guidance on how to assess consistency of semiquantitative summaries of association studies. AHRQ guidance for assessing consistency across (primarily intervention) studies suggest consideration of direction and/or magnitude of effect (depending on the research question) and promotes the judgment of the researchers to determine consistency.[60] For the purpose of the qualitative assessment of the evidence base for this report, we established the following arbitrary criteria for different levels of consistency:

- A minimum of 3 studies had to evaluate the same factor category (e.g., age) for the same outcome (e.g., long-term opioid use). Associations with only one or two studies were not evaluated for consistency.
- "Consistent" – All studies agreed in both direction and statistical significance of association (e.g., all found significant associations between history of depression and increased likelihood of long-term opioid use). Description of whether associations were strong or weak are noted.

- "Mostly consistent" – At least 75 percent of studies agreed in both direction and statistical significance of association. No more than one study found a statistically significant association in the opposite direction (e.g., that men, not women, were at increased risk of outcome). Remaining studies found no significant association.
    - Note that where three studies evaluated a given association, a determination of "mostly consistent" was not possible.
- "Variable" – Studies are neither consistent nor mostly consistent.

We separately analyzed the studies of identifiable interventions used in (or for) older adults that pertain to the Guiding Questions. These are each described individually.

Findings

Conceptual Framework

The Conceptual Framework (Figure 1) outlines the stages of care for older adults who use (or may use) opioids and factors that impact management decisions and patient outcomes, including assessment of pain, selection of pain treatment, choice of opioid regimen, assessment for opioid misuse or OUD, and management of misuse or OUD. It incorporates "pathways" by which older adults start using (or misusing) opioids (namely, via a "pain pathway" [**Box A1** in the figure] resulting in opioid prescription by a licensed healthcare professional or via a "recreational use pathway," [**Box A2**] in which people start using opioids for recreational purposes).

For patients who enter through the "pain pathway," (**Box A1**) the clinician first assesses their pain to determine its cause (**Rectangle B**) and then considers possible treatment options (**Rectangle C**). Providers can (or should) use the pain assessment to estimate the risks and benefits of various pain treatments in a given older patient. For example, kidney or liver disease identified during pain assessment influences the relative harms and benefits of using one treatment option versus another, such as nonsteroidal anti-inflammatory drugs versus opioids.

While opioids are an option (**Rectangle C**), nonopioid medications could be used to manage pain. These medications include acetaminophen, nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen), corticosteroids, antidepressants, antiepileptics, and others (e.g., topical capsaicin products). Nonpharmacological options are available as well and include a wide array of potential interventions, such as yoga, massage therapy, and acupuncture. Importantly, older adults may start "multimodal" treatment (of more than one intervention) that comprises a pain treatment approach that 1) combines medications from different pharmacologic classes and 2) combines pharmacologic and nonpharmacologic therapies or multiple nonpharmacologic therapies.

The framework prioritizes three potential targets to determine factors associated with and interventions for 1) reducing opioid prescriptions where harms outweigh benefits, 2) preventing opioid misuse and OUD, and 3) reducing other opioid-related harms.

Many factors play a role in the decision to use (or avoid using) opioids to manage pain (**Octagon R1**). A key consideration is whether the benefits of opioid treatment outweigh its harms. Such benefit-harm assessments are difficult and can be erroneous when information about key factors is lacking or not considered and can be skewed when there is limited access to effective nonopioid treatment alternatives. Interventions to support benefit-risk assessments (**Triangle I1**) could be employed at this point in the care pathway. For example, patient-level tools could, in theory, help clinicians assess the expected benefits and risks of opioid or other pain treatment

use. These may be instruments that predict effectiveness or risks based on easily assessable factors available to the clinician during the patient encounter. System-level interventions (at the clinic, hospital, pharmacy, healthcare system, or State levels) to increase access to and the affordability of effective non-opioid alternatives may also be impactful.

If opioids are prescribed to an older adult (**Rectangle D**), prescribers must select a dose, schedule, form, and route of administration, and decide if and how they will monitor for opioid effectiveness, adverse events, misuse, and OUD. Opioid use in older adults may eventually result in opioid misuse or OUD, and a variety of factors may predict transition to misuse, OUD, or both (**Octagon R2**). Pharmaceutical, non-pharmaceutical (e.g., behavioral), nonmedical (e.g., educational, community-based), and other interventions could, at least conceptually, help older adults to safely use prescription opioids and prevent or reduce the risks of transition to opioid misuse and OUD (**Triangle I2**).

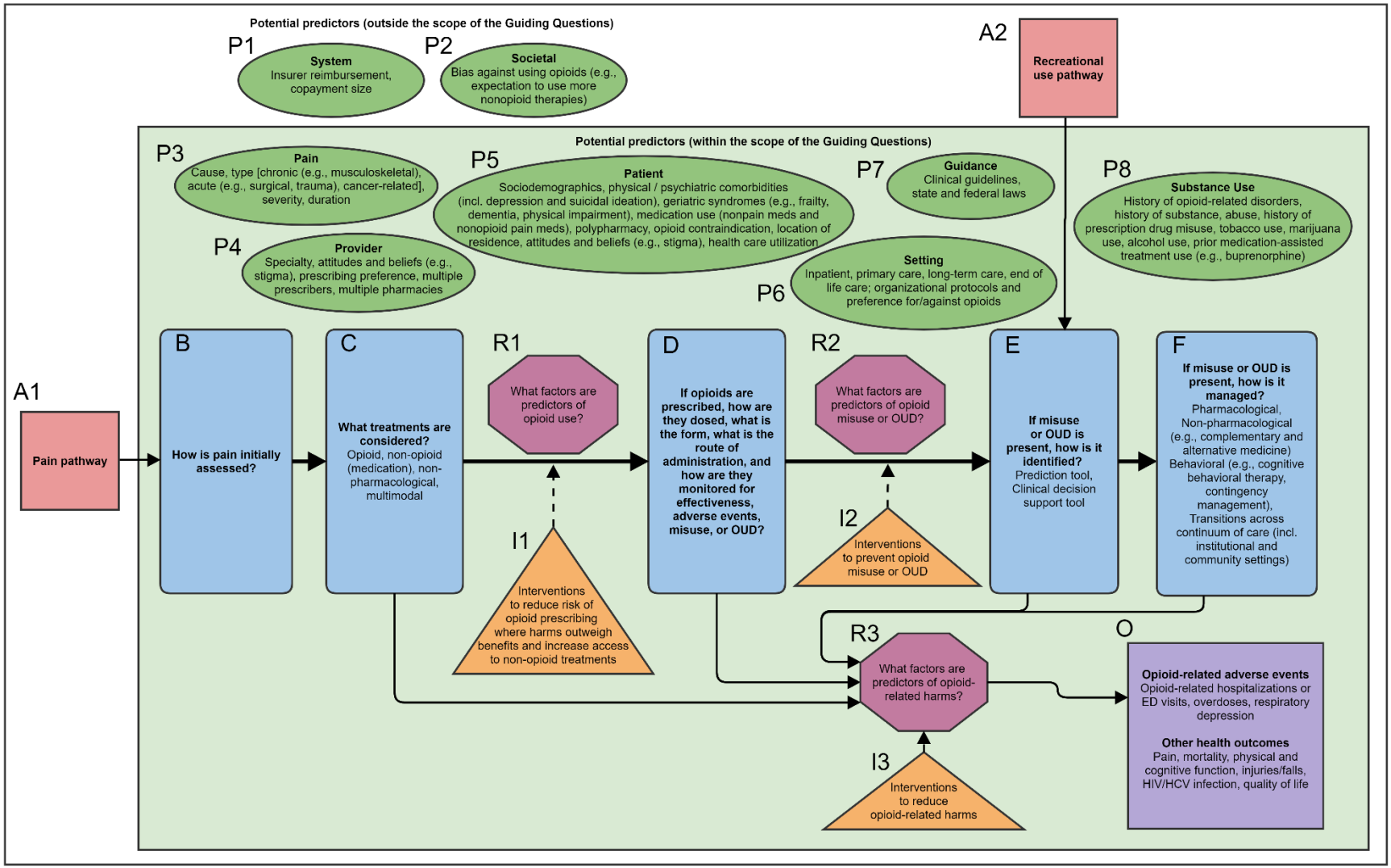
If older adults do engage in opioid misuse or develop OUD, the next stage in the care pathway (**Rectangle E**) relates to how misuse or OUD is identified. Similar to the idea that prediction tools could be used to assess likely benefits and harms at the time of opioid prescribing to reduce prescribing where harms outweigh benefits, tools could also help practitioners (and patients) determine who is at increased risk of opioid misuse and OUD. **Rectangle E** is where individuals from the "recreational use pathway" (**Box A2**) may enter into the Conceptual Framework. Identification of misuse or OUD among this group of older adults may require different methods or tools from those used to identify misuse or OUD among those in the "pain pathway".

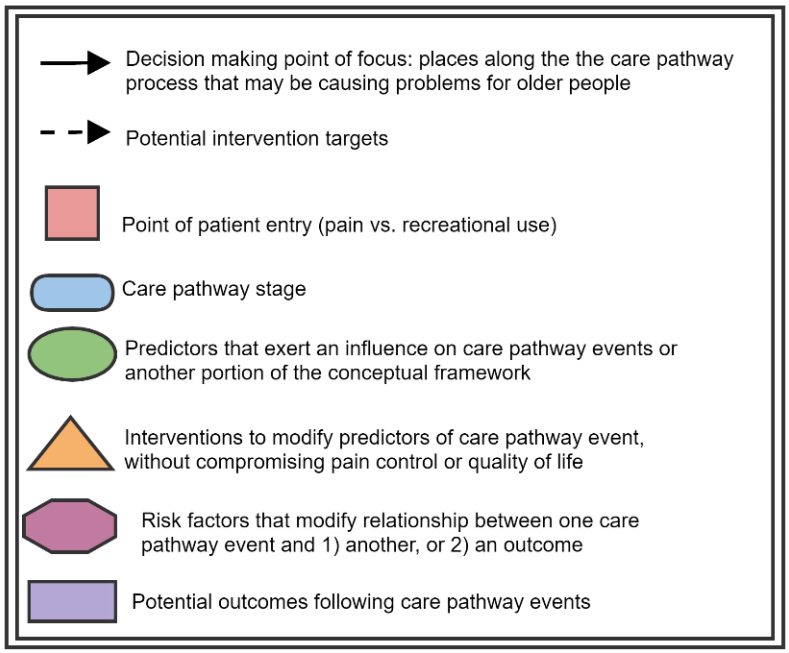
Older adults identified with opioid misuse or OUD require management to reduce or stop associated harms (**Rectangle F**). Potential management options include interventions to coordinate care or improve healthcare transitions, pharmacological, nonpharmacological, and behavioral treatments, and combinations thereof. Examples include naloxone availability (to acutely counteract opioid overdose), ensuring proper nutrition, and preventing homelessness among older adults with misuse or OUD.

Each care pathway stage (**Rectangles C through F**) may ultimately give rise to an array of factors that predict opioid-related harms other than misuse or OUD (**Octagon R3**). Interventions (**Triangle I3**) could affect the factors that predict opioid-related harms (other than opioid misuse or OUD). If effective, they would prevent opioid-related adverse events and optimize other health outcomes (**Box O)**. Rather than solely preventing harms, some intervention may also improve affected individuals' quality of life, physical and cognitive function, and other outcomes, and ultimately reduce death. Improved knowledge of factors to predict these outcomes could inform an understanding of which interventions (in **Triangle I3**) might be most effective.

As indicated by the light green rectangle that encompasses most of the conceptual framework, there are many interconnected variables or potential predictors (represented by green ovals **P1-P8** at the top of the figure) that influence many aspects of the care management process and associated events, as well as each other. These relationships are too numerous, implicit, and complex to be depicted using arrows in the framework and thus are shown through the shaded rectangle. They include pain type, provider, patient, setting, guidance, and substance use factors (ovals **P3-P8**). Other predictors, included outside the light green rectangle, represent system and societal factors (ovals **P1** and **P2**) outside the scope of this Technical Brief. These are likely to impact opioid use, misuse, and OUD, but are beyond the scope of research considered.

Figure 1. Conceptual framework





Abbreviations: ED = emergency department, HCV = hepatitis C virus, HIV = human immunodeficiency virus, OUD = opioid use disorder.

Evidence Map

The literature search yielded 5402 citations, of which 3312 were screened in duplicate. The remaining citations were predicted to be of low probability of relevance by software. Additional details about screening can be found in Appendix D. Overall, we identified 150 articles of potential interest that addressed associations or interventions. From these, we included 35 studies that reported multivariable analyses of factors associated with outcomes of interest, and 14 studies that evaluated interventions.

Detailed information about these 49 studies are included in Appendix D, Tables D-3 to D-6. The other 101 articles reported unadjusted (univariable) or other analyses and were thus excluded. Appendix E (Tables E-1 and E-2) lists the rejected articles and reasons for rejection. Appendix D (first paragraph) provides further details about the literature flow.

We first present the evidence base of factors independently associated with outcomes of interest followed by the evidence base of relevant interventions.

Relation of Evidence to Conceptual Framework

Factors Associated With Opioid-Related Outcomes in Older Adults

Overview of Literature

We restricted our review to the 35 studies that reported multivariable analyses, since findings from unadjusted analyses are more likely to be spurious and therefore do not add much to the evidence base (for the purpose of determining likely candidates for independent predictors of outcomes of interest). None of the models (multivariable analyses) was designed or evaluated as a screening or prediction tool.

We organized the 35 studies based on their analyzed outcomes. We categorized these into seven overall types of outcomes:

i. long-term opioid use
ii. opioid-related disorders
iii. multiple opioid prescribers (or pharmacies)
iv. clinical harms, related to either mental or physical health conditions
v. opioid-related hospitalization or ED visit
vi. opioid overdose
vii. death

This categorization roughly corresponds to the temporal order that people interact with opioid use. Referring to the Conceptual Framework (Figure 1), category i aligns with opioid use (Octagon R1), categories ii and iii align with opioid misuse or OUD (Octagon R2 and Rectangle E) and categories iv to vii align with opioid-related adverse events and other health outcomes (Octagon R3 and Box O).

We also categorized the numerous specific evaluated factors into 31 categories that fell into 9 factor types, which are depicted in the Conceptual Framework (Figure 1) as noted below. These factors are:

- System factors: insurance feature (Oval P1)
- Pain factors: cause and severity (P3)
- Provider factors: specialty (P4)
- Patient factors (P5)
    - Demographics: age, gender, race/ethnicity
    - Socioeconomic factors: income, employment, education, rural vs. urban, social factors, insurance status
    - Health conditions: comorbidities (physical health), mental health, activities of daily living, quality of life, healthcare utilization
    - Pharmaceutical treatments: nonopioid pain treatments, nonpain treatments
- Guidance: opioid stewardship (P7)
- Substance use: opioid-related disorders (opioid misuse, OUD, high-risk behaviors), methadone use, number of opioid prescribers, substance misuse, tobacco use, benzodiazepine use or misuse (P8)
- Opioid factors: history of opioid use, opioid duration, opioid amount, opioid type, and opioid prescription rates (addressed in Rectangles C and D)

Evaluated factors did not evaluate societal factors (Oval P2) or setting factors (Oval P6).

Half (17 of 35) of the multivariable studies evaluated factors independently associated with long-term use of opioids. Many fewer studies evaluated outcomes pertaining to opioid-related harms (such as overdose or OUD) or high-risk or undesirable behaviors (such as opioid misuse). The factors most commonly evaluated included demographic factors, comorbidities, medication factors, history of pain or opioid use, social conditions, and history of substance use.

Roadmap for Reading the Description of the Evidence Map

We describe the evidence pertaining to each "predictor" octagon in the Conceptual Framework (Figure 1) separately. Namely, we separately describe studies pertaining to "predictors" of opioid use (Octagon R1), "predictors" of opioid misuse and OUD (Octagon R2), and "predic-

tors" of opioid-related harms (Octagon R3). While, in theory, we were seeking studies that evaluated predictors, many studies were either cross-sectional or otherwise did not evaluate whether variables included in their models predicted future events. We use the term "factor" to cover any variable entered into the multivariable models (including true predictors, risk factors, or other measures).

Within each "risk factor" category section (R1, R2, R3), we separately summarize particular categories (and subcategories) of outcomes (e.g., the category Opioid-Related Disorders, with the subcategories OUD, opioid misuse, and high-risk obtainment of prescription opioids). Within each (sub)section, we describe the evidence and discuss relevant research needs. Additional research needs are discussed at the end of this section on "Factors Associated With Opioid-Related Outcomes in Older Adults".

To help frame the following detailed summaries of the various association studies, in Table 1 we provide an overall summary of the factor-outcome pairs for which there were at least three studies, summarizing findings as well as consistency and strength of association (as defined in the Methods). This table summarizes all but sparse evidence (with only one or two studies).

Table 1. Summary of consistency and direction of associations across multivariable analyses

Outcome/Factor	Specific Factor	Strong + Assn	Weak + Assn	Strong − Assn	Weak − Assn	NS	Total	Consistency	Association
Long-term Opioid Use									
Opioid use	Early (or preoperative)	**6**	2				8	Consistent	Strong (mostly)
Opioid amount	More[B]	**5**	1				6	Consistent	Strong (mostly)
Pain cause	Back pain	**2**	2				4	Consistent	Strong/weak
Mental health	Depression		10				10	Consistent	Weak
Tobacco	Tobacco	**1**	3				4	Consistent	Weak (mostly)
Pain cause	Fibromyalgia		3				3	Consistent	Weak
Nonopioid pain treatment	NSAID		3				3	Consistent	Weak
Income	Low income[C]		5			1	6	Mostly consistent	Weak
Benzodiazepine use		**1**	3			1	5	Mostly consistent	Weak (mostly)
Substance misuse	Alcohol		1			4	5	Mostly consistent	NS
Healthcare utilization	Greater use	**1**				3	4	Mostly consistent	NS
Gender	Female		6	**1**	1	6	14	Variable	
Age	Younger[D]	**2**	4		1	3	10	Variable	
Race	Black		3		3	2	8	Variable	
Comorbidities	Dementia	**1**	1		2	1	5	Variable	
Opioid Misuse									
Gender	Female		1			2	3	Variable	
Substance misuse	Alcohol	**1**	1			1	3	Variable	

This table includes only factor-outcome pairs that were reported by at least 3 studies. Broad (nonspecific) factor categories (e.g., pain cause) are omitted. Within each outcome, factors are sorted based by consistency, strength of association, and number of studies. Specific factors within broad factor categories are included (i.e., pain cause/back pain, pain cause/fibromyalgia, mental health/depression, nonopioid pain treatment/NSAID, substance misuse/alcohol, race/black, comorbidities/dementia).

[B] Number of prescriptions or opioid dose.

[C] Note that this factor, and thus the directions of the associations, has been inverted compared with Table 2.

[D] Note that this factor, and thus the directions of the associations, has been inverted compared with Table 2.

Strong association: measure of association (e.g., relative risk) ≥2.0 (or ≤0.5) and statistically significant.
Weak association: measure of association between 0.5 and 2.0 and statistically significant.
NS = not statistically significant.
+ = "positive" association (presence or magnitude of factor associated with increased likelihood of outcome).
− = "negative" association (presence or magnitude of factor associated with decreased likelihood of outcome).
Consistent: 100% agreement in direction and statistical significance across studies, irrespective of strength of association.
Mostly consistent: ≥75% agreement (and <100%) across studies, irrespective of strength of association.
Variable: <75% agreement across studies.

Numbers of studies with strong associations are bolded. Columns are colored only to enhance visualization of directionality of association (see abbreviations list).

Other abbreviations: Assn = association, NSAID = nonsteroidal anti-inflammatory drug.

Factors Associated With Opioid Use (Octagon R1)

None of the eligible studies evaluated factors associated with opioid use, per se. However, the largest number of eligible studies evaluated long-term opioid use. As the studies acknowledge, long-term opioid use is not a clinical harm in and of itself, since chronic, long-term pain may require long-term analgesia, and thus appropriate long-term opioid use. Nevertheless, it is commonly considered a worrisome signal that the opioids are being used inappropriately. However, the evidence, in the general population, is sparse and inconclusive regarding whether long-term opioid use is itself a predictor of (or surrogate measure for) opioid misuse (or OUD).[61] Notably, as will be described in the next section, only a single study evaluated whether duration of opioid use is independently associated with opioid misuse. It found no statistically significant association with opioid abuse, but that it was associated with a higher risk of opioid dependence (both per International Classification of Diseases [ICD] codes).[62]

Thus, one set of studies has evaluated factors associated with opioid use among older adults, Octagon R1 in the Conceptual Framework (Figure 1): factors associated with long-term opioid use (Tables 2 to 5).

Factors Associated With Long-Term Opioid Use

Evidence Base

Seventeen studies reported multivariable models of long-term opioid use in older adults.[63-79] Definitions of long-term opioid use varied across studies: seven evaluated at timepoints between 3 and 6 months of use, two evaluated 9 to 12 month data, six evaluated approximately 1 year, and two did not define long-term opioid use.

In brief, several factor categories (and specific factors) have been found to be associated with increased likelihood of long-term opioid use. Furthermore, many of the associations are strong. Given the large number of specific factors evaluated, to help the reader, in addition to bolding the factor categories, in the text of this section we also underline the specific factor.

Demographic Factors Associated With Long-Term Opioid Use

Ten studies evaluated **age** (within the cohort of older adults) as a factor associated with long-term use (Table 2). Studies were variable in regard to whether age (within the cohort of older adults) is associated with increased likelihood of long-term opioid use; however, the majority of studies found (mostly weak) associations between <u>older</u> age and decreased likelihood of long-term opioid use. Among 14 studies evaluating **gender**, associations were also variable, but only

two found that men were more likely to use opioids long-term. Notably, the only strong association was in a study of people with oropharyngeal cancer that, counter to most others, found that men were twice as likely to have continuous opioid use at 6 months. Eight studies found variable associations between **race** and likelihood of long-term use, but all associations were weak (or nonsignificant). Among the six studies that reported statistically significant associations, three studies found that blacks (or non-whites) had an increased likelihood of long-term opioid use while three others found an association with decreased likelihood.

Health Status Factors Associated With Long-Term Opioid Use

Twelve studies evaluated a large range of **comorbidities**, both within and between studies (Table 2). Studies were variable in their findings, but most found that there were associations between at least some comorbidities and the likelihood of long-term opioid use; these associations were mostly weak. The only strong associations found were for presence of 3 to 4 comorbidities (in one study) and (separately) migraine, mild liver disease, and weight loss (not fully defined, but described in the study as a nutritional or medical comorbidity after total hip arthroplasty). A third study found a strong association between an AIDS diagnosis and a *decreased* likelihood of long-term opioid use. The evidence for dementia is variable among five studies: dementia was found to be strongly associated with increased likelihood of long-term use in one study and weakly associated in a second study, but, in contrast weakly associated with *decreased* likelihood in two other studies, and no significant association in the final study.

Four studies of **healthcare utilization** were *mostly consistent*, with three finding no statistically significant association with likelihood of long-term opioid use (Table 2). The exception found a strong association between "any hospitalization" and increased likelihood of long-term use. Eleven studies evaluated **mental health** factors. Ten of these studies were *consistent* in finding weak associations between depression and increased likelihood of long-term opioid use. Only psychosis, in a single study, was found to be strongly associated with increased likelihood of long-term opioid use. Two studies reported that people with schizophrenia or bipolar disease were less likely to use opioids long-term.

Socioeconomic and Related Factors Associated With Long-Term Opioid Use

Six studies evaluated measures of **income** as factors associated with long-term opioid use (Table 3). Although definitions of income status varied, six studies were *mostly consistent*, with five of the studies finding weak associations between higher income and *decreased* likelihood of long-term opioid use. Only two studies evaluated geographic location (categorized as **rural** in the table). One found that urban residents were (weakly) more likely to have long-term opioid use than "metropolitan" residents (they found no statistically significant association with rural residents). The other study found no statistically significant association with metropolitan residence.

Only two studies evaluated **social** factors (Table 3) and they evaluated different social constructs. One found that married participants had a (strongly) *decreased* likelihood of long-term opioid use. The other found that whether people dwelled in their home was not associated with long-term use. Only a single study evaluated **insurance** status, finding a weak association between Medicare Advantage coverage and increased likelihood of long-term opioid, relative to standard Medicare coverage.

Pain Factors Associated With Long-Term Opioid Use

Fourteen of the studies evaluated a variety of **causes of pain** (Table 4). In brief, a large number of specific causes were associated with long-term use. The four strong associations found were all musculoskeletal conditions: back pain (in two studies), bilateral total knee arthroplasty (TKA) (vs. unilateral TKA), and osteoporosis. Two specific causes of pain were evaluated by at least three studies, each with *consistent* findings. Long-term opioid use was associated with back pain in four studies (two strong, two weak associations) and with fibromyalgia in three studies (all weak)

Prescription Drug Treatment Factors Associated With Long-Term Opioid Use

Six studies evaluated (concomitant) **nonopioid pain treatments** as factors associated with long-term opioid use (Table 4). It should be noted that the concomitant use of nonopioid pain treatments may be a marker of less-well controlled chronic pain. The most frequently analyzed nonopioid pain treatment was nonsteroidal anti-inflammatory drugs (NSAIDs). The three studies were *consistent* in finding weak associations between NSAID use and long-term opioid use. Across the studies, the two strong associations were found with acetaminophen use (in one study) and with antineuropathic pain treatments (either antidepressants or antiepileptics, in one study). Five studies evaluated a variety of **nonpain treatments**. One of these found a weak association with rheumatoid arthritis; another found a weak association with anxiolytics.

Opioid Use Factors Associated With Long-Term Opioid Use

Eight studies evaluated different measures of **opioid use** (Table 4). The studies *consistently* found that prior use (including preoperative use) or early use after surgery or an injury were associated with increased likelihood of long-term opioid use; six of the eight studies found strong associations. Two studies disagreed regarding **dependence** as an associated factor. Neither study defined "dependence." One study found a weak association between dependence as an independent variable and opioid use 9 to 12 months postoperatively (as the dependent variable). The second study, counterintuitively, reported that people with opioid dependence (as a comorbidity) were almost half as likely to be using opioids 9 to 12 months postoperatively. No explanation for this finding was given. In contrast, six studies were *consistent* in finding that increased **opioid amounts** (more prescriptions or higher dose opioids) were strongly associated with long-term use (strong associations in five of the studies). This association was found for both greater number of prescriptions (four studies) and higher dose (two studies).

Two studies evaluated different **opioid types** (Table 4). The first study found that transdermal opioids were strongly associated with increased likelihood of long-term use. This study also found a weak association with the use of strong opioids (see Table 4 footnote). The other study found a strong association for oxycodone use (compared with hydrocodone) but no statistically significant associations with codeine use or long-acting opioid use.

Substance Use and Misuse Factors Associated With Long-Term Opioid Use

A single study reported that **methadone** users were at strongly increased likelihood of long-term use (Table 5). Twelve studies evaluated (nonopioid) **substance misuse** as factors associated with long-term opioid use. The studies were *variable* in their findings, with eight finding (mostly weak) associations between substance (or "drug") use (or abuse; mostly not specifically defined) and long-term opioid use, but four finding no significant association. However, most of the associations with specific substances were not statistically significant. In particular, five studies were *mostly consistent* in finding no significant association with alcohol abuse, with only one study

finding a weak association. This study was also the only study to evaluate use of marijuana, cocaine, and amphetamines, finding that marijuana use was weakly associated with increased likelihood of long-term opioid use, but there were nonsignificant associations with cocaine and amphetamine use.

Four studies evaluated **tobacco use** as a factor associated with long-term opioid use (Table 5). The studies were *consistent* in finding that people who used tobacco had increased likelihood of long-term opioid use, but only one of the studies found a strong association. Five studies were *mostly consistent* that people who used **benzodiazepines** also had increased likelihood of long-term opioid use. One of these five studies found a strong association, but one found no statistically significant association.

Two studies evaluated proxy measures for **opioid stewardship** (Table 5). One found a strong association between prescribers being concordant with guidance and decreased likelihood of long-term opioid use. Based on evaluation of a claims database,[72] Jeffrey 2018 found that those participants (not seen in an ED) whose opioid prescriptions were for no more than 3 days, no more than 50 mean morphine equivalents, and were not for a long-acting opioid were less than one-fourth as likely to use opioids for at least 12 months. A similar, but weak association, was found for those participants seen in the ED. In the second study, participants whose medical records indicated that they were provided with any type of tapering plan for their opioids had a (weakly) decreased likelihood of long-term opioid use. Neither study evaluated opioid stewardship as an intervention, per se.

Summary of Factors Associated With Long-Term Opioid Use

Overall, 17 multivariable models have evaluated a large number of potential factors associated with long-term opioid use among older adults. Table 1 highlights the findings for factor-outcome pair associations analyzed by at least three studies.

Studies were **consistent** (in full agreement) that—in eight studies—opioid use prior to surgery or injury (or early use after surgery) and—in six studies—greater amount of opioids (more prescriptions or higher dose) are the factors *with mostly strong associations*.

Other consistent associations, but with largely weak associations, were found with back pain (4 studies, two with strong associations), depression (10 studies, all weak associations), tobacco use (4 studies, one with a strong association), fibromyalgia (3 studies, all weak associations), and concomitant NSAID use (3 studies, all weak associations).

Studies were **mostly consistent** (≥75% agreement) that low income (5 of 6 studies, all with weak associations) and benzodiazepine use (4 of 5 studies, 1 with a strong association) were associated with long-term opioid use.

Studies were also mostly consistent that alcohol abuse (4 of 5 studies) and healthcare utilization (3 of 4 studies) were *not* associated with long-term opioid use; however, one of these latter studies found a strong association between "any hospitalization" and long-term use.

Factors with variable findings of association (evaluated by at least 3 studies) included gender (6 of 14 studies found weak associations with female gender; 2 found associations with male gender, one strong), age among older adults (6 of 10 studies found mostly weak associations with younger age; 1 found a weak association with older age), black race (3 each, among 8 studies, found weak associations with increased and with decreased likelihood), and dementia (2 each, among 5 studies found associations with increased and with decreased likelihood).

Research Needs on Predictors of Long-Term Opioid Use

Additional research would be valuable regarding how specific comorbidities, geographic factors (e.g., rural/urban setting), social determinants of health, insurance features (type, status), use of specific treatments for indications other than pain, specific opioid types and methadone, and opioid stewardship programs relate to long-term opioid use. To improve confidence, new research may be warranted to test the consistency of race and healthcare utilization characteristics as predictors of long-term opioid use.

Table 2. Heat map of multivariable analyses of demographic and health status factors and long-term opioid use[E]

Study PMID	Outcome (Per Study)	Age	Gender	Race	Comorbidity	HC Util	Mental Health
Al Dabbagh 2016 26707940	Earlier discontinuation of opioid prescriptions (undefined)[F]	↓ (Older)	NS				
Cancienne 2018 28887020	Prolonged postoperative opioid use (3-6 months)		NS	↓ (Black)	↑ Obesity		↑ Depression
Curtis 2017 28635179	Long-term opioid use (undefined)	▽ (Older)	↓ (Female)	↑ Black	↑↓ Multiple (Multiple)[G]	⬆ Hospitali-zation [DME weak]	↑ Depression Anxiety
Daoust 2018 28767563	Opioid use 1 year after injury		↑ Female			NS	↑ Depression
Hadlandsmyth 2018 28927564	Opioid use at 12 months	NS	NS	NS	NS [Dementia NR]	NS	NS [Depression NR]
Hamina 2017 28092324	Long-term opioid use (6 months)	↑ Older	↑ Female		↑ Multiple, Including dementia		
Inacio 2016 27130165	New chronic opioid use (3-4 months)		↑ Female		⬆ Multiple[H] Dementia		↑ Depression
Jain 2018 29561298	Long-term opioid use (12 months)	⬇ (Older)	↑ Female	↑ Black			↑ Depression Anxiety
Karttunen 2019 30370943	Prolonged opioid use (3 months)	↓ (Older)			↑↓ Multiple (Alzheimer)		↑↓ Depression or bipolar (Schizophre-nia)
Lalic 2018 29451672	Opioid persistence (12 months)		NS		⬆ 3-4 comorbidities		⬆ Psychosis [Depression, weak]

[E] 2 studies that evaluated long-term opioid use did not evaluate the factors in this table: Alam 2012 (PMID 22412106), Jeffrey 2018 (PMID 28967517).
[F] Note that this outcome is of short, not prolonged, duration of use. The arrows in this row are consistent with other studies (up arrows indicated increased risk of *not* early discontinuation).
[G] Seven medical conditions were weakly associated with increased risk, three medical conditions were weakly associated with decreased risk.
[H] Migraine, mild liver disease, weight loss

Study PMID	Outcome (Per Study)	Age	Gender	Race	Comorbidity	HC Util	Mental Health
Lindestrand 2015 25952252	Persistent opioid use (3-6 months)	NS	NS		NS (including dementia)	NS	
McDermott 2019 30396321	Continuous opioid use at 6 months	⬇ (Older)	⬇ (Female)	NS	NS (Dementia NR)		
Namba 2018 29753617	Number of prescriptions days 271-360 postoperative	NS	NS	↑↓ Black (Asian)	↑/⬇ Multiple, weak (AIDS, strong) (Dementia, weak)		↑↓ Depression, others (Bipolar)
Rao 2018 29891412	Opioid use days 271-360 postoperative		↑ Female	↓ (Black)	↑ ASA Class ≥3 Neurodegenerative		↑ Depression Anxiety
Shah 2019 31026356	Prolonged opioid prescribing (3 months)	↓ (Older)	↑ Female	↓ (Non-White)	↑ Cancer Charlson Comorbidity Score		↑ Depression

The heat map lays out each analyzed outcome within each article across rows. The colors and arrows indicate which factor categories were reported in each article and the strength and direction of the association, as described in the code below. Direction of the arrows indicates the direction of the association. Accompanying text within the cells indicates the factor that is at increased risk (e.g., females were at increased risk of opioid use 1 year after injury). Downward arrows are accompanied by text (in parentheses) that indicates the factor that is at *decreased* risk for the outcome, in keeping with the direction of the arrow (e.g., people in older age categories at *decreased* risk of long-term opioid use). In the Comorbidity column, dementia is also highlighted since it frequently, but not universally, was associated with decreased risk, in contrast with other comorbidities.
Across heat map tables, the columns are presented in the same order: demographics, markers of health status, socioeconomic and related factors, pain cause and severity, healthcare specialist, opioid factors, other medication factors, opioid misuse, other substance use/misuse, and opioid stewardship. Studies are presented in alphabetical order.

Abbreviations: ASA = American Society of Anesthesiologists, DME = durable medical equipment use, HC Util = healthcare utilization, NR = not reported, PMID = PubMed identifier.

Code (for all heat maps):

- Bright pink ⬆ = Strong, statistically significant association between (categorical) factor and higher risk of outcome (e.g., measure of association ≥2).
- Light orange ↑ = Weak, statistically significant association between (categorical) factor and higher risk of outcome (e.g., measure of association <2).
- Light pink △ = statistically significant "positive" association between (higher values of a) continuous factor and risk of outcome (no estimate of "strength" of association).
- Bright blue ⬇ = Strong, statistically significant association between (categorical) factor and lower risk of outcome (e.g., measure of association ≤0.5).
- Light blue ↓ = Weak, statistically significant association between (categorical) factor and lower risk of outcome (e.g., measure of association >0.5).
- Middle blue ▽ = statistically significant "negative" association between (lower values of a) continuous factor and risk of outcome (no estimate of "strength" of association).
- Grey NS = no statistically significant association between factor and outcome.
- Light yellow Mixed/variable directionality or strength of association. Each arrow is coded as above.

Table 3. Heat map of multivariable analyses of socioeconomic and related factors and long-term opioid use[I]

Study PMID	Outcome (Per Study)	Income	Rural	Social	Insurance
Curtis 2017 28635179	Long-term opioid use (undefined)	↓ (High income)			
Hamina 2017 28092324	Long-term opioid use (6 months)	↓ (High SES)			
Jain 2018 29561298	Long-term opioid use (12 months)				↑ MCare Advantage
Karttunen 2019 30370943	Prolonged opioid use (3 months)	↓ (High SES)			
Lalic 2018 29451672	Opioid persistence (12 months)	↓ (No subsidy)			
Lindestrand 2015 25952252	Persistent opioid use (3-6 months)			NS	
McDermott 2019 30396321	Continuous opioid use at 6 months	NS	NS	↓ (Married)	
Shah 2019 31026356	Prolonged opioid prescribing (3 months)	↓ (Not MCaid eligible)	↓ (Non-urban)		

See legend for Table 2.

Abbreviations: MCaid = Medicaid, MCare Advantage = Medicare Advantage, NS = not statistically significant, PMID = PubMed identifier, SES = socioeconomic status.

[I] 9 studies that evaluated long-term opioid use did not evaluate the factors in this table: Al Dabbagh 2016 (PMID 26707940), Alam 2012 (PMID 22412106), Cancienne 2018 (PMID 28887020), Daoust 2018 (PMID 28767563), Hadlandsmyth 2018 (PMID 28927564), Inacio 2016 (PMID 27130165), Jeffrey 2018 (PMID 28967517), Namba 2018 (PMID 29753617), Rao 2018 (PMID 29891412).

Table 4. Heat map of multivariable analyses of pain, prescription drug, and opioid use factors and long-term opioid use[J]

Study PMID	Outcome (Per Study)	Pain Cause	Nonop Pain Tx	Nonpain Tx	Opioid Use	Opioid Dependence	Opioid Amount	Opioid Type
Al Dabbagh 2016 26707940	Earlier discontinuation of opioid prescriptions (undefined)[K]	NS (injuries)						
Alam 2012 22412106	Opioid use ~10-14 months postoperative				↑ Early use			
Cancienne 2018 28887020	Prolonged postoperative opioid use (3-6 months)	↑ Back pain, fibromyalgia, migraine,	↑ Muscle relaxant	↑ Anxiolytic	⬆ Pre-op		⬆ Rxs	
Curtis 2017 28635179	Long-term opioid use (undefined)	⬆ Back pain [Cancer, rheumatic weak]	↑ NSAID	↑ Bio-DMARD				
Daoust 2018 28767563	Opioid use 1 year after injury	↑ Various injuries			⬆ Early use		⬆ Rxs	
Hadlandsmyth 2018 28927564	Opioid use at 12 months	⬆ Bilateral TKA	↑ Muscle relaxant	NS (various)	↑ Pre-op			
Hamina 2017 28092324	Long-term opioid use (6 months)	↑ Multiple skeletal						
Inacio 2016 27130165	New chronic opioid use (3-4 months)	⬆ Back pain	⬆ Antidepressant or antiepileptic	NS (various)				
Jain 2018 29561298	Long-term opioid use (12 months)	↑ Arthritis			⬆ Pre-op			
Karttunen 2019 30370943	Prolonged opioid use (3 months)	↑ RA, cancer						

[J] 1 study that evaluated long-term opioid use did not evaluate the factors in this table: Jeffrey 2018 (PMID 28967517).
[K] Note that this outcome is of short, not prolonged, duration of use. The arrows in this row are consistent with other studies (up arrows indicated increased risk of *not* early discontinuation).

Study PMID	Outcome (Per Study)	Pain Cause	Nonop Pain Tx	Nonpain Tx	Opi-oid Use	Opioid Depend-ence	Opioid Amount	Opioid Type
Lalic 2018 29451672	Opioid persistence (12 months)		⬆ Acetamino-phen [NSAID, pregabalin weak]	NS (stimu-lants)			⬆ MME	⬆ Transder-mal[L] Strong opi-oids[M]
Lindestrand 2015 25952252	Persistent opioid use (3-6 months)	⬆ Osteoporo-sis			⬆ Pre-op			
McDermott 2019 30396321	Continuous opioid use at 6 months	NS (Cancer-re-lated)			⬆ Prior		⬆ High-dose	⬆NS Oxycodone [Codeine, long-acting NS]
Namba 2018 29753617	Number of prescriptions days 271-360 postoperative	↑↓ Back pain, fibromyal-gia, others (Carpal tun-nel, joint pain)	↑ NSAID			↓ (Depend-ence)	△ Rxs	
Rao 2018 29891412	Opioid use days 271-360 postoperative	↑↓ Fibromyal-gia multiple musculo-skeletal (Fracture, Limb pain)				↑ Depend-ence	⬆ Rxs	
Shah 2019 31026356	Prolonged opioid prescribing (3 months)	↑ Lung can-cer[N]			⬆ Prior			

See legend for Table 2.

Abbreviations: Bio-DMARD = biologic disease-modifying antirheumatic drug, MME = mean morphine equivalents, Nonop Pain Tx = nonopioid pain treatment (use of), Nonpain Tx = nonpain treatment (use of), NS = not statistically significant, NSAID = nonsteroidal anti-inflammatory drug, PMID = PubMed identifier, Pre-op = preoperative use, Rxs = (larger number of) prescriptions, RA = rheumatoid arthritis, TKA = total knee arthroplasty (replacement).

[L] The study also found a weak association with use of strong opioids.

[M] Strong opioids included: morphine, oxycodone, buprenorphine, fentanyl, hydromorphone, and methadone. Weak opioids included single-ingredient codeine, combination codeine preparations, tramadol, and tapentadol.

[N] Versus prostate cancer.

Table 5. Heat map of multivariable analyses of substance use or misuse and related factors and long-term opioid use[O]

Study PMID	Outcome (Per Study)	Methadone	Substance Misuse	To-bacco	Benzo	Opioid Stewardship
Cancienne 2018 28887020	Prolonged postoperative opioid use (3-6 months)	↑ Methadone use	↑ Alcohol abuse, marijuana use [Cocaine use, amphetamine use NS]	↑ Tobacco		
Daoust 2018 28767563	Opioid use 1 year after injury		NS (Alcoholism)			
Hadlandsmyth 2018 28927564	Opioid use at 12 months		↑ Substance use		NS	
Hamina 2017 28092324	Long-term opioid use (6 months)		↑ Substance abuse		↑ Benzo	
Inacio 2016 27130165	New chronic opioid use (3-4 months)		NS (Alcohol abuse)		↑ Benzo	
Jain 2018 29561298	Long-term opioid use (12 months)		↑ Drug abuse	↑ Tobacco		
Jeffrey 2018 28967517	Long-term opioid use (12 months)					↓ (Guideline concord-ant)[P]
Karttunen 2019 30370943	Prolonged opioid use (3 months)		↑ Substance abuse		↑ Benzo	
Lalic 2018 29451672	Opioid persistence (12 months)		NS (Alcohol dependence)	↑ Tobacco	↑ Benzo	
Lindestrand 2015 25952252	Persistent opioid use (3-6 months)					↓ (Tapering plan)[Q]
McDermott 2019 30396321	Continuous opioid use at 6 months		NS (Alcohol or substance abuse)	↑ Tobacco		
Namba 2018 29753617	Number of prescriptions days 271-360 postoperative		↑ Substance abuse			
Rao 2018 29891412	Opioid use days 271-360 postoperative		↑ Substance abuse			
Shah 2019 31026356	Prolonged opioid prescribing (3 months)		↑ Drug abuse [Alcohol abuse NS]			

[O] 4 studies that evaluated long-term opioid use did not evaluate the factors in this table: Al Dabbagh 2016 (PMID 26707940), Alam 2012 (PMID 22412106), Curtis 2017 (PMID 28635179), Hoffman 2017 (PMID 28531306).
[P] Administrative claims database determination that prescriptions were for ≤3 days, ≤50 mean morphine equivalents/day, and not a long-acting opioid.
[Q] Nonspecific tapering plan, based off of chart review.

See legend for Table 2.

Abbreviations: Benzo = benzodiazepine use, NS = not statistically significant, PMID = PubMed identifier.

Factors Associated With Opioid-Related Disorders (Octagon R2)

Two sets of studies have evaluated factors associated with opioid-related disorders (Octagon R2 in Figure 1: Conceptual Framework):

i. Opioid-related disorders (Tables 6 to 8)
ii. Multiple opioid prescribers (Table 9)

Factors Associated With Opioid-Related Disorders

Evidence Base

Six studies reported multivariable model of factors associated with opioid-related disorders, including opioid use disorder (OUD), opioid misuse, and high-risk obtainment of prescription opioids (Tables 6 to 8).[62, 80-84] The models evaluated a large number of factors related to demographics, patient health status, socioeconomic and related factors, insurance status, pain factors, opioid use factors, and substance use/misuse.

Factors Associated With Opioid Use Disorder

Only one study evaluated the risk of **OUD**, finding that the strongest factors were **mental health** (history of anxiety disorder; Table 6), **pain severity** ("interference," whether one's pain interferes with their daily activities; Table 8), and other **substance misuse** (both marijuana and alcohol; Table 8). The model also found evidence that younger **age** and Hispanic **ethnicity** (Table 6), being **unemployed** (Table 7), and **using tobacco** (Table 8) are associated with increased risk of OUD.

Factors Associated With Opioid Misuse

Four studies evaluated **opioid misuse** (or "abuse"). Substance misuse and gender were the only factors evaluated by at least three studies. Three studies had *variable* findings regarding **substance misuse**, specifically alcohol (Table 8): one study found a strong association between a history of an alcohol-related healthcare visits and opioid misuse, another found a statistically significant association between higher scores on the CAGE Questions for Alcohol Use and misuse, but a third study found no statistically significant association between hazardous drinking and opioid misuse. Three studies also had *variable* findings regarding **gender** (Table 6): one study found a weak association that women were at increased risk of opioid use, but the other two found no statistically significant difference between genders.

Rural versus urban residence was evaluated by two studies, both of which found no association (Table 7). Among the other factor categories evaluated by two studies (**age**, **comorbidities**, **mental health conditions** [Table 6], **cause of pain**, and **pain severity** [Table 8], in all cases one study found a statistically significant association and the second study found no statistically significant association). Other factors were evaluated by only a single study.

Factors Associated With High-Risk Behaviors

A single study evaluated high-risk obtainment of prescription opioids as an outcome. The study found strong associations for older **age** (≥65, at various thresholds vs. 60-64; Table 6), college **education** (Table 7), and **opioid misuse** (recreational use; Table 8). Increased associations were also found for **women** (Table 6) and people with less **social** connectedness (Table 7). No statistically significant associations were found for **quality of life** (Table 6) or **tobacco use** (Table 8).

Summary of Factors Associated With Opioid-Related Disorders

In summary, six studies have evaluated factors associated with opioid-related disorders among older adults, including OUD, opioid misuse, and high-risk behaviors, but since the researchers largely analyzed different sets of factors, there is little consistency or replication across models. Three studies each reported variable findings regarding the associations of alcohol misuse and of gender with opioid misuse. Only single studies have evaluated specific factors and OUD or high-risk obtainment of prescription opioids among older adults. The OUD study reported strong associations with a history of anxiety, pain interference (a measure of pain severity), and both marijuana and alcohol use. Older age, college education, and a prior history opioid misuse were each found to be associated with high risk obtainment of prescription opioids (in one study).

Research Needs on Predictors of Opioid-Related Disorders

While several studies have evaluated the relationships between factors and opioid misuse in older adults, additional research is needed to confirm (or refute) the observed associations. To improve confidence and increase the strength of the evidence base, additional studies that include factors in common (i.e., analyzed by others) should be considered.

Furthermore, there is a need to develop and validate accurate measures of opioid misuse among older adults. Studies have used multiple concurrent or proximal dispensing of opioid medications (drawn from claims data) as a measure of opioid misuse, but research validating such measures was not identified, and questions remain about the appropriateness of such measures. Provider factors, such as poor communication and coordination, could be an equally plausible explanation for the presence of multiple opioid prescriptions or dispensing in an older adults' drug claims. The use of multiple prescribers and pharmacies as a proxy for opioid misuse was also common, especially in large administrative database studies. Research should explicitly focus on the performance characteristics of various measures combining number of days of overlap between opioid prescriptions, number of different opioid prescribers, and number of different opioid dispensing pharmacies. If many such measures are, in fact, not a good proxy for opioid misuse (e.g., because these are actually palliative care patients appropriately using opioids), then much of the limited evidence base on factors associated with opioid misuse in older adults is unlikely to be provide information useful for identifying opioid misuse.

In addition, more research is necessary to understand the role of stress, anxiety, depression, and other behavioral and mental health conditions in increasing the risks of opioid misuse and development of OUD. If these conditions are associated with opioid misuse and OUD among older adults, stress, mental health conditions, and behavioral conditions may serve as key predictors to intervene on.

Table 6. Heat map of multivariable analyses of associations between demographic and health status factors and opioid-related disorders[R]

Study PMID	Outcome (Per Study)	Age	Gender	Race	Comorbidity	ADL	QoL	Mental Health
	Opioid use disorder							
Choi 2017 28699829	Opioid use disorder	▽ (Older)	NS	↑ Hispanic	NS			⬆ Anxiety
	Opioid misuse							
Carter 2019 30863796	Opioid misuse	⬇ (Older)	↑ Female		△ Chronic conditions			
Cochran 2017 28489491	Prescription Opioid Misuse Index		NS		NS			NS
Park 2010 20664342	Opioid misuse	NS	NS	NS		▽ (Better ADL)		△ Depression
	High risk behaviors							
Gold 2016 27564407	High-risk obtainment of prescription opioids	⬆ Older	↑ Female				NS	

The heat map lays out each analyzed outcome within each article across rows. The colors and arrows indicate which factor categories were reported in each article (or outcome) and the strength and direction of the association, as described in the code below. Direction of the arrows indicates the direction of the association. Accompanying text within the cells indicates the factor that is at increased risk (e.g., people in older age categories were at increased risk of high-risk obtainment of prescription opioids). Downward arrows are accompanied by text (in parentheses) that indicates the factor that is at *decreased* risk for the outcome, in keeping with the direction of the arrow (e.g., people in older age categories were at decreased risk of opioid use disorder).
Across heat map tables, the columns are presented in the same order: demographics, markers of health status, socioeconomic and related factors, pain cause and severity, healthcare specialist, opioid factors, other medication factors, opioid misuse, other substance use/misuse, and opioid stewardship. This heat map is organized by type of outcome (reason for hospitalization, reason for ED visit). Studies are presented in alphabetical order within outcome categories.

Abbreviations: ADL = activities of daily living, PMID = PubMed identifier, QoL = quality of life.

Code (for all heat maps):

- Bright pink ⬆ = Strong, statistically significant association between (categorical) factor and higher risk of outcome (e.g., measure of association ≥2).
- Light orange ↑ = Weak, statistically significant association between (categorical) factor and higher risk of outcome (e.g., measure of association <2).
- Light pink △ = statistically significant "positive" association between (higher values of a) continuous factor and risk of outcome (no estimate of "strength" of association).
- Bright blue ⬇ = Strong, statistically significant association between (categorical) factor and lower risk of outcome (e.g., measure of association ≤0.5).
- Light blue ↓ = Weak, statistically significant association between (categorical) factor and lower risk of outcome (e.g., measure of association >0.5).

[R] 1 study that evaluated opioid misuse did not evaluate the factors in this table: Hoffman 2017 (PMID 28531306).

Middle blue ▽ = statistically significant "negative" association between (lower values of a) continuous factor and risk of outcome (no estimate of "strength" of association).
Grey NS = no statistically significant association between factor and outcome.
Light yellow Mixed/variable directionality or strength of association. Each arrow is coded as above.

Table 7. Heat map of multivariable analyses of associations between socioeconomic and related factors and opioid-related disorders[S]

Study PMID	Outcome (Per Study)	Income	Employment	Education	Rural	Social	Insurance
	Opioid use disorder						
Choi 2017 28699829	Opioid use disorder		↑ Unemployed	NS		NS	
	Opioid misuse						
Carter 2019 30863796	Opioid misuse	↑ Poorer			NS		↑ Medicaid Medicare[T]
Cochran 2017 28489491	Prescription Opioid Misuse Index			NS	NS		
Park 2010 20664342	Opioid misuse					NS	
	High risk behaviors						
Gold 2016 27564407	High-risk obtainment of prescription opioids			⬇ (No college)		▽ (Connectedness)	

See legend for Table 6.

Abbreviations: NS = not statistically significant, PMID = PubMed identifier.

[S] 1 study that evaluated opioid misuse did not evaluate the factors in this table: Hoffman 2017 (PMID 28531306).
[T] Primary payer (Medicaid at increased risk compared with Medicare, which in turn was at increased compared with neither Medicare nor Medicaid).

Table 8. Heat map of multivariable analyses of associations between pain and substance use disorder factors and opioid-related disorders

Study PMID	Outcome (Per Study)	Pain Cause	Pain Severity	Opioid Duration	Opioid Misuse	Substance Misuse	Tobacco
	Opioid use disorder						
Choi 2017 28699829	Opioid use disorder	NS	⬆ Interference			⬆ Marijuana Alcohol	↑ Use
	Opioid misuse						
Carter 2019 30863796	Opioid misuse	⬆ Injury				⬆ Alcohol	
Cochran 2017 28489491	Prescription Opioid Misuse Index		NS		△ Misuse	NS (alcohol)	
Hoffman 2017 28531306	Opioid abuse			NS			
	Opioid dependence (per ICD codes, not further defined)			⬆ ≥90 days			
Park 2010 20664342	Opioid misuse	NS	△ Severity			△ Alcohol	
	High risk behaviors						
Gold 2016 27564407	High-risk obtainment of prescription opioids				⬆ Misuse		NS

See legend for Table 6.

Abbreviations: NS = not statistically significant, PMID = PubMed identifier.

Factors Associated With Multiple Opioid Prescribers

Evidence Base

Only two studies reported a multivariable model of factors associated with having multiple opioid prescribers in older adults (Table 9).[85, 86] The models evaluated a variety of factors related to demographics, patient health status, socioeconomic and related factors, insurance status, pharmaceutical treatments, and substance use/misuse. While having multiple opioid prescribers is not technically an indication of opioid misuse, it might reflect patients intentionally seeking out multiple providers to procure more than recommended prescriptions (i.e., "doctor shopping") and also might indicate fragmented, and thus high-risk, patient care.[87-90] In the general population of all adults, multiple opioid pharmacies has been strongly associated with opioid abuse.[91]

The two models largely overlapped in their evaluated factors; however, consistency varied both across and within models. Both models evaluated **age** and found that among older adults, the younger individuals (i.e., 65 to 74 and 75 to 84 years of age compared to ≥85 years;[85] each age decile compared to ages 66 to 70 years[86]) were at increased risk of using multiple prescribers (or as shown in the table, that older age groups were at decreased risk), with either strong or weak associations. Similarly, both found that **insurance** coverage (lower copays, Medicare Advantage vs traditional Medicare, and Medicare Part D benefit in addition to VA only) was associated with increased risk, strongly for no copay versus full copay, weakly for Medicare Advantage versus other Medicare coverage.

One of the two studies found weak associations for **gender** and **race**, such that men and non-Hispanic blacks were at increased risk; however, the other study found no such statistically significant associations. The former study also found that **rural** residents were at decreased risk (weak association) with multiple prescribers, but the latter study found the opposite (also weak association). Regarding **income**, one study found weak associations between various measures of higher income and increased risk of multiple prescribers; the second study reported seemingly contradictory findings that higher median income was associated with lower risk, but that increased percentage of households below the poverty level (a poorly defined variable) was also associated with lower risk.

Among the factors evaluated by a single study only, strong associations were found for **mental health** conditions (sleep disorder and psychiatric diagnoses, but not suicide or self-injury), other associations were found for **comorbidities** (Hierarchical Condition Category risk score), **health utilization** (number of days), and **substance misuse**. No statistical association was found for **tobacco** use.

In summary, two multivariable models have identified a number of potential factors associated with having multiple opioid prescribers among older adults. Both found that younger age and specific insurance coverage factors (lower copays, Medicare Advantage vs. traditional Medicare, and Medicare Part D benefit in addition to VA only) were associated with having multiple prescribers. Other variables were inconsistently associated with having multiple opioid prescribers or were only evaluated by one model.

Research Needs on Predictors of Multiple Opioid Prescribers

Since only two studies are available and they report some inconsistencies in findings, additional research is necessary to identify predictors (or risk factors) for having multiple opioid prescribers in older adults. Additional studies should aim to include the factors examined by the prior two studies, in addition to other putative predictors, and assess the consistency of reported associations.

Furthermore, polypharmacy, not just coprescribing, deserves additional focus. Understanding the relationship between the number of medications an older adult is taking and subsequent opioid-related hospitalizations and ED visits would be a reasonable next step. Subdividing polypharmacy into potentially appropriate and inappropriate subtypes would then offer additional information valuable information. Medication appropriateness criteria like the Beers List might play a role in this future research.[92] Employing alternative measures of drug burden such as the Drug Burden Index, cumulative anticholinergic burden, and number of medications with sedative-hypnotic properties could also be valuable.[93]

Table 9. Heat map of multivariable analyses of associations between factors and multiple opioid prescribers

Study PMID	Outcome (Per Study)	Age	Gender	Race	Comorbidity	HC Util	Mental Health	Income	Rural	Insurance	Nonop Pain Tx	Nonpain Tx	Substance Misuse	Tobacco
Jena 2014 24553363	Multiple prescribers	↓ (Older)	↓ (Female)	↑ Non-Hispanic Black				↓ (Poorer)	↓ (Rural)	↑ MC Advantage	↑ Non-narcotic	↑ Various		
Suda 2017 28408172	Multiple prescribers	⬇ (Older)	NS	NS	△ HCC	△ Days of care	⬆ Sleep d/o Psych Dx	△▽ Variable[U]	↑ Rural	⬆ Smaller copay			↑ Abuse	NS

The heat map lays out each analyzed outcome within each article across rows. The colors and arrows indicate which factor categories were reported in each article (or outcome) and the strength and direction of the association, as described in the code below. Direction of the arrows indicates the direction of the association. Accompanying text within the cells indicates the factor that is at increased risk (e.g., non-Hispanic Blacks are at increased risk of having multiple prescribers). Downward arrows are accompanied by text (in parentheses) that indicates the factor that is at *decreased* risk for the outcome, in keeping with the direction of the arrow (e.g., people in older age categories at *decreased* risk of having multiple prescribers).
Across heat map tables, the columns are presented in the same order: demographics, markers of health status, socioeconomic and related factors, pain cause and severity, healthcare specialist, opioid factors, other medication factors, opioid misuse, other substance use/misuse, and opioid stewardship. Studies are presented in alphabetical order.

Abbreviations: HC Util = healthcare utilization, HCC = Hierarchical Condition Category risk score, MC = Medicare, Nonop Pain Tx = nonopioid pain treatment (use of), Nonpain Tx = nonpain treatment (use of), PMID = PubMed identifier, Psych Dx = psychiatric diagnosis, Sleep d/o = sleep disorder.

Code (for all heat maps):

- Bright pink ⬆ = Strong, statistically significant association between (categorical) factor and higher risk of outcome (e.g., measure of association ≥2).
- Light orange ↑ = Weak, statistically significant association between (categorical) factor and higher risk of outcome (e.g., measure of association <2).
- Light pink △ = statistically significant "positive" association between (higher values of a) continuous factor and risk of outcome (no estimate of "strength" of association).
- Bright blue ⬇ = Strong, statistically significant association between (categorical) factor and lower risk of outcome (e.g., measure of association ≤0.5).
- Light blue ↓ = Weak, statistically significant association between (categorical) factor and lower risk of outcome (e.g., measure of association >0.5).
- Middle blue ▽ = statistically significant "negative" association between (lower values of a) continuous factor and risk of outcome (no estimate of "strength" of association).
- Grey NS = no statistically significant association between factor and outcome.
- Light yellow Mixed/variable directionality or strength of association. Each arrow is coded as above.

[U] Conflicting signals within regression (median income vs. percent of households below poverty level).

Factors Associated With Opioid-Related Harms (Octagon R3)

Four sets of studies have evaluated factors associated with opioid-related harms (Octagon R3 in Figure 1: Conceptual Framework):

i. Mental or physical health harms (Table 10)
ii. Hospitalizations or ED visits (Table 11)
iii. Opioid overdose (Table 12)
iv. Death (Table 13)

Factors Associated With Mental Health or Physical Health Harms

Evidence Base

Four studies reported eight multivariable models of associations between opioid-related factors and mental or physical health outcomes (harms) (Table 10).[62, 94-96] The models analyzed six mental health outcomes, including depression, suicidal ideation, and substance misuse (alcohol or nonalcohol, nonopioid substance misuse), and two physical health outcomes (hip fracture and respiratory exacerbation). The models evaluated the association between these factors and opioid use, opioid use duration, opioid type, and opioid misuse.

Given that each study reported a different outcome (or set of outcomes), there is a lack of replication of findings across studies. Across studies (and outcomes), there were disparate associations related to **opioid use**. There was a strong association between status as an opioid user and risk of hip fracture in one study, but a weak association that new opioid users were at *decreased* risk of respiratory exacerbations compared with nonusers. However, as described elsewhere, this study found strong associations between new opioid use and chronic obstructive pulmonary disease (COPD) or pneumonia-related death and weak associations with COPD or pneumonia-related ED visits and all-cause mortality. The third study that evaluated opioid use found no statistically significant association between past-year opioid use (without misuse) and suicidal ideation.

Opioid use duration was evaluated by two studies across six outcomes. Longer duration of opioid use was strongly associated with increased risk of hip fracture and weakly associated with depression and other substance (nonalcohol, nonopioid) dependence, but not "alcohol abuse", other "substance abuse", or other substance overdose.

Opioid type and opioid misuse were each evaluated by a single study. **Opioid type** (buprenorphine and, separately, strong opioids) was found to be strongly associated with increased risk of hip fracture. **Opioid misuse** was found to be weakly associated with increased risk of suicidal ideation.

In summary, multivariable models have identified various measures of opioid use and misuse as potential factors associated with mental and physical health harms, but given the heterogeneity of analyzed outcomes and the sparseness of evaluated associations, no given association has been replicated.

Research Needs on Predictors of Mental Health or Physical Health Harms

Few studies have evaluated mental and physical health harms, each evaluating a unique set of outcomes. Additional studies are needed that focus on replication or better establish associations and replicate observed associations.

Furthermore, additional research is necessary on the relationships between isolation, psychiatric or mental health conditions, and caregiver support (lack thereof) and opioid-related harms.

Efforts to link measures of isolation and caregiver support to medication data, or to employ existing datasets that have already combined this information, would be worthwhile to generate more empirical evidence.

Table 10. Heat map of multivariable analyses of opioid-related factors and opioid-related harms

Study PMID	Outcome (Per Study)	Opioid Use	Opioid Duration	Opioid Type	Opioid Misuse
	Mental Health				
Hoffman 2017 28531306	Depression		↑ Long-term use		
	Alcohol abuse		NS		
	Other substance dependence		↑ Long-term use		
	Other substance abuse		NS		
	Other substance overdose		NS		
Schepis 2019 30328160	Suicidal ideation	NS			↑ Misuse
	Physical Health				
Taipale 2019 30325873	Hip fracture	⬆ Use	⬆ Long-term use	⬆ Buprenorphine Strong opioid	
Vozoris 2016 27418553	Respiratory exacerbation	↓ (New use)			

The heat map lays out each analyzed outcome within each article across rows. The colors and arrows indicate which factor categories were reported in each article (or outcome) and the strength and direction of the association, as described in the code below. Direction of the arrows indicates the direction of the association. Accompanying text within the cells indicates the factor that is at increased risk (e.g., those with long-term opioid use were at increased risk of depression). Downward arrows are accompanied by text (in parentheses) that indicates the factor that is at *decreased* risk for the outcome, in keeping with the direction of the arrow (e.g., new opioid users were at *decreased* risk of respiratory exacerbation compared to no opioid use).
Across heat map tables, the columns are presented in the same order: demographics, markers of health status, socioeconomic and related factors, pain cause and severity, healthcare specialist, opioid factors, other medication factors, opioid misuse, other substance use/misuse, and opioid stewardship. This heat map is organized by type of outcome (mental and physical health harms). Studies (and outcomes) are presented in alphabetical order within outcome category.

Abbreviation: PMID = PubMed identifier.

Code (for all heat maps):

Bright pink	⬆ = Strong, statistically significant association between (categorical) factor and higher risk of outcome (e.g., measure of association ≥2).
Light orange	↑ = Weak, statistically significant association between (categorical) factor and higher risk of outcome (e.g., measure of association <2).
Light pink	△ = statistically significant "positive" association between (higher values of a) continuous factor and risk of outcome (no estimate of "strength" of association).
Bright blue	⬇ = Strong, statistically significant association between (categorical) factor and lower risk of outcome (e.g., measure of association ≤0.5).
Light blue	↓ = Weak, statistically significant association between (categorical) factor and lower risk of outcome (e.g., measure of association >0.5).
Middle blue	▽ = statistically significant "negative" association between (lower values of a) continuous factor and risk of outcome (no estimate of "strength" of association).
Grey	NS = no statistically significant association between factor and outcome.
Light yellow	Mixed/variable directionality or strength of association. Each arrow is coded as above.

Factors Associated With Hospitalizations or ED Visits

Evidence Base

Four studies reported 10 multivariable models of opioid use-related factors associated with hospitalization and ED visits in older adults (Table 11).[85, 96-98] The models analyzed outcomes

pertaining to all-cause hospitalization, opioid-related hospitalization, nonopioid-specific hospitalization, all-cause ED visit, and nonopioid-specific ED visit. The models evaluated factors associated with number of prescribers and opioid use, type, and misuse.

Outcomes varied across studies. Two studies evaluated all-cause hospitalization and, separately, all-cause ED visits, but they evaluated different types of factors (opioid use and opioid type). Each of the other outcomes was evaluated by a single study.

The most commonly evaluated factor category was **opioid use** (7 analyses/outcomes in 2 studies), although it was variably defined (new opioid use; history of opioid use, not misuse). Most analyses found associations between opioid use and risk of hospitalization or ED visit. One study found no statistically significant association with COPD or pneumonia-related hospitalizations or intensive care unit admissions.

No other factor category was analyzed by more than a single study. One study found that **opioid type** (schedule II opioids) was weakly associated with increased risk of all-cause hospitalization and ED visits. One study found that **opioid misuse** was strongly associated with all-cause hospitalization and ED visits, but not statistically significantly associated with number of nights in the hospital or number of ED visits. One study found that increased **number of opioid prescribers** was strongly associated with increased risk of opioid-related hospitalizations.

In summary, four studies have reported multivariable analyses of opioid-related factors associated with hospitalization or ED visits among older adults with no replication of analyses. Overall, there is an indication that opioid use, opioid type, opioid misuse, and the number of opioid prescribers are all associated with increased risks of hospitalization and ED visits, but no specific analysis (between a given factor category and outcome category) was evaluated by more than one study.

Research Needs on Predictors of Hospitalizations or ED Visits

Each of the identified studies evaluated different combinations of factors and outcomes. Thus, additional studies are needed that focus on replication or better establish or reproduce observed associations.

Table 11. Heat map of multivariable analyses of factors associated with hospitalization or emergency department visits

Study PMID	Outcome (Per Study)	Opioid Use	Opioid Type	Opioid Misuse	No. Prescribers
	All-cause hospitalization				
Choi 2019 30585135	All-cause hospitalization	⬆ Use		⬆ Misuse	
	Number of nights in the hospital	↑ Use		NS	
Kuo 2016 26522794	All-cause hospitalization		↑ Schedule II		
	Opioid-related hospitalization				
Jena 2014 24553363	Opioid-related hospitalization				⬆ More prescribers
	Nonopioid-specific hospitalization				
Vozoris 2016 27418553	COPD or pneumonia-related hospitalization	NS			
	ICU admission during COPD or pneumonia-related hospitalization	NS			
	All-cause ED visit				
Choi 2019 30585135	All-cause ED visit	⬆ Use		⬆ Misuse	
	Number of ED visits	↑ Use		NS	
Kuo 2016 26522794	All-cause ED visit		↑ Schedule II		
	Nonopioid-specific ED visit				
Vozoris 2016 27418553	COPD- or pneumonia-related ED visit	↑ New use			

The heat map lays out each analyzed outcome within each article across rows. The colors and arrows indicate which factor categories were reported in each article (or outcome) and the strength and direction of the association, as described in the code below. Direction of the arrows indicates the direction of the association. Accompanying text within the cells indicates the factor that is at increased risk (e.g., opioid users were at increased risk of all-cause hospitalization).
Across heat map tables, the columns are presented in the same order: demographics, markers of health status, socioeconomic and related factors, pain cause and severity, healthcare specialist, opioid factors, other medication factors, opioid misuse, other substance use/misuse, and opioid stewardship. This heat map is organized by type of outcome (reason for hospitalization, reason for ED visit). Studies (and outcomes) are presented in alphabetical order within outcome categories.

Abbreviations: COPD = chronic obstructive pulmonary disease, ED = Emergency Department, ICU = Intensive Care Unit, PMID = PubMed identifier.

Code (for all heat maps):

- Bright pink ⬆ = Strong, statistically significant association between (categorical) factor and higher risk of outcome (e.g., measure of association ≥2).
- Light orange ↑ = Weak, statistically significant association between (categorical) factor and higher risk of outcome (e.g., measure of association <2).
- Light pink △ = statistically significant "positive" association between (higher values of a) continuous factor and risk of outcome (no estimate of "strength" of association).
- Bright blue ⬇ = Strong, statistically significant association between (categorical) factor and lower risk of outcome (e.g., measure of association ≤0.5).
- Light blue ↓ = Weak, statistically significant association between (categorical) factor and lower risk of outcome (e.g., measure of association >0.5).
- Middle blue ▽ = statistically significant "negative" association between (lower values of a) continuous factor and risk of outcome (no estimate of "strength" of association).
- Grey NS = no statistically significant association between factor and outcome.
- Light yellow Mixed/variable directionality or strength of association. Each arrow is coded as above.

Factors Associated With Opioid Overdose

Evidence Base

Three studies reported multivariable models of factors associated with opioid overdose in older adults (Table 12).[62, 99, 100] The models each evaluated a unique set of factors related to demographics, patient health status, opioid factors, and substance use/misuse.

One study, Lo-Ciganic 2019,[99] reported a unique analysis of a machine-learning algorithm, which produced a "prediction score" for 268 "predictor" candidates. They report the 50 predictors with the highest prediction scores. However, they do not report association estimates that are comparable to other studies. Upon reviewing their bar graph of the 50 highest predictor scores, we noted that six predictors had scores of 0.6 or higher and the rest had scores <0.4. We, thus, arbitrarily categorized the top scores as strong associations. These included **age** (direction not reported), **comorbidities** (disability status), **opioid amount** (separately, average and total mean morphine equivalents and number of opioid fills), and **substance misuse** (combined substance or alcohol use disorder).

We did not extract or tabulate the other 44 reported predictors; however, these included: **race** (not defined), other **comorbidities** (falls, fractures, and other injuries; area-level percentage of poor to fair health), **mental health** (mood disorders, anxiety disorders, psychoses), low **income** (low-income subsidy, area-level percentage of children in poverty), area-level percentage of **unemployment**, **insurance** status (area level penetration of Medicare Advantage, area level percentage of women in fee-for-service Medicare), **opioid type** (not defined; duration of short-acting opioid use, duration of long-acting opioid use), **nonpain treatments** (antidepressants), **opioid misuse** (days from last overdose event), other **substance misuse** (early refills, area-level percentage of excessive drinking, drug use disorders), and **benzodiazepine** use (and days of concurrent opioid and benzodiazepine use).

Also of note, as implied above, many of the predictors were poorly defined, such as age (for which no direction of association was indicated), type of opioid, and race (for which there was no indication of which category was at increased risk).

The second study reported only that **long-term opioid use** was strongly associated with opioid overdose. The third study found that **opioid misuse** (supplied opioids exceeded daily prescription) and increased **numbers of prescribers** or, separately, pharmacies were both strongly associated with opioid overdose.

In summary, three studies evaluated factors associated with opioid overdose in older adults. One study ranked numerous (often poorly defined) factors by strength of association; the other two evaluated nonoverlapping sets of factors. Nevertheless, one study each reported strong associations for opioid overdose among older adults with age, disability status, opioid use duration, amount of opioids used, opioid misuse, other substance misuse, and number of opioid prescribers.

Research Needs on Predictors of Opioid Overdose

Most of the results are from various machine learning algorithms reported by one large study, so a need likely exists for researchers to replicate the findings of this study through the use of parametric statistical regression models. This will require at least one or more confirmatory studies.

Table 12. Heat map of multivariable analyses of associations between factors and opioid overdose

Study PMID	Outcome (Per Study)	Age	Comorbidity	Opioid Duration	Opioid Amount	Opioid Mis-use	Sub-stance Misuse	No. Prescribers
Carey 2018 29800019	Opioid overdose					↑ Misuse		↑ More prescribers More pharmacies
Hoffman 2017 28531306	Opioid overdose			↑ Long-term use				
Lo-Ciganic 2019 30901048[V]	Opioid overdose	ND[W,X]	↑[Y] Disability status		↑[Z] MME Opioid fills		↑[AA] Substance or alcohol	

The heat map lays out each analyzed outcome within each article across rows. The colors and arrows indicate which factor categories were reported in each article and the strength and direction of the association, as described in the code below. Direction of the arrows indicates the direction of the association. Accompanying text within the cells indicates the factor that is at increased risk (e.g., those with comorbidities are at increased risk of opioid overdose).
Across heat map tables, the columns are presented in the same order: demographics, markers of health status, socioeconomic and related factors, pain cause and severity, healthcare specialist, opioid factors, other medication factors, opioid misuse, other substance use/misuse, and opioid stewardship. Studies are presented in alphabetical order.

Abbreviations: MME = mean morphine equivalents, ND = no data reported, PMID = PubMed identifier.

Code (for all heat maps):

Bright pink	↑ = Strong, statistically significant association between (categorical) factor and higher risk of outcome (e.g., measure of association ≥2).
Light orange	↑ = Weak, statistically significant association between (categorical) factor and higher risk of outcome (e.g., measure of association <2).
Light pink	△ = statistically significant "positive" association between (higher values of a) continuous factor and risk of outcome (no estimate of "strength" of association).
Bright blue	↓ = Strong, statistically significant association between (categorical) factor and lower risk of outcome (e.g., measure of association ≤0.5).
Light blue	↓ = Weak, statistically significant association between (categorical) factor and lower risk of outcome (e.g., measure of association >0.5).
Middle blue	▽ = statistically significant "negative" association between (lower values of a) continuous factor and risk of outcome (no estimate of "strength" of association).
Grey	NS = no statistically significant association between factor and outcome.
Light yellow	Mixed/variable directionality or strength of association. Each arrow is coded as above.

Factors Associated With Death

Evidence Base

Five studies reported nine multivariable models of either factors associated with opioid-related mortality or opioid-related factors associated with nonopioid-related deaths in older adults (Table 13).[82, 96, 101-103] The models analyzed the following outcomes: all-cause death; opioid-related death; nonopioid-specific death, including COPD- or pneumonia-related death and drug overdose death (any drug). The models evaluated factors related to demographics; opioid use, misuse, and prescription; socioeconomic and related factors; clinician factors; and other substance use.

[V] In total, 50 "predictors" are ranked.
[W] Among the most important predictors ("importance factor" >40%).
[X] Study does not indicate the directionality of the association.
[Y] Among the most important predictors ("importance factor" >40%).
[Z] Among the most important predictors ("importance factor" >40%).
[AA] Among the most important predictors ("importance factor" >40%).

Across outcomes, no factor category was reported on by more than two studies. **Race** and **income** were each examined by two studies, both of which found associations between these factors and death. The two studies reported models for five separate outcomes, and both found that higher percentages of white people (or non-black/non-Hispanic) in a cohort (e.g., county) were associated with higher death rates. The same two studies reported that higher poverty rates were also associated with increased risk of death.

Two studies (reporting on three outcomes) evaluated different aspects of **opioid use**. One study found that new users of opioids were (strongly) at increased risk of COPD or pneumonia-related death and (weakly) at increased risk of all-cause death. The other found a statistically significant association between the percentage of opioid users among older adults in a county and drug-overdose death.

Single studies identified the following factors as being associated with higher risk of death: lower level of **education**, *not* **rural** residency, **specialty** of the opioid prescriber (various, including emergency medicine), **opioid type** (tramadol), and concomitant **benzodiazepine** use. Possibly counterintuitively, one study found that history of **opioid misuse** was associated with *lower* odds of patient encounters ending in death versus routine discharge. Only the association between tramadol use and risk of COPD or pneumonia-related death could be classified as a strong association.

In summary, across five studies, multivariable models have identified a number of potential factors associated with death related to opioid use (or among older adults using opioids), but only race and income have been replicated, and only by two studies. However, these factors applied to communities at high risk, not necessarily to individuals. Two factors have been found to be strongly associated with death (new opioid use and tramadol prescription), but each by only a single study and for different outcomes (all-cause death and non-opioid related death, respectively).

Research Needs on Predictors of Death

Since the associations between most factors and death have been evaluated by only a single study, additional studies are needed to determine likely candidates as predictors of death pertaining to opioid use in older adults. In particular, studies employing a specific and, if possible, validated definition of *opioid-related* death are needed.

Table 13. Heat map of multivariable analyses of opioid-related associations between factors and death

Study PMID	Outcome (Per Study)	Race	In-come	Educa-tion	Rural	Spe-cialty	Opioid Rx Rate	Opioid Use	Opioid Type	Opioid Misuse	Benzo
	All-cause death										
Carter 2019 30863796	Death (in emergency depart-ment)									↓ (Misuse)	
Vozoris 2016 27418553	All-cause death							↑ New use			
Zeng 2019 30860559	All-cause death								⬆ Tramadol		
	Opioid-related death										
Grigora 2018 29159797	Opioid-related death	△ White	△ Poverty			△ Various	△ Higher rate				
	Synthetic opioid-related death	△ White	△ Poverty				△ Higher rate				
	Natural and semisynthetic opi-oid-related death	△ White	△ Poverty				△ Higher rate				
	Methadone-related death	△ White	△ Poverty				△ Higher rate				
	Nonopioid-related death										
Vozoris 2016 27418553	COPD or pneumonia-related death							⬆ New use			
Zoorob 2018 29537112	Drug overdose death	△ Non-Black/ Hispanic	△ Poverty	△ <HS	↓ (Rural)			△ Higher use			△ Benzo use

The heat map lays out each analyzed outcome within each article across rows. The colors and arrows indicate which factor categories were reported in each article (or outcome) and the strength and direction of the association, as described in the code below. Direction of the arrows indicates the direction of the association. Accompanying text within the cells indicates the factor that is at increased risk (e.g., whites were at increased risk of death). Downward arrows are accompanied by text (in parentheses) that indicates the factor that is at *decreased* risk for the outcome (e.g., rural residents were at *decreased* risk of drug overdose death).
Across heat map tables, the columns are presented in the same order: demographics, markers of health status, socioeconomic and related factors, pain cause and severity, healthcare specialist, opioid factors, other medication factors, opioid misuse, other substance use/misuse, and opioid stewardship. This heat map is organized by type of outcome (cause of death). Studies are presented in alphabetical order within outcome categories.

Abbreviations: <HS = less than a high school education; Benzo = benzodiazepine use, COPD = chronic obstructive pulmonary disease, HS = high school education, Op Rx Rate = rate of opioid prescribing, PMID = PubMed identifier, Specialty = prescriber specialty.

Code (for all heat maps):

Bright pink	⬆ = Strong, statistically significant association between (categorical) factor and higher risk of outcome (e.g., measure of association ≥2).
Light orange	↑ = Weak, statistically significant association between (categorical) factor and higher risk of outcome (e.g., measure of association <2).
Light pink	△ = statistically significant "positive" association between (higher values of a) continuous factor and risk of outcome (no estimate of "strength" of association).
Bright blue	⬇ = Strong, statistically significant association between (categorical) factor and lower risk of outcome (e.g., measure of association ≤0.5).
Light blue	↓ = Weak, statistically significant association between (categorical) factor and lower risk of outcome (e.g., measure of association >0.5).
Middle blue	▽ = statistically significant "negative" association between (lower values of a) continuous factor and risk of outcome (no estimate of "strength" of association).
Grey	NS = no statistically significant association between factor and outcome.
Light yellow	Mixed/variable directionality or strength of association. Each arrow is coded as above.

Other Issues Pertaining to Associations of Factors With Outcomes

Additional Research Needs and Gaps Pertaining to Predictors

Based on discussions with Key Informants and within the research team, we identified a number of research needs that are not addressed by published multivariable risk factor analyses or that do not cleanly fit within Octagons R2 or R3 in the Conceptual Framework. These are discussed in roughly the temporal order that people interact with opioid use, starting with patient demographics.

Research Needs About the Definition of "Older Adult"

Future research should consider whether it is appropriate to identify individuals aged 50 to 60 or 50 to 65 as "older". If that term is applied to individuals younger than 60 or 65 years of age, researchers should consider providing a clear justification or rationale (e.g., biological aging) for the application of one age threshold versus another. Research into the impact of varying the age threshold used to define adults as "older" might be warranted for many of the questions related to opioid use, misuse, and OUD in older adults. The rationale is that intergenerational or birth cohort differences could result in qualitatively different inferences depending on the age groups chosen for a given study. The group of individuals aged 50 to 65 years is likely to have unique predictors of opioid-related harms compared to those individuals aged 65 and older. Thus, an important gap in knowledge is what, if any, evidence on predictors of opioid-related outcomes in younger adults or overall populations spanning many age groups is generalizable to older adults. Similarly, individuals aged 75 or older (sometimes referred to as the "oldest old") may have unique predictors related to age-related physiological changes that are not present in younger subgroups of the older adult population.

Research Needs About Birth Cohort, Age, and Substance Use

Research has not explicitly quantified the interaction or interplay between birth cohort, age, and nonopioid substance use (e.g., alcohol) as predictors of opioid misuse and OUD. The aging of the "baby boomer" cohort, along with the differing patterns of substance use and misuse among these individuals, might result in unique patterns of opioid misuse compared to the prior birth cohort (born in the early 1940s or before). In addition to nonopioid substance use and use disorders, baby boomers may have unique characteristics that result in an increased rate of opioid

misuse, OUD, and overdose as they age into the older adult cohort over time. More research is necessary to distinguish between these potential age and birth cohort influences.

Summary of Evidence Base on Predictors Across Outcomes

This section repeats observations from preceding sections.

Most of the current evidence base regarding factors associated with opioid-related outcomes is sparse, particularly for definitive opioid-related harms. Table 1 summarized the evidence base for factor-outcome associations with at least three studies. (More detailed summaries of the evidence base is provided in Appendix D, Tables D-3, D-5, and D-6.) Most notable is that the bulk of such evidence relates to long-term opioid use, an outcome which for some individuals might indicate high-risk behavior or even opioid misuse, but for many individuals may indicate appropriate treatment of chronic pain.

Summary of Factors Associated With Opioid Use (Octagon R1)

One set of studies has evaluated factors associated with opioid use (Octagon R1 in Figure 1: Conceptual Framework). The only outcome pertaining to opioid use among eligible studies was long-term opioid use. The largest set of studies evaluated this outcome. No study evaluated opioid use where benefits outweigh harms.

Overall, 17 multivariable models have evaluated a large number of potential factors associated with long-term opioid use among older adults. Table 1 highlights the findings for factor-outcome pair associations analyzed by at least three studies.

Studies were **consistent** (in full agreement) that—in eight studies—opioid use prior to surgery or injury (or early use after surgery) and—in six studies—greater amount of opioids (more prescriptions or higher dose) are the factors *with mostly strong associations*.

Other consistent associations, but with largely weak associations, were found with back pain (4 studies, two with strong associations), depression (10 studies, all weak associations), tobacco use (4 studies, one with a strong association), fibromyalgia (3 studies, all weak associations), and concomitant NSAID use (3 studies, all weak associations).

Studies were **mostly consistent** (≥75% agreement) that low income (5 of 6 studies, all with weak associations) and benzodiazepine use (4 of 5 studies, 1 with a strong association) were associated with long-term opioid use.

Studies were also mostly consistent that alcohol abuse (4 of 5 studies) and healthcare utilization (3 of 4 studies) were *not* associated with long-term opioid use; however, one of these latter studies found a strong association between "any hospitalization" and long-term use.

Factors with variable findings of association (evaluated by at least 3 studies) included gender (6 of 14 studies found weak associations with female gender; 2 found associations with male gender, one strong), age among older adults (6 of 10 studies found mostly weak associations with younger age; 1 found a weak association with older age), black race (3 each, among 8 studies, found weak associations with increased and with decreased likelihood), and dementia (2 each, among 5 studies found associations with increased and with decreased likelihood).

Summary of Factors Associated With Opioid Misuse and Related Outcomes (Octagon R2)

Two sets of studies have evaluated factors associated with opioid misuse (Octagon R2 in Figure 1: Conceptual Framework): opioid-related disorders and multiple opioid prescribers.

Six studies have evaluated factors associated with **opioid-related disorders** among older adults, including OUD, opioid misuse, and high-risk behaviors, but since the researchers largely analyzed different sets of factors, there is little consistency or replication across models. Three studies each reported variable findings regarding the associations of alcohol misuse and of gender with **opioid misuse**. Only single studies have evaluated specific factors and OUD or high-risk obtainment of prescription opioids among older adults. The **OUD** study reported strong associations with a history of anxiety, pain interference (a measure of pain severity), and both marijuana and alcohol use. Older age, college education, and a prior history opioid misuse were each found to be associated with **high risk obtainment of prescription opioids** (in one study).

Summary of Factors Associated With Opioid-Related Harms (Octagon R3)

Four sets of studies have evaluated factors associated with opioid-related harms (Octagon R3 in Figure1: the Conceptual Framework): mental or physical health harms, hospitalizations or ED visits, opioid overdose and death.

Few studies (two each) have evaluated opioid-related factors associated with **mental health** or **physical health harms** in older adults. A single study found that opioid use, duration of use, and opioid type are strongly associated with increased risk of hip fracture, but other studies found weak or no associations with outcomes. Each of the four studies evaluated different outcomes and no factor-outcome association was replicated. Additional research is needed.

Outcomes related to **hospitalizations** or **ED visits** have been evaluated in multivariable models in four studies. Among the studies, there were strong associations reported between incident opioid use and opioid misuse. Strong associations were also reported between use or misuse and both all-cause hospitalization and ED visits, as well as between increased number of opioid prescribers and opioid-related hospitalizations. However, the four studies each evaluated different combinations of factor categories and outcome categories, such that no finding has been replicated. Additional research is needed.

Three studies evaluated factors associated with **opioid overdose** in older adults. One study ranked numerous (often unclearly defined) factors by strength of association; the other two evaluated nonoverlapping sets of factors. Nevertheless, one study each reported strong associations for opioid overdose among older adults with age, disability status, opioid use duration, amount of opioids use, opioid misuse, other substance misuse, and number of opioid prescribers. Additional research is needed.

Among five studies that have evaluated factors associated with **death** related to opioid use in older adults, two reported that counties with higher percentages of people who are white or in poverty are associated with higher risks of opioid-related or drug overdose deaths. Notably, these measures apply to communities, not necessarily individuals, at high risk. Other specific associations have each been evaluated by only a single study (including strong associations for new opioid use and tramadol prescription). Additional research is needed.

Interventions Related to Opioid Use in Older Adults

Overview of Literature

We identified 14 studies that address interventions to appropriately reduce opioid prescriptions, reduce harms, identify misuse, or treat misuse in older adults. A summary of the identified intervention studies is presented in Table 14. The descriptions are organized by topic (or purpose) of the interventions, by level of the intervention (screening, patient, clinician, and

healthcare system), then by study. Appendix D Tables D-4 to D-6 include further details of each study.

Only one was a randomized trial. No others were direct comparisons of specific interventions (with distinct groups receiving each intervention). Most studies were secondary database or registry analyses (e.g., among Medicare Part D enrollees) or cross-sectional survey studies. Four studies were pre-post studies (before and after an intervention). Two studies were conducted in caregivers, in one study as a focus group and in the other for training of motivational interviewing. Further descriptions are provided below.

Seven of the studies evaluated interventions to reduce opioid prescriptions or use, which align with Triangle I1 in the Conceptual Framework (Figure 1), which primarily addresses the stage at which decisions are being made about which treatment(s) to use (Conceptual Framework Rectangle C). One of these interventions also was designed to minimize patient activities that may lead to opioid misuse (Triangle I2). Six additional studies evaluated screening tools to identify people at increased risk of opioid-related disorders (also Triangle I2). Only one study addressed an intervention to manage opioid misuse in older adults (Rectangle F and Triangle I3 in the Conceptual Framework); although, it evaluated a clinician-level intervention for hypothetical older adults with opioid misuse. No identified studies addressed reducing harms among older adults appropriately using opioids (Rectangle D).

There are numerous gaps in the evidence base related to the various stages depicted in the Conceptual Framework (Rectangles B to F) and the types of interventions (Triangles I1 to I3), not to mention issues related to applicability or heterogeneity of treatment effect suggested by the various potential predictors (or effect modifiers). Even where there is evidence, almost none of the intervention studies have been replicated.

Table 14. Studies that evaluate interventions of interest

Intervention Topic	Intervention Category	Study PMID	Intervention	Design	Sample Size	Result*
Reduce opioid prescriptions or use where harm outweighs benefit (Conceptual Framework Triangle I1)	Patient-level	Darchuk 2010 20735746	Pain rehabilitation program	Single group, prospective	78	Improved
		Rose 2016† 26431852	Patient education pamphlet†	NRCS, prospective	172	NS
	Clinician-level	Pasquale 2017 29199396	Provision of patient information; Educational materials	RCT	2391	NS
		Gugelmann 2013 23906621	Bundle of educational modalities	NRCS, prospective	2212	Improved
	Healthcare system-level	Yarbrough 2018 28101955	PDMP	NRCS, retrospective (registry)	6920	Improved
		Moyo 2017 28498498	PDMP	NRCS, retrospective (registry)	310,105	Improved
		Schaffer 2018 29581162	Tamper-resistant oxycodone	NRCS, retrospective (registry)	5055	NS
Prevent opioid-related disorders (Conceptual Framework Triangle I2)	Screening	Park 2011 21143370	PMQ	Single group, prospective	150	Useful tool
		Tiet 2015 26075352	SoDU	Single group, prospective	1283	Validated tool
		Beaudoin 2016 27426210	PDUQp	Single group, retrospective	38	Validated tool
		Hendersen 2015 RI Med J	PDUQp	Single group, prospective	88	Validated tool
		Cheng 2019 31234786	SDS	Single group, prospective	246	Validated tool
		Draper 2015 25247846	ASSIST	Single group, retrospective	210	Unclear
	Patient-level	Rose 2016† 26431852	Patient education pamphlet†	NRCS, prospective	172	Improved
Manage opioid-related disorders (Conceptual Framework Rectangle F and Triangle I3)	Clinician-level	Chang 2019 31187888	Motivational interviewing training	Single group, prospective	31 students	Possibly improved

* Qualitative assessment of effect of intervention, categorized as statistically nonsignificant (NS), Improved (statistically significant effect of intervention to reduce harm or to increase benefit), Worsened (statistically significant effect of intervention to increase harm or to decrease benefit), Mixed (benefit for some outcomes, harm for others).
† Note that this study is in the table twice.

Abbreviations: ASSIST = Alcohol, Smoking and Substance Involvement Screening Test, AUDIT-C = Brief Alcohol Use Disorders Identification Test, NRCS = nonrandomized comparative study, PDMP = prescription drug monitoring programs, PDUQp = Prescription Drug Use Questionnaire, patient version, PMID = PubMed identifier, PMQ = Pain Medication Questionnaire, RCT = randomized controlled trial, SDS = Severity of Dependence Scale, SoDU = Screen of Drug Use.

Interventions to Reduce Opioid Prescribing for Older Adults for Whom Harms Outweigh Benefits (Triangle I1)

Evidence Base

We identified seven studies of interventions to reduce opioid prescribing or use in older adults (first set of subrows in Table 14). These studies align with Triangle I1 in the Conceptual Framework (Figure 1) at the stage where decisions are being made regarding treatment. Interventions were aimed at patients (rehabilitation and education), clinicians (providing information and education), and healthcare systems (PDMP and tamper-resistant opioids). Of note, among studies that had the goal of reducing overall opioid prescriptions or use, none specifically assessed "appropriate" reduction of opioid prescriptions or use (e.g., for patients whose risks of harms outweigh benefits).

Training Patients

Two studies assessed training or education of patients with the goal of reducing opioid use (identified as "Patient-level" in Table 15).

Darchuk 2010[104] described the Mayo Clinic Comprehensive Pain Rehabilitation Center program, an **intensive 3-week, group-based, outpatient interdisciplinary pain rehabilitation program**. As described by the authors, the cognitive–behavioral model serves as the basis for treatment, which incorporates physical therapy, occupational therapy, biofeedback and relaxation training, stress management, wellness instruction (e.g., sleep hygiene, healthy diet), chemical health education, and pain management training (e.g., activity moderation, elimination of pain behaviors). The program's goals emphasize functional restoration and self-management of chronic pain symptoms. An important treatment goal for all patients in this program is the discontinuation of opioid and simple analgesics taken for relief of chronic pain. The study was conducted as a pre-post design, without a separate concurrent comparator group. The authors reported on an older adult subgroup comprising 78 individuals aged ≥60. The study found a large reduction in opioid use after discharge from the program.

Rose 2016[105] evaluated the effect of a **patient education pamphlet** on opioid use. The pre-post study was conducted in 172 patients who had received either a total knee or hip arthroplasty, with a mean age of 63 years. The goal of the education was not specifically designed to reduce opioid use. The pamphlet covered educational domains about safe opioid storage, opioid weaning, and opioid disposal. However, the study also reported on postoperative opioid cessation, finding no difference in opioid cessation rates between groups.

One systematic review is ongoing that, at least tangentially, will address issues related to appropriate prescriptions. The ongoing systematic review by Alvan et al.[106] is investigating risks

and benefits of pharmacological treatment of older (≥65 years) patients with common pain conditions. They are also looking for qualitative research studies that assessed the experiences of older adults with pain. The review is expected to be published in 2020.

Clinician-Level Interventions (Information and Training)

Two studies assessed education of or providing information to clinicians with the goal of reducing opioid use (identified as "Clinician-level" in Table 15).

The only randomized controlled trial among the 15 studies assessed the value of providing information to physicians about Medicare patients' opioid abuse risk. Pasquale 2017[107] used a regression model to predict that 2391 patients enrolled in Medicare plans were at increased risk for opioid abuse and then linked the patients with their prescribing physicians (N=4353). Those physicians were randomized to be sent either **"patient information," educational materials for diagnosis and management of pain, both patient information and educational materials, or there was no communication.** The study evaluated patients' opioid prescriptions, chronic high-dose opioid use, uncoordinated opioid use, and opioid-related ED visits. The study found that the interventions did not affect pain- and opioid-related outcomes.

Gugelmann 2013[108] evaluated a **"bundle" of interdisciplinary educational modalities** provided to ED nurse practitioners with the specific goal of decreasing opioid discharge pack use in patients treated and released from the ED, particularly those at risk for dependence. These included: lectures, journal clubs, case discussions, and an electronic medical record decision support tool." In a larger evaluation of all ED patients, they report the results for a subgroup of 2212 individuals aged 65 years or older who were treated before (N=1360) or after (N=852) the training (interrupted pre-post design). The single result reported for this older adult subgroup related to prescription of oxycodone/acetaminophen "4-packs," with a statistically significant decrease in prescriptions during the postintervention period. Of note, Gugelmann et al. was the only pertinent study related to opioid use found by a 2016 systematic review, by Maree et al.,[50] of opioid (and benzodiazepine) misuse in older adults.

Healthcare System-Level Interventions

Three studies evaluated the association of national or State-level systems changes and changes in opioid prescriptions (at a population level).

Two of the studies evaluated **prescription drug monitoring programs (PDMP)** in the U.S. Yarbrough 2018[109] evaluated data on Medicare enrollees in all 50 states, comparing states with PDMPs that 1) allowed both prescribers and dispensers to have access to the program, 2) provided online access to the program, and 3) required reporting of all pharmacy prescriptions with states whose PDMPs did not meet these criteria. The number of opioid prescriptions were compared between states. The study concluded PDMPs had a modest effect on oxycodone use. Moyo 2017[110] also evaluated data on Medicare enrollees, but in 21 states that either did or did not have PDMPs. The study reported opioid prescriptions at the state level, as measured by kilograms of opioids dispensed, number of dispensed prescriptions, and opioid dose per prescription. This study also found significant reductions in opioid prescriptions associated with PDMP.

The third study evaluated the effect of the introduction of a **tamper-resistant formulation** of oxycodone CR (controlled release) on opioid use in Australia. As part of a larger study of individuals prescribed controlled-release oxycodone, Schaffer 2018[111] evaluated 5055 older adults ≥65 years. The study compared prescriptions for oxycodone CR specifically, changes to "strong" opioids, and switches to other opioids related to the change in formulation, but found no significant association between oxycodone formulation and opioid use.

An ongoing randomized controlled trial (NCT02691754) is evaluating the effect of **pharmaceutical pricing**, comparing acetaminophen provided free from the pharmacy with standard drug prescriptions for osteoarthritis pain control in Italy. The study is restricted to adults ≥65 years old. A secondary outcome for the study is opioid consumption. The record indicates that the study was completed in 2013 with 16 participants, but no results have been posted nor were we able to find published study results.

Research Needs Regarding Interventions to Reduce Opioid Prescribing for Older Adults For Whom Harms Outweigh Benefits (Triangle I1)

With the exception of PDMP, each of the interventions to reduce opioid use was evaluated by only a single study; thus, there is a need to replicate the findings and expand upon the research base. Furthermore, the studies all evaluated overall opioid use, instead of aiming to reduce opioid use where harms outweigh benefits. Future studies should attempt to better focus on minimizing inappropriate use.

Research Needs Specific to Multidisciplinary Pain Treatment Teams

Significantly more research is needed on care models that organize multiple providers (e.g., geriatrics, pain medicine, mental health, behavioral health, pharmacy, nursing) into a pain treatment team (e.g., as in interdisciplinary pain programs or clinics). While the ED intervention described in Gugelmann 2013[108] addressed the portion of the conceptual framework related to reducing suboptimal opioid prescribing, it did not involve any formal efforts to organize providers into a pain treatment team. Furthermore, no interventions appear to address how exactly to establish clear delineations of responsibility for pain management in a multidisciplinary pain team. Furthermore, Key Informants and others believe that interdisciplinary pain teams could or should include a pharmacist capable of performing a comprehensive geriatric medication evaluation, who would then either make recommendations to prescribers or function semi-autonomously under a collaborative practice agreement (i.e., protocol) to make modifications to an older adult's medication regimen. Studies of this potential care model would be highly valuable.

Research Needs Specific to Deprescribing Protocols and Sharing Responsibility

Related to care models that organize multiple providers, one of the most important areas for future research is understanding who is responsible for prescribing an opioid, monitoring its continued use, and deprescribing the opioid. In particular, research is necessary on how to address deprescribing of an opioid by a provider who did not prescribe the drug. Furthermore, recognizing that older patients often have many providers due to their multiple chronic conditions, deprescribing protocols should explicitly address how responsibility will be shared for deprescribing of an opioid. Future research should therefore 1) identify what providers perceive as their set of responsibilities and locus of control, 2) develop interventions that explicitly address provider responsibility, and 3) test interventions to determine if explicitly incorporating provider responsibility into deprescribing protocols and other interventions is effective, especially in comparison with protocols that do not address how to divided or share responsibility among multiple providers.

Research Needs Specific to Multimodal Stepped Care Pain Therapy

Research specific to older populations is necessary on the outcomes of interventions related to multimodal stepped care pain therapy—a pain treatment approach that 1) combines medications from different pharmacologic classes and 2) combines pharmacologic and nonpharmacologic therapies or multiple nonpharmacologic therapies.

In particular, research on how to implement this approach in resource-constrained clinical settings should be conducted. More evidence is also necessary to confirm that multimodal stepped therapy improves older adults' outcomes, including functioning, disability (especially related to pain), quality of life, and any other outcomes valued by older adults. While opioids are more effective if they are combined with nonpharmacologic treatments, more evidence is necessary to provide a better understanding about how, given a specific source of pain or combination of sources, different interventions should be combined and modified for older adults.[112] The number of treatment combinations is nontrivial considering that in addition to medications, multimodal stepped therapy may also include cognitive-behavioral therapy, massage, physical therapy, rehabilitation, exercise, acupuncture, meditation, and more.

Interventions to Identify or Reduce Opioid-Related Disorders in Older Adults (Triangle I2)

Evidence Base

As listed in the second set of subrows in Table 15, we identified seven studies pertaining to identifying or reducing opioid-related disorders (including misuse). These align with Triangle I2 in the Conceptual Framework (Figure 1). Six of the studies evaluated screening tools (at the patient level) to predict risk of opioid-related disorders. While we have aligned these with Triangle I2, one could equally argue that they align with Triangle I1 (reducing opioid prescribing where harms may outweigh benefits) since the tools may be used during decisionmaking regarding choice of treatment. The seventh study also addresses issues related to Triangles I1 and I2. The study (Rose 2016) was described in the section above (*Interventions to Reduce Opioid Prescribing*), but also evaluating that relate to avoiding opioid misuse.

Screening Tools

Six studies evaluated tools to identify older adults either at risk of, or with, opioid misuse, dependence, or OUD, but only two assessed the same tool.

Park 2011[113] analyzed a validated tool (for the general population) to develop a tool specifically for older adults with chronic pain. They **modified** the existing **Pain Medication Questionnaire (PMQ)** into a 7-item version and evaluated it in 150 older adults (≥65 years) who had chronic pain (≥3 months) and were using opioids for at least 30 days. The tool was evaluated to predict opioid misuse. The authors concluded that the modified PMQ may be useful in assessing opioid misuse in community-dwelling older adults with chronic pain, but that future studies are needed to confirm the reliability, validity, and factor structure.

Tiet 2015[114] developed and validated a new instrument, the **Screen of Drug Use (SoDU)** tool, in patients seen at primary clinics in the VA system, with a mean age of 62 years. The purpose of the tool was to screen and identify those with drug, including opioid, use. Among 1283 patients, the researchers validated the tool to identify OUD, and negative consequences of drug use independent of OUD (related to impulse control, social responsibility, physical consequences, and interpersonal consequences). The authors concluded that the 2-item SoDU tool had

excellent statistical properties and is a brief screening instrument for drug use disorders and negative consequences of drug use that is suitable for busy VA primary care clinics.

Beaudoin 2016[115] validated an existing tool, the **Prescription Drug Use Questionnaire, patient version (PDUQp)** in a set of patients known to have used opioids in the previous 30 days. The article reported on a subgroup of 38 patients aged ≥65 years. The tool was validated for opioid misuse and OUD. Hendersen 2015[116] also assessed the PDUQp in 88 older adults (≥65 years) with subcritical illnesses or injuries seen in the ED who were using opioids daily. The study assessed the population for opioid misuse and abuse. The authors concluded that the PDUQp may be a viable instrument to screen for prescription opioid misuse and OUD, but likely requires modifications to optimize its predictive ability in adults over age 50 years.

Cheng 2019[117] evaluated a different existing tool (validated in the general population), the **Severity of Dependence Scale (SDS)** in 246 older adults (aged 65-90 years) who were prolonged users of central nervous depressants, including opioids (and benzodiazepines and hypnotics). The study evaluated medication misuse or dependence (as a combined outcome), specific to opioid use (and specific to other drugs). The authors concluded that the SDS is reliable, valid and capable of detecting medication misuse and dependence among hospitalized older patients, with good diagnostic performance.

Finally, Draper 2015[118] categorized 210 older adults (≥60 years) who were receiving outpatient clinical care at an urban hospital based on their score on the **Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)** and their opioid (and alcohol and benzodiazepine) misuse status. However, only two included individuals were classified as having opioid misuse. The authors did not appear to make recommendations about the use of ASSIST and noted that there may be several important complexities with using the tool as a screen.

Two ongoing systematic reviews may be pertinent to the evaluation of screening tools in older adults. Raposo Galindo et al.[119] are conducting a systematic review of validated assessment tools for measuring the risk of behavior suggestive of opioid abuse in adults with noncancer pain. The review, as a whole, does not focus on older adults, but plans to focus on "different age groups" including older adults, as data allow. Listed outcomes include opioid use. The researchers planned to publish in 2018, but we found no record of the finalized review. Pask et al.[120] also have an ongoing systematic review of how opioids affect cognition in older adults (≥65 years). In particular, they are investigating which "screening and assessment tools can be used to detect and assess opioid-induced cognitive impairment in older adults", excluding those with opioid misuse. Listed outcomes include cognitive function and cognitive impairment. The researchers planned to publish in early 2019, but we found no record of the finalized review.

Patient-Level Intervention to Reduce Misuse

Only one study evaluated a specific intervention whose goal was to reduce opioid misuse. As described above, Rose 2016[105] evaluated an **patient education pamphlet** in 172 patients undergoing major joint replacement (mean age 63). The goal of the pamphlet was to inform patients about safe opioid storage, opioid weaning, and opioid disposal. Reported outcomes included ease of weaning off opioids, opioid withdrawal symptoms, opioid disposal, opioid storage, and opioid use cessation. The authors concluded that the pamphlet improved self-reported proper opioid disposal rates in postoperative patients.

Research Needs Regarding Interventions to Reduce Opioid-Related Disorders in Older Adults (Triangle I2)

Studies of interventions that clinicians, patients, healthcare systems, or other entities can use to reduce either inappropriate opioid prescriptions or the risk of opioid misuse are sparse or lacking for older adults. Although we did not evaluate the effectiveness of interventions in the studies, overall, the reported results are not impressive, suggesting that new tools, methods, and specific interventions are needed to ensure more appropriate opioid prescribing among older adults and to minimize the risk of older adults becoming dependent on their opioid prescriptions.

Research Needs Specific to Validation of Existing Tools to Identify Opioid Misuse or OUD

Several tools have been validated and/or evaluated to identify older adults at increased risk of opioid misuse or OUD, but there has been little to no replication of findings. Validation of existing screening tools for opioid misuse or OUD in large, national populations of older adults is a clear research need to ensure that the tools are feasible to use and accurate for populations other than the small, limited ones in which the tools were developed and tested. It is also unclear to what extent many of the tools can be implemented in multiple care settings, as well as whether setting might modify the accuracy (i.e., discriminative ability) of the tools. Another key related research need is validation of the Opioid Risk Tool (ORT) and Screening, Brief Intervention, and Referral to Treatment (SBIRT) tool in older adults. Whether the findings from studies of ORT and SBIRT among younger or middle-aged adults can be extrapolated to older adults is unknown. Given the multitude of unique characteristics of older adults, it is unclear if the tools will generalize well without any modifications. It is possible that the items of the ORT are unlikely to be impacted by age, but this remains unknown without further study. Studies of the tools are particularly needed for primary care settings. Such studies should carefully document the validity and reliability in the overall population of older adults and within strata of older age (e.g., 60 to 69.9 years, 70 to 79.9 years). If an alternative tool were to be developed specifically for older adults, research should focus on the brevity of the tool as a key feature that is necessary for it to have meaningful uptake among clinicians caring for medically complex older patients in busy primary care settings.[BB]

Research Needs Specific to Implementation and Effectiveness of SBIRT

In addition to foundational research on the implementation and effectiveness of SBIRT for OUD in older adults, there is a need for research on how to integrate SBIRT into existing care management for older adults. Medication reviews are a prime target because SBIRT could be integrated into regular medication reviews for older adults. How exactly this should be done, though, remains empirically unstudied. Research identifying the optimal and most effective ways to combine SBIRT with medication reviews and other routine care management is highly important.

[BB] Some discordance existed among Key Informants about the generalizability of available screening tools, with some experts arguing that the screening tools developed in younger adults can be readily applied to older adults (without needing replication in studies of older adults) while others arguing that further research is necessary to adapt and validate the tools, particularly for OUD prevention.

Research Needs Specific to Provider Perception of OUD Risk

We did not identify any studies documenting providers' beliefs about OUD risk in older adults. Providers may prescribe opioids long-term to older adults because they believe that the risk of OUD is particularly low in this population, especially considering the marketing materials providers received from pharmaceutical companies in the 1990s and possibly beyond suggesting that OUD and addiction risk were low. Qualitative, survey, or other research may necessary to empirically document provider beliefs and understand provider perceptions. These perceptions may be an important predictor of prescribing and opioid-related harms. If true, that information could eventually inform the development or tailoring of behavioral interventions aimed at reducing suboptimal opioid prescribing for older adults. Key Informants also noted that many caregivers and patient family members do not believe older adults are at a high risk, or any risk, of misusing opioids or developing OUD. These beliefs and perceptions could be very important to study as potential predictors of misuse and OUD as they would inform future interventions attempting to incorporate caregivers or family members into misuse or OUD surveillance efforts.

Research Needs Specific to Care Coordination

Research is needed on whether interventions to improve care coordination between providers can help to reduce misuse and OUD (and also opioid-related harms). The lack of communication about what medications are being prescribed by providers in one setting to providers in other settings can either directly result in harms (e.g., through therapeutic duplication resulting in overdose) or facilitate opioid misuse. Research on how interventions to improve coordination between an older adult's primary care provider and other providers (i.e., collaborative capacity) impact the risk of opioid misuse and OUD is particularly necessary. A better understanding of the characteristics of one provider in relation to another will likely need to accompany research on communication; in particular, understanding the relationship between co-location or geographic proximity of primary care, pain management, mental health, and substance use services.

Research Needs Specific to Safe Storage and Disposal

While we found a single study about educating older adult opioid users about safe handling of opioid prescriptions, further evaluation of safe storage and disposal programs to reduce opioid misuse may be a topic for future examination in research studies.

Interventions to Reduce Opioid-Related Hospitalizations, ED Visits, or Other Adverse Outcomes (Triangle I3)

Evidence Base

We did not find studies of interventions specific to reducing opioid-related hospitalization, ED visits, or other adverse outcomes such as falls, cognitive decline, or death. As highlighted in the next section (*Research Needs*), we found no evidence pertaining to tools to predict harms, self-management interventions, OUD treatment settings, use of naloxone rescue kits, care coordination, tailoring opioid-related information, or interventions to reduce coprescribing and polypharmacy, among other outcomes.

Research Needs Regarding Interventions to Reduce Opioid-Related Hospitalizations, ED Visits or Other Adverse Outcomes (Triangle I3)

Research Needs Specific to Tools to Predict Harms During Appropriate Opioid Use

Distinct from validation of existing tools to identify misuse or OUD (addressed in the prior section pertaining to Triangle I2 in the Conceptual Framework), tools are necessary to help providers identify older adults who are likely to experience opioid-related adverse events despite using opioids appropriately (which address Triangle I3 in the Conceptual Framework). While the evidence map suggests some potential tools may exist for identifying opioid misuse and related harms that occur during misuse, we identified no person-level screening or prediction tools that attempted to identify older adults who were most likely to experience an opioid-related harm despite using opioids as prescribed by a provider. Research is necessary to develop these tools, which are foundational for expanding efforts to avoid or mitigate adverse events when an older person truly requires opioids for pain management.

Research Needs Specific to Self-Management

Self-management is becoming a more prevalent component of pain treatment approaches. This raises important questions how self-management (and interventions more broadly) might need to be adapted for older adults, especially those with cognitive impairment or other challenges to self-management. A particular program, the Chronic Pain Self-Management Program (CPSMP), may be in use by some National Aging Network partners, but studies were not identified in the evidence map that report on the effectiveness or outcomes of this program in an older adult population.[3] Studies of the outcomes of CPSMP may help advance our understanding of the role of self-management in improving opioid prescribing for older adults.

Research Needs Specific to Settings for OUD Treatment

There is no empirical information about the comparative effectiveness of various settings for treatment of OUD for older adults. Standard outpatient versus more controlled residential treatment facilities are both options for OUD treatment and provision of medication assisted treatment, but the comparative effectiveness of these settings, especially when taking into account the severity of older patients' OUD or medical complexity, is unknown. Each setting and the way they provide medication assisted treatment may have important differential effects on subsequent outcomes, including relapse prevention.

Research Needs Specific to Naloxone Kits

While emergency naloxone rescue kits are now recommended for all patients receiving medication assisted treatment, research is necessary to confirm that older adults have also been receiving these kits. Perhaps even more importantly, research is necessary to understand how family members and other caregivers are engaged and educated about the use of these kits. Older adults often have complex caregiving circumstances and unique strategies may be necessary to engage all of their caregivers in opioid overdose prevention through education or other means. In the event of an overdose, it is unclear if caregivers are prepared to use the rescue kit.

Research Needs Specific to Care Coordination

As suggested by other portions of the conceptual framework and evidence map, interventions that organize multiple providers from different specialties or disciplines and provide training in

pain medicine or related principles are likely to be particularly fruitful topics for future research. Poor pain-related care coordination is a likely driver of hospitalizations and ED visits. The development and assessment of interventions that improve care coordination for older adults with pain may therefore reduce the risk of opioid-related hospitalizations and ED visits.

Research Needs Specific to Tailoring Opioid-Related Information

Since providers need to discuss the benefits and risks of opioids with their older patients, but have little information about how benefits and risks may manifest and result in a future opioid-related hospitalization or ED visit for a particular patient, research is necessary on how to individualize and tailor information about opioids during discussions with older patients, both prior to starting opioids and while they are continued. The provision of relevant information or education may help older patients avoid hospitalizations or ED visits by avoiding or minimizing the adverse events of opioids. An important area of future research might explore how best to provide patients with information about their opioid prescription (e.g., with follow-up phone calls made by a pharmacist or health professional) and what information might be most relevant (e.g., information focused on modifiable patient risk factors like alcohol use and how to avoid falls).

Research Needs Specific to Coprescribing and Polypharmacy Tools

Screening for coprescribing and drug-drug interactions alone is an important component of efforts to reduce opioid-related hospitalizations and ED visits among older adults. Research is necessary to formally develop and validate screening or prediction tools to quantify the risk of opioid-related events due to coprescribing, drug-drug interactions, and polypharmacy. This is especially true for circumstances where older adults are taking medications as prescribed (i.e., not misusing opioids). Key Informants noted that some providers simply screen for coprescribed medications or drug-drug interactions (usually followed by stopping ≥1 medications or modifying treatment regimens) as their primary approach in clinical practice to reduce opioid-related hospitalizations or ED visits. Research would be helpful to develop a systematic interventional approach that formalizes this practice and examines its effectiveness using the outcome measure of subsequent risk of opioid-related ED visits or hospitalizations.

Research Needs Specific to Other Opioid Outcomes

It is possible to take a broader view on what constitutes an “opioid-related” hospitalization or ED visit. Beyond respiratory depression and overdoses, opioids have been associated with a variety of outcomes, many of which are surprisingly understudied. For instance, high-quality empirical evidence on motor vehicle crashes associated with opioid use is surprisingly scarce. Beyond overdoses and respiratory depression, further research on some of these opioid-related events that result in hospitalizations or ED visits could result in novel interventions, such as programs that intervene to balance an older adult’s need to drive for mobility against their need to take opioids for pain management. Suicide, violent deaths, falls and other injuries may all be particularly valuable foci for future studies.

Interventions to Manage Opioid-Related Disorders (Rectangle F and Triangle I3)

Evidence Base

One study evaluated an intervention designed to help manage patients with an opioid-related disorder (as shown in the last row of Table 15). This study best aligns with Rectangle F (management of opioid-related disorders) and Triangle I3 (interventions to reduce opioid-related harms). The study was of a clinician-level intervention.

Clinician-Level Interventions to Manage Opioid-Related Disorders

The only study that pertained to management of older adults with (potential) opioid misuse, Chang 2019,[121] was an evaluation of **motivational interviewing training** for 31 doctorate of nursing practice students. The training used as an example of an older adult who took more prescription opioids than prescribed (thus, misuse), and then evaluated the students' motivational interviewing knowledge, confidence, attitude, skills, and their "substance abuse" knowledge. The authors concluded that the preliminary findings suggested motivational interviewing education with standardized patient simulation could improve nursing students' knowledge of and confidence in motivational interviewing techniques to manage prescription opioid abuse among older adults. The study did not measure the effect of the educational approach on subsequent clinical practice or older adults' outcomes.

Patient-Level Interventions to Managed Opioid-Related Disorders

Of note, a systematic review, by Wylie et al.,[122] is ongoing and evaluating opioid agonist therapy in older adults. However, it is unclear whether the review is specifically addressing interventions. Their protocol describes the goal "to gain an understanding of older adult (50+) service user experiences during opioid agonist therapy" and to "assess the [opioid agonist therapy] experiences of older adults with an opioid disorder". Their reported primary outcomes include "the identification of the facilitators, barriers, incompatibilities and potential areas for improvement of [opioid agonist therapy] for an older adult population". They expect to publish their results in 2019, but we have found no record of the finalized review.

Research Needs Regarding Interventions to Manage Opioid-Related Disorders (Rectangle F and Triangle I3)

In addition to the relevant needs identified in the section titled "Research Needs Specific to Interventions to Reduce Opioid-Related Hospitalizations or ED Visits (Triangle I3 in the Conceptual Framework)", more research is necessary to develop patient- and clinician-level interventions that focus on managing an existing OUD in older adults.

Research Needs Specific to Peer Support and Mutual Help Meetings

Narcotics Anonymous (NA) and other mutual help meetings are popular sources of support for individuals who use illicit opioids like heroin. The role of NA and other mutual help meetings or organizations is poorly understood for older adults with OUD. The social support provided through those venues could have a beneficial effect on outcomes. More research is necessary to understand the role of NA or similar organizations in the care of older adults with OUD. Related to NA and mutual help, more research is necessary about the effects of peer support programs, which have been employed to engage and retain middle-aged adults in "substance abuse"

and mental health treatment, but for which no studies were identified by the evidence map for older adults.

Research Needs Specific to Recovery

No studies of older adults were identified that addressed recovery—the process of change through which older adults overcome their OUD, regain their health and social function, and live self-directed lives while reaching their full potential. It is thus unknown whether recovery support services for OUD exist for older adults and if they are effective. Additionally, identifying the features of such services that might best promote recovery is a major research need. For example, older adults often have important individual needs and strong unique preferences; interventions that reflect these may be more effective at promoting engagement in OUD treatment and recovery from OUD among older adults.

Other Research Needs Pertaining to the Management of Opioid Use in Older Adults

Although our evidence review did not cover several of the topics below, there were clear needs to fill gaps in knowledge about them to address the topic of the review. Many of these needs directly or indirectly relate to Rectangle C in the Conceptual Framework.

Research Needs Specific to Management of Cancer Pain for Older Adults

Experts believe that older adults with cancer and those at end-of-life frequently require opioids for pain management. However, there are concerns among stakeholders that many providers consider cancer as a condition that provides an exemption from the application of pain management principles; in particular, for individuals who have treatable cancers versus those for whom cancer is end-stage. As a result, cancer patients may not receive an adequate examination of the cause of their pain. For example, some older adults with cancer may have neuropathic pain from the malignancy while others may have postsurgical pain, each of which might respond better to different treatments. Furthermore, providers may be more willing to prescribe opioids and to prescribe them at higher doses than they ordinarily would for patients without cancer. Individuals with cancer are excluded from some opioid prescribing guidelines.[112] Prescribing guidelines that are not specific to older adults do exist for individuals with cancer.[123] Research is likely necessary to understand whether cancer presents a unique set of factors that influence opioid prescribing and outcomes, and if yes, to ultimately develop more rigorous pain assessment tools to guide opioid prescribing for older adults with cancer.

Research Needs Specific to Comparative Effectiveness of Opioids and Nonopioids in Older Adults

Our evidence map did not include studies that evaluated the effectiveness of interventions to reduce pain, *per se*. However, discussions with stakeholders raised several concerns about the lack of evidence regarding which interventions are adequately, or most, effective to treat pain in older adults. The following research needs discussions are primarily based on those discussions.

Research is necessary to fill the gap in knowledge about the comparative effectiveness of opioid versus nonopioid interventions in older adults. Selecting nonopioid therapies in place of opioids requires comparative effectiveness and safety evidence that is lacking, especially for nonpharmacologic interventions. Research to develop tools or algorithms that help providers better understand which of their older patients are likely to derive benefits from opioids in excess of any harms, especially compared to nonopioid alternatives, is also lacking. Some of this research

has been recently funded (in September 2019) by the National Institutes of Health (NIH), in part under the Helping to End Addiction Long-term (HEAL) Initiative launched in April 2018, and results will become available in coming years, though these studies were not considered for the current technical brief. These investments by NIH in understanding the role of nonopioid and nonpharmacologic treatments is important and will likely be relevant for older adults.

Research Needs Specific to Adapting Nondrug Interventions for Older Adults and Frail Patients

A broad knowledge gap exists about what, if any, evidence on interventions in younger adults is transferrable to older adults or can be tailored to meet the specific needs of older adults. In particular, research will likely be necessary on how to adapt nondrug (and, thus, nonopioid) interventions for the older adult population. For example, exercise, physical therapy, and complementary and alternative medicine interventions studied in younger adults will likely require geriatric modifications, especially for older adults who are frail, multimorbid, or have disability and functional limitations. These medically complex older adults are often excluded from most RCTs of drug and nondrug interventions, even among those that included older adults. Therefore, frail individuals and those with multimorbidity should be a crosscutting focus of many future research studies.

Research Needs Specific to Cost and Reimbursement of Nonopioid Therapies

Major cost barriers may exist to accessing nonopioid therapies, especially nonpharmacologic ones. Most of these (e.g., massage therapy) are often not reimbursed by insurers. If they are reimbursed, patients may frequently be responsible for paying a large proportion of the cost out of pocket. Evidence was unavailable about how interventions to improve access to nonpharmacologic therapies might be implemented and what the effects on patient utilization and outcomes would be among older adults. Along with comparative effectiveness and safety research, information on reimbursement and access to nonpharmacologic therapies is fundamentally necessary to decrease opioid use through the substitution of alternative therapies. Additionally, research into how older adults' income, financial assets, and socioeconomic status influence use of nonpharmacologic therapies may also be necessary. Such information could be used to identify older adults who are forced to select alternative interventions that are relatively more affordable (e.g., cannabis or marijuana) and target interventions to them.

Research Needs Specific to Marijuana and Cannabis as Cointerventions

Greater research is likely necessary to understand the role, if any, that cannabis and marijuana have in a pain treatment plan for older adults. Comparative effectiveness research focused on comparing the safety and effectiveness of cannabis/marijuana and other therapies is likely a key area for future research. This need exists partly because some older patients perceive cannabis and marijuana as being more readily accessible than other nonopioid therapies like acupuncture, especially in terms of cost, since many insurers do not cover acupuncture, massage, and other alternative nonopioid therapies. Research into the safety of combining opioids and cannabis is likely also urgently necessary since older adults are currently combining these substances on their own.

Research Needs Specific to Goal-Setting and Shared Decisionmaking

Tools have not been reported that could explicitly help providers establish opioid-related treatment goals for pain, function, and other relevant outcomes through shared decisionmaking

with their older patients or caregivers. Such tools could, in theory, help to avoid opioid prescribing entirely or promote the use of lower and/or less frequent doses. Evidence is also necessary to address how providers and patients should come to an agreement about when opioid use should be stopped, how often that plan or agreement should be discussed, and to what extent patients might self-manage their opioid regimen to make adjustments in response to inadequate pain relief or adverse events without engaging in misuse.

Additional Pertinent Ongoing Research

In fiscal year 2019 alone, several hundred studies of opioids have been funded by the NIH. Many of these studies were funded through the NIH HEAL Initiative that coalesced in April 2018.[124] The studies covered by this initiative address different aspects of opioid use and misuse across a wide variety of populations. These newly funded studies were not considered for the current technical brief unless they had registered in ClinicalTrials.gov between the years 2000 and 2019. The number of newly funded studies that specifically address older adults is therefore unclear. However, it is important to note that these investments by the NIH are likely to advance our understanding of different subtopics address by this current report. For example, projects have been funded to optimize new targeted, nonaddictive medications and nonpharmacological treatments for various types of pain, which could be highly relevant for older adults with limited treatment options due to prevalent comorbidities and contraindications.

On August 31, 2018, the Centers for Disease Control and Prevention (CDC) provided over 150 million dollars to U.S. states and territories to address opioid overdose with the explicit goals of advancing the understanding of the opioid overdose epidemic and scaling up prevention and response activities to make an immediate impact and save lives.[125] Several of these grants may address relevant subtopics that are the focus of this technical brief. For example, under RFA-CE-18-004, "Research to Evaluate Medication Management of Opioids and Benzodiazepines to Reduce Older Adult Falls," more information is likely to become available in coming years about how to taper or discontinue opioids in older adults to reduce falls and unintentional injuries.

Summary and Implications

Summary of Conceptual Framework and Evidence Base

As part of this technical brief on prevention, diagnosis, and management of opioid use, misuse, and opioid use disorder in older adults, we created a Conceptual Framework that outlines the stages of care for older adults who use (or may use) opioids and factors that impact management decisions and patient outcomes, including assessment of pain, selection of pain treatment, choice of opioid regimen, assessment for opioid misuse or OUD, and management of misuse or OUD (Rectangles B to F in the Conceptual Framework, Figure 1). Multiple potential patient, provider, and societal predictors (Ovals P1 to P8) may influence opioid-related harms and other outcomes, and the Framework at large. Predictors and interventions to reduce opioid prescriptions where harms outweigh benefits (Octagon R1 and Triangle I1), prevent opioid misuse and OUD (Octagon R2 and Triangle I2), and reduce other opioid-related harms (Octagon R3 and Triangle I3) are included.

This broad overview of the evidence base identified 35 studies with multivariable models of factors associated with opioid-related outcomes. We believe it is likely that only (or mostly) the multivariable analyses could provide adequate evidence that putative factors are likely to be reliable predictors of outcomes. The studies addressed one outcome (long-term opioid use) related to

factors that are predictors of opioid use (Octagon R1 in the Conceptual Framework), two sets of outcomes (opioid misuse and multiple opioid prescribers) related to factors that are predictors of opioid use or OUD (Octagon R2) and four sets of outcomes (mental or physical harms, hospitalizations or ED visits, opioid overdose, and death) related to factors that are predictors of opioid related harms (Octagon R3).

The largest body of evidence (17 studies) evaluated factors associated with long-term opioid use. Of note, however, is that the outcome long-term opioid use does not address whether the harms associated with use outweigh the benefits. Long-term use may be a poor proxy for potential harms or problematic opioid use and may simply be an indicator of greater need for long-term use to manage chronic pain. Nevertheless, the studies were consistent (in full agreement) that opioid use prior to surgery or injury (or early use after surgery) and greater amount of opioids (more prescriptions or higher dose) are the factors with mostly strong associations. Other consistent associations, but with largely weak associations, were found with back pain, depression, tobacco use, fibromyalgia, and concomitant NSAID use. Studies were mostly consistent (≥75% agreement) that low income and benzodiazepine use were associated with long-term opioid use. Studies were also mostly consistent that alcohol abuse and healthcare utilization were *not* associated with long-term opioid use. Factors with variable findings of association included gender, age among older adults, black race, and dementia.

Across six studies of factors associated with developing opioid-related disorders, three studies each had variable findings regarding the associations of alcohol misuse and of gender with opioid misuse. All other evaluations of specific associated factors and outcomes of interest were evaluated by only one or two studies each. These included analyses of opioid use disorder, high-risk obtainment of prescription opioids, procuring multiple opioid prescribers, mental health outcomes, physical health outcomes, all-cause hospitalization, opioid-related hospitalization, nonopioid-specific hospitalization, emergency department visits, opioid overdose, all-cause death, opioid-related death, and nonopioid-related death.

Only 14 studies addressed interventions of any kind to appropriately reduce opioid prescriptions (Triangle I1 in the Conceptual Framework), prevent opioid-related disorders like OUD in older adults (Triangle I2), or reduce opioid-related harms (Triangle I3). The most-studied interventions are screening tools to predict opioid-related harms but none have been tested in clinical practice to assess real-world results. Two studies found that PDMPs, aligned with Triangle I1, are associated with less opioid use (at the State level). Other studied interventions included a nationally-mandated tamper-resistant opioid formulation (Triangle I1), patient education (Triangle I2), and clinician education (Triangle I3). However, each intervention was evaluated by only a single study. Another important point is that the recreational pathway (Box A2) was unaddressed by the empirical evidence.

Future Research Needs

As noted, there are many gaps in the evidence base regarding factors associated with opioid-related outcomes and of the effectiveness of interventions for older adults. We describe numerous research needs derived from clear gaps in the evidence base and based on issues raised by a range of stakeholders. In particular, future research should emphasize the adaptation of existing interventions for use in older adults. Studies among older adults to confirm the reliability, validity, and factor structure of screening tools for detecting opioid misuse are an especially salient

and attainable next step. The development, validation, and evaluation of new interventions tailored to the needs of older adults will likely also be necessary to manage opioid misuse and OUD in older adults.

Limitations

We developed an evidence map to describe the amount and type of practically available evidence related to the core of the Conceptual Framework, but in keeping with the scope of a Technical Brief, we did not fully assess studies (e.g., their risk of bias) or the body of evidence (e.g., strength of evidence). For feasibility, we did not consider research published more than 20 years ago (specifically, earlier than 1/1/2000), because older empirical data are less likely to be relevant to today's setting. While it is plausible that earlier studies are applicable, important questions are often addressed by more recent replication studies, in which case they would be represented in the evidence map. Furthermore, the more recent literature is probably more relevant for informing the future research agenda. We decided not to search EMBASE or any other large, international general database because, based on empirical data on the added utility of searching databases beyond PubMed, we deemed that the added benefit of searching multiple targeted databases was more cost and time efficient and would yield more relevant studies than a second large general database search.[126] However, we may have missed some relevant studies.

It is important to note that we did not review articles to determine whether they would meet any specific set of eligibility criteria for a systematic review of a specific Key Question. In our estimation, it is likely that many of these articles would be rejected for a given systematic review based on the specific populations of interest, the eligible definitions of predictors (or risk factors) and outcomes, study design features, and analytic methods. For example, although we assessed whether studies performed a multivariable (versus univariable) analysis when examining factors associated with opioid-related harms, we did not assess whether studies adequately controlled for all potentially important covariates in a given multivariable model. Thus, it is likely that many studies we identified in the evidence map would not be relevant to address a specific, well-formulated research question. Furthermore, the reader should be reminded that our literature search, screening, and eligibility criteria did not allow for us to delve into the large number of studies that did not focus on older adults or opioids that may have had relevant, potentially eligible, subgroup analyses. If the abstract provided no indication of an analysis regarding opioid use in older adults, it was not included. Undoubtedly, we thus missed pertinent studies that would have required more in-depth searching and screening.

While we did include studies conducted in other countries besides the U.S., we restricted to those countries with high-income economies where opioid misuse and OUD were anticipated as being most prevalent.

Finally, we did not include studies of older adults in palliative care, those who were terminally ill, those in hospice care, or others with limited life expectancy because opioid misuse, harms, or OUD were of significantly less concern in such populations. This should not be interpreted as a suggestion that these populations are not important.

Conclusions

Prevention, diagnosis, and management of opioids, opioid misuse and OUD in older adults are significant and challenging issues for which a greater understanding is necessary. The evidence base that is directly applicable to older adults who are prescribed opioids or have opioid-related disorders is sparse. Fundamental research is necessary to determine which factors may

predict opioid-related harms; studies to date suggest that the amount of prescribed opioids, prior use of opioids, musculoskeletal conditions, and substance misuse are potentially important factors. Research is also needed to identify interventions to reduce opioid treatment where harms outweigh benefits, to reduce opioid-related harms and disorders, and to treat existing misuse or OUD among older adults. Future research should emphasize the adaptation of existing interventions for use in older adults, but the development, validation, and evaluation of new interventions tailored to the needs of older adults will likely also be necessary to manage opioid misuse and OUD in older adults.

In summary, two immediately actionable next steps are 1) to conduct additional research focused on multivariable analyses replicating findings for factors that already have some information available, and 2) to further validate and adapt screening tools for identifying opioid misuse in older adults. Ultimately, developing the evidence base will enable policymakers, healthcare providers, and older adults to reduce inappropriate opioid use and the harms associated with opioid use and misuse.

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Abbreviations

This list of does not include abbreviations used only in tables or figure.

AHRQ	Agency for Healthcare Research and Quality
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
CDC	Centers for Disease Control and Prevention
COPD	chronic obstructive pulmonary disease
CPSMP	Chronic Pain Self-Management Program
CR	controlled release
ED	emergency department
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
HEAL	Helping to End Addiction Long-term
NA	Narcotics Anonymous
NIH	National Institutes of Health
NSAID	nonsteroidal anti-inflammatory drug
ORT	Opioid Risk Tool
OUD	opioid use disorder
PDMP	prescription drug monitoring program
PDUQp	Prescription Drug Use Questionnaire, patient version
PMQ	Pain Medication Questionnaire
SBIRT	Screening, Brief Intervention, and Referral to Treatment
SDS	Severity of Dependence Scale
SoDU	Screen of Drug Use
TKA	total knee arthroplasty (replacement)
TOO	Task Order Officer
VA	Veterans Administration