VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE USE OF OPIOIDS IN THE MANAGEMENT OF CHRONIC PAIN

Department of Veterans Affairs
Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs and the Department of Defense guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This Clinical Practice Guideline is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendation.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation with a patient-centered approach.

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Use of Opioids in the Management of Chronic Pain Work Group

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&

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I. Introduction

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Work Group (EBPWG) was established and first chartered in 2004, with a mission to advise the Health Executive Committee (HEC) "… on the use of clinical and epidemiological evidence to improve the health of the population …" across the Veterans Health Administration (VHA) and Military Health System (MHS), by facilitating the development of clinical practice guidelines (CPGs) for the VA and DoD populations.(1) Development and update of VA/DoD CPGs is funded by VA Evidence Based Practice, Office of Quality and Patient Safety. The system-wide goal of evidence-based CPGs is to improve patient health and well-being.

In February 2017, the VA and DoD published a CPG on Opioid Therapy for Chronic Pain (2017 VA/DoD Opioids CPG), which was based on evidence reviewed through December 2016. Since the release of that CPG, a growing body of research has expanded the evidence base and understanding of the use of opioids in the management of chronic pain. Consequently, the VA/DoD EBPWG initiated the update of the 2017 VA/DoD Opioids CPG in 2020. This updated CPG's use of Grading of Recommendations Assessment, Development and Evaluation (GRADE) reflects a more rigorous application of the methodology than previous iterations. Consequently, the strength of some recommendations may have been modified due to the confidence in the quality of the supporting evidence (see Evidence Quality and Recommendation Strength).

This CPG provides an evidence-based framework for evaluating and managing care for patients with chronic pain who are on or who are being considered for prescribed opioids toward improving clinical outcomes. Successful implementation of this CPG will:

- Assess the patient's condition and collaborate with the patient, family, and caregivers to determine optimal management of patient care
- Emphasize the use of patient-centered care and shared decision making
- Minimize preventable complications and morbidity
- Optimize individual health outcomes and quality of life (QoL)

II. Background

A. Opioid Epidemic

Chronic pain is a national public health problem. In 2018, the Centers for Disease Control and Prevention (CDC) reported one in five or about 50 million Americans suffer from some form of chronic pain, which accounts for an estimated $560 billion each year in direct medical costs, lost productivity, and disability programs.(2) In 2016, the CDC released a guideline for prescribing opioids for chronic pain, and, in 2017, the VA and DoD published a CPG to educate providers on the prescribing of opioids and mitigate opioid-related harms.

In 2019, over 70% of the 71,000 deaths due to a drug overdose involved an opioid. Moreover, the National Safety Council reported a higher likelihood to die from an accidental opioid overdose than a motor vehicle crash.(3, 4) There has been limited research on the effectiveness of long-term opioids for non-end-of-life pain; however, there is mounting evidence to suggest the ill effects of long-term opioid use. These include

increased mortality, opioid use disorder (OUD), overdose, sexual dysfunction, fractures, myocardial infarction, constipation, and sleep-disordered breathing.(5-7) Cognitive impairment may also be affected. A study from 2016 demonstrated that opioid use for longer than 30 days increased the risk of new-onset depression.(8)

Despite the known harms of opioids, these agents continue to be widely employed in daily practice. However, from 2012 through 2019, the overall quantity of opioids and the dispensing rate decreased. In 2012, for every 100 persons in the United States (U.S.), 82.5 opioid prescriptions were written by healthcare providers, compared to 46.7 in 2019.(4) In emergency departments, overall opioid prescribing declined about 30% from 2006 through 2017.(6) Although the number of prescriptions for opioids has decreased, deaths involving drug overdose increased over 4% from 2018 to 2019 alone.(3) This data suggests opioid users are increasingly seeking and accessing these drugs outside of legitimate medical channels.

The increase in illicit opioid use and overdose has involved heroin and fentanyl (a synthetic opioid). Deaths due to synthetic opioid use contributed to over 70% of all opioid-related deaths.(9) The death rates involving synthetic opioid use increased by 11% from 2013 to 2019.(9) The American Medical Association (AMA) reported nearly half of all heroin users started with an addiction to an opioid medication prior to switching for ease of availability.(10) In 2019, more than 14,000 people died from a drug overdose involving heroin, a rate of more than four deaths per 100,000 Americans.(11)

The opioid epidemic disproportionately affects Veterans. According to a study evaluating opioid prescribing habits and risk mitigation strategies in the VHA, not only do Veterans suffer from more severe chronic pain when compared to non-Veterans, but VHA patients are twice as likely to die from accidental overdose with either an opioid medication or cocaine when compared to the general population.(78) Increased opioid use in VHA patients also increased the risk of developing treatment-resistant depression.(12) Changes in opioid prescribing, as described above, have also led to increased use of illicit opioids within the VHA patient population. A study from 2019 involving Veterans showed a decline in opioid prescriptions but an increase in opioid overdose rates with heroin and synthetic drugs.(13)

The opioid epidemic is a national crisis, affecting public health and social and economic welfare, with prescription opioid misuse alone costing an estimated $78.5 billion per year.(14) The COVID-19 pandemic has reinforced the continued need to address this epidemic, with preliminary CDC data from 2019 to 2020 reporting an overdose increase of nearly 30% and over 90,000 deaths in that time window.(15) Opioid overdose, as well as associated morbidity, mortality, and other adverse outcomes, has called attention to the need for continuous updating of pain treatment options. Consult the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders (VA/DoD SUD CPG)[b] for further information on SUD and OUD. Other VA/DoD Clinical Practice Guidelines[c] provide guidance for specific disease categories.

[b] See the VA/DoD CPG for the Management of Substance Use Disorders, available at: https://www.healthquality.va.gov/
[c] See other VA/DoD CPGs, available at: https://www.healthquality.va.gov/

B. Paradigm Shift in Pain and Its Treatment

The U.S. is undergoing a cultural transformation in the way pain is viewed and treated. The biomedical model of pain care, in which the pain experience is reduced to a "find-it, fix-it" model, dominated the 1990s and the first decade of the 2000s. In this model, there was a focus on finding the pain generator and pain treatments aimed at "fixing" or numbing pain with medications, interventions, or surgery. During the same period, opioid use expanded beyond acute and perioperative care, palliative care, end-of-life care, and cancer pain. Chronic pain management became synonymous with opioid prescribing, with significant numbers of patients in pain clinics receiving opioids long-term.(16) The causes for this biomedical focus on pain management included a complex mix of factors including the shifting economics of healthcare delivery with inadequate time to provide care, the pharmaceutical industry's development and promotion of new opioids, and insufficient provider training on pain management. The narrowly described biomedical problem inappropriately diverted seeing the patient as a whole person.

Despite the absence of long-term safety or efficacy data, opioids for chronic pain became a mainstay of therapy. However, as observational and epidemiologic data of harm from long-term use of opioids accumulated, a much more cautious approach to opioids for chronic pain emerged in the decade of the 2010s that prioritized patient safety. Per the 2016 CDC guideline for prescribing opioids for chronic pain,(17) experts agree that opioids should not be considered first line or routine therapy for chronic pain, outside of active cancer, palliative, and end-of-life care. This approach, supported by the evidence of both the safety and efficacy for non-pharmacologic and non-opioid pharmacologic pain therapies, has led to the recommended transformation in how pain is viewed and treated by providers and patients alike.

The biopsychosocial model of pain recognizes pain as a complex, multidimensional experience requiring multimodal and integrated care approaches. Further, the stepped care model for pain management is used as a framework within VA and DoD to optimize the use of patient-centered, evidence-based treatments and support guideline-concordant pain practices across the continuum of care.(18) The stepped care model for pain management calls for interventions that promote screening, assessment, and management of pain via low intensity interventions followed by the introduction of more intensive, specialized, and individually-tailored approaches based on complexity and need as individuals progress through the steps.(19) Step one, occurring in primary care, includes routine screening and low intensity interventions, followed by secondary and tertiary steps with more specialized pain care that may include more aggressive, expensive, and comprehensive treatment options when appropriate.(18) Identification of those with greater risk factors assists in improved triage for more intensive care, including the evaluation and treatment of OUD. Within this context, clinicians should communicate and collaborate with patients throughout the process of developing and evaluating pain management treatment plans. Decisions should be individualized, with careful consideration given to the risks and benefits of all treatment options. This approach emphasizes equitable care across groups that is focused on functional improvement, pain reduction, and risk mitigation.

In addition, in 2016, Congress passed the Comprehensive Addiction and Recovery Act (CARA) to address the national opioid epidemic. The bill specifically directs the VA to address pain management for Veterans. In response, the VA's Office of Patient Centered Care and Cultural Transformation formalized an approach to care called the Whole Health System of Care (Whole Health), incorporating patient-centered care and complementary and integrative health. Whole Health promotes health and wellness by emphasizing a

personalized, proactive, patient-driven model of care focused on self-empowerment, self-healing, and self-care. The Whole Health effort in VA has supported a biopsychosocial approach to pain care and evidence suggests that the Whole Health approach has had a positive impact on reducing opioid use among Veterans, as opioid use decreased 38% among Whole Health users compared with an 11% decrease among those with no use of Whole Health services.(20) VA and DoD have taken a multipronged approach to shift the focus of care to the individual, recognizing pain as a complex and personal experience.

C. Taxonomy and Pain Assessment

In 2020, the International Association for the Study of Pain (IASP) formed a task force (21, 22) that updated their 1979 definition of pain to "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."(23) This definition is thought to be more inclusive of all persons despite ability to verbally articulate the pain experience. The IASP noted six key points to consider about persons in pain: (23, 24)

- Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.
- Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.
- Through their life experiences, individuals learn the concept of pain.
- A person's report of an experience as pain should be respected.
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.
- Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain.

All of these facets signify the complexity of pain as a condition by itself and how the brain's protective response affects the body.(25) Pain as a symptom is multifaceted and is described and characterized by many factors such as its quality (e.g., sharp versus dull), intensity, timing, location, and whether it is associated with position or movement. Other factors such as fear avoidance beliefs and pain catastrophizing can also contribute to the pain experience and whether an acute pain experience morphs into a persistent pain state. Fear avoidance beliefs can lead to a vicious chronic pain cycle where a person's fears of increased pain/reinjury lead to avoidance, negative emotions and distress, decreased participation in activity, increased disability, and pain chronification.(26, 27)

Chronic pain is defined as persistent or recurrent pain lasting longer than three months,(28, 29) though this definition lacks the nuance and complexity to describe different presentations of chronic pain. In 2015, an IASP Task Force (21, 22) further described the classification of chronic pain into seven groups: (1) chronic primary pain; (2) chronic cancer pain; (3) chronic post-traumatic and post-surgical pain; (4) chronic neuropathic pain; (5) chronic headache and orofacial pain; (6) chronic visceral pain; and (7) chronic musculoskeletal pain.(28, 29) Chronic pain is thought to be associated with changes in the central nervous system (CNS) known as central sensitization.(24, 30) Acute and subacute pain are thought to involve primarily nociceptive processing areas in the CNS.

Chronic pain with prolonged and intense exposure to nociceptive stimuli is thought to lead to changes in nociceptive processing through peripheral and central sensitization of nociceptive pathways. With chronic pain, brain centers involved in pain processing become more sensitized, and emotional and cognitive factors become more prominent than sensory/nociceptive circuits. Psychological and social elements take on a greater role, serving as a vicious cycle and contributing to the persistence of pain.(31-34) Central sensitization can lead to altered modulation of pain processing within the CNS that leads to either an increased excitability and/or reduced inhibition of specific neural networks leading to feelings of allodynia or hyperalgesia.(35)

A comprehensive pain assessment includes a biopsychosocial interview and focused physical exam. Elements of the biopsychosocial pain interview include:

- Pain assessment (25)
    - Includes the following information about pain:
        - Pain Onset
        - Location
        - Duration
        - Exacerbating factors
        - Relieving factors
        - Radiation
        - 24-hour pain pattern
        - Quality of pain
    - Assessment of history of previous treatments and effect on pain
    - Assessment of impact of pain on daily functioning and QoL
    - Assessment of patient's functional goals
    - Evaluation of psychological/behavioral factors that may affect treatment
    - Evaluation of social factors that may affect treatment
    - Assessment of current and past co-occurring conditions
    - Physical exam
    - Diagnosis confirmation
    - Consideration of consultations and referral
    - Discussion of patient beliefs and understanding of the cause of their pain, their preferences, and perceived efficacy of various treatment options.

See Sidebar A of the algorithm for more information on biopsychosocial assessments.

Patients with chronic pain may also experience worsened QoL, behavioral health, immune system function, physical function, sleep, employment status, and impaired personal relationships.(36-39) Worsening of some of these factors (e.g., QoL, change in employment status) seems to also be associated

with pain severity and the presence of psychiatric comorbidities.(40, 41) Patients with chronic pain report psychological complaints (e.g., depression, anxiety, poor self-efficacy, poor general emotional functioning) more often than patients without chronic pain.(42) Further, there can be social and psychological consequences such as decreased ability to successfully maintain relationships and career roles and increased depression, fear, and anxiety as a result of pain.(39, 43)

D. Epidemiology and Impact

a. General Population

Chronic pain is among the most common, costly, and disabling chronic medical conditions in the U.S.(2, 39, 44, 45) Approximately 50.2 million adults experience chronic pain on most days or every day,(46) and pain is associated with approximately 20% of ambulatory primary care and specialty visits in the U.S.(39, 43, 47) As noted above (see Opioid Epidemic), from the late 1990s until about 2008, the proportion of pain visits during which patients received opioids increased significantly, as did opioid-related morbidity, mortality, overdose death, and substance use disorder (SUD) treatment admissions.(47-49) However, the annual percentage of U.S. adults who had an opioid prescription filled decreased by 31% from 2008–2018.(50) This decline might be attributed to the implementation of several opioid prescribing guidelines, enhanced prescription drug monitoring programs (PDMP), and other quality improvement initiatives. From 2000 until 2010, approximately one in five patients with non-cancer pain or pain-related diagnoses were prescribed opioids in an office-based setting.(47, 51) According to the CDC, a steady increase in the overall national opioid dispensing rate started in 2006 and peaked in 2012 at more than 255 million prescriptions and a dispensing rate of 81.3 prescriptions per 100 persons.(52) The overall national opioid dispensing rate declined from 2012 to 2020, and in 2020, the dispensing rate fell to the lowest in 15 years at a rate of 43.3 prescriptions per 100 persons.(52) However, in 2020, dispensing rates continued to remain very high in certain areas across the country (e.g., Alabama, Mississippi, Louisiana, Arkansas, Tennessee, Kentucky). In 3.6% of U.S. counties, the number of opioid prescriptions dispensed matched or exceeded the county population.(52)

The absolute number of deaths associated with the use of prescribed and illicit opioids increased four-fold between 2000 and 2014.(53) In 2019, nearly 50,000 people in the U.S. died from opioid-involved overdoses.(54) Of those 50,000 individuals, 14,019 (28%) died from a heroin overdose.(55) This is a significant increase from the 1,960 overdose deaths involving heroin in 1999.(55) The connection between heroin use and prescription opioids is important; it is estimated that about 80% of people who use heroin first misused prescription opioids.(56) Deaths involving synthetic opioids other than methadone (primarily fentanyl) continued to rise, with 56,516 overdose deaths reported in 2020.(57) Provisional data from the CDC's National Center for Health Statistics estimated that overdose deaths from opioids increased to 75,673 in the 12-month period ending in April 2021, up from 56,064 the year before.(58)

Despite the opioid crisis initially being seen in white communities, there are now demographic shifts. Between 2018 and 2019, overdose deaths increased disproportionately among non-Hispanic black individuals compared to individuals in other racial and ethnic groups.(59) Larochelle et al. (2021) concludes that "an antiracist public health approach is needed to address the crisis of opioid-related harms."(59) Mossey et al. (2011) demonstrates that racial and ethnic minorities consistently receive inadequate care for acute and chronic pain.(60) This disparity reflects a lack of sufficient clinician awareness of minority individuals, cultural beliefs, and stereotypes regarding pain.(60) Burgess et al. (2014) found that black

patients under the age of 65 were less likely to receive prescription opioids than white patients for moderate (3.2% less likely, p=0.0025) and high (3.1% less likely, p=0.0011) levels of pain.(61) Hausmann et al. (2013) found that black patients were less likely than white patients to be referred to a pain specialist.(62) Gaither et al. (2018) demonstrated that among patients who test positive for illicit drug use while receiving long-term opioids, black patients are considerably more likely to be discontinued from opioids than other racial and ethnic groups.(63)

b. VA Population

From fiscal years 2004 to 2012, the prevalence of opioid prescriptions among Veterans increased from 18.9% to 33.4%, an increase of 76.7%.(64) Recognizing opioid-related harms, the VA has since reduced prescription opioid use in patients within the VA health care system by 64% from 2012 to 2020.(65)

From Q4 FY 2012 to Q1 FY 2020, VHA opioid dispensing peaked in 2012 with 679,376 Veterans receiving an opioid prescription, and when including tramadol, in 2013 with 869,956 Veterans.(66) Since 2012, the number of Veterans dispensed an opioid decreased 56% and co-prescribed opioids/benzodiazepines decreased 83%. Veterans with high-dose opioids (≥100 mg morphine equivalent daily dose) decreased 77%.(66) In Q1 FY 2020, among Veterans on long-term opioid therapy, 91.1% had written informed consent, 90.8% had a urine drug screen, and 89.0% had a prescription drug monitoring program query.(66)

The groups with the highest prevalence of opioid use were women and young adults (i.e., 18-34 years old).(64) In a sample of non-treatment-seeking members of the military who were interviewed within three months of returning from Afghanistan, 44% reported chronic pain and 15% reported using opioids—percentages much higher than in the general population.(67-69) Chronic pain was associated with poorer physical function, independent of comorbid mental health concerns in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans.(69, 70) Several demographic groups were also found to be at increased risk of chronic pain diagnosis, including women and black non-Hispanic individuals.(71)

In a study of Veterans with chronic pain who had been on opioids for at least 90 days, over 90% continued to use opioids one year later and nearly 80% continued to use opioids after completion of the study's 3.5 year follow-up period.(72) Conversely, in a study of civilian patients who had been on opioids for at least 90 days, approximately 65% remained on opioids through the 4.8 year follow-up period.(73) Rates of continuation in Veterans, based on this study, appeared to be related to age, marital status, race, geography, mental health comorbidity, and dosage. Compared to others, those who were age 50-65, were married, were of a race other than African American, and who lived in a rural setting were more likely to continue using opioids. Veterans on higher doses of opioids were also more likely to continue their use. Another study found that individuals with major depressive disorder (MDD) and bipolar disorder diagnoses were over two times more likely to receive chronic opioid medication prescriptions compared to matched controls.(74)

The rate of opioid overdose among Veterans increased from 14.47 per 100,000 person-years in 2010 to 21.08 per 100,000 person-years in 2016.(75) The overall increase in overdose rates among Veterans was driven by an increase in heroin and synthetic opioid (including fentanyl) overdose rates, similar to the general population. Where synthetic opioid and heroin overdose rates increased substantially, methadone overdoses declined and there were no significant changes in natural/semisynthetic opioid overdoses.(75)

To address the opioid epidemic, the VA implemented the Whole Health initiative (see Paradigm Shift in Pain and Its Treatment), for which preliminary evidence is showing positive effects on pain burden and opioid prescribing.(20) An evaluation of this initiative demonstrated a threefold reduction in opioid use among Veterans with chronic pain who used Whole Health services, as compared to those who did not.(20) Further detail on this can be found in the Prioritizing Safe Opioid Prescribing Practices and Use section below.

c. DoD Population

The DoD's active duty Service Members (ADSMs) have shown a significant increase in pain concerns over the last 10 years. In a 2018 survey, 30% of ADSMs reported they were bothered by at least one or more bodily pain(s) in the last 12 months and two in five reported at least one chronic condition to include pain as the cause.(76) The 2020 Medical Surveillance Monthly Report (MSMR) revealed that between 2009-2018, chronic pain diagnoses increased from 85.5 per 10,000 person-years to 261.1 per 10,000 person years.(77) Being female, non-Hispanic black, older, or enlisted correlated with increased risk of chronic pain diagnoses. The Army has the highest risk of chronic pain diagnosis, and Navy has the lowest risk. The number of ADSMs with medical encounters attributed to or affected by a pain diagnoses increased by over 320% and 207% respectively.(77)

The 2018 Health Related Behaviors Survey (HRBS) points out the potential for pain to reduce physical functioning or lead to health risks associated with prescription analgesic use, including use of opioids.(76) The HRBS found almost 17% of ADSMs report prescription drug use and over 12% report using prescription pain relievers in the past 12 months. In regards to misuse of prescription drugs, 1.4% of ADSMs report misuse, and misuse was the highest for pain relievers.(78) Among ADSM's, taking opioids can increase the risk of both overdose and suicide deaths. In the U.S. Army Public Health Center's Surveillance of Suicidal Behavior Report, the second most common method of suicide among ADSMs was overdosing on drugs/alcohol.(79) Among Army Service Members, the Office of the Surgeon General (OTSG) identified three major polypharmacy risk factors that could increase likelihood of overdose: (1) prescriptions for four or more of any type of medication, including one or more opioid, within the previous 30 days; (2) prescriptions for four or more medications from the seven categories of psychotropics and CNS depressants (opioid, stimulant, anxiolytic, antidepressant, antipsychotic, anticonvulsant, or sleep medication) within the previous 30 days; and (3) three or more emergency room visits in the last 12 months where each visit is linked with a new opioid prescription and at least one of these visits occurred in the last 30 days.(80)

A ten-year surveillance (2007-2017) of opioid prescription fills among ADSMs shows decreasing fill rates. Despite this decrease, nearly one in four ADSMs filled an opioid prescription in 2017, equivalent to retired Service Member fill rates. Furthermore in 2017, ADSMs tended to have an average of two fills per patient while retired Service Members had an average of seven fills per patient.(81) Instituting occupational health policy interventions has been shown to decrease opioid use among ADSMs. Policy implementation could decrease annual opioid prescriptions by 6.6%, which would result in over 120,000 less opioid prescriptions dispensed over 12 months.(82) MSMR findings suggest the importance of tracking opioid fills, monitoring patients with opioid prescriptions, expanding surveillance efforts to assess prescription practices, and limiting opportunities for opioid misuse and abuse.(81)

E. Prioritizing Safe Opioid Prescribing Practices and Use

The past decade has brought a series of changes and lessons learned as the country has grappled first with the harmful effects of opioid overprescribing and, subsequently, the significant harms of rapid opioid tapers that occurred as deprescribing became more commonplace. Here, we outline the history, legislation, guidelines, and program development related to opioid prescribing and safety.

As discussed earlier, throughout the 1990s and 2000s, physicians increasingly incorporated opioid prescribing as part of pain care plans for patients living with chronic pain. By 2010, opioid prescribing was recognized as an important contributor to the nation's increasing rate of opioid overdose deaths, which disproportionately affected Veterans.(83, 84) In response, in 2013, the VHA deployed the Opioid Safety Initiative (OSI) with the aim of ensuring the use of opioids in a safe, effective, and judicious manner. VHA employed four broad strategies to address this crisis: education, pain management, risk mitigation, and addiction treatment.(66, 85). The OSI uses the VHA's electronic health record to identify patients who may be high-risk for adverse outcomes related to use of opioids and providers whose prescribing practices may not reflect best evidence. Early outcome data showed a substantial reduction in high-dose opioid prescribing and concurrent benzodiazepine-opioid prescribing from pre-OSI data compared to post-OSI implementation.(66, 86) A key element of VHA's OSI education strategy is VHA Pharmacy Benefits Management's Academic Detailing Service (PBM ADS). Academic Detailing (AD) is a knowledge translation intervention through educational outreach delivered by clinicians to providers and staff with the goal of aligning their practice with current evidence.(87) In VHA, this is primarily done in one-on-one, face-to-face settings by trained clinical pharmacists who use dashboards with prescriber-level data and educational tools to inform and engage clinicians in adopting best practices.[d] Academic Detailing initiatives have supported components of the OSI, including the Opioid Overdose Education and Naloxone Distribution (OEND) program (aimed at reducing deaths from opioid overdose through education and distribution of naloxone kits), reevaluating the risks of benzodiazepines and providing guidance on dose reduction and discontinuation, and encouraging providers to prescribe medications for OUD (MOUD), among others.

In 2014, VHA issued a directive requiring patient education and written informed consent for long-term treatment with opioids, excluding patients enrolled in hospice care and on opioids for cancer pain, when oral consent can be used instead.

Passed in 2016, CARA (also known as the "Jason Simcakoski Memorial and Promise Act") further expanded the monitoring of opioid prescribing and risk mitigation by requiring disclosure of Veteran information to state PDMPs. This helped to address the critical need for improved communication between healthcare providers in the U.S. healthcare system. That same year, the VHA issued Directive 1306, requiring providers to query the PDMP for patients receiving a controlled substance prescription for longer than five days and for shorter courses with refills (except for hospice care).(88) These PDMP queries provide clinicians with a complete and cohesive controlled substance prescription history, across all care locations, to drive more informed decisions. In November 2020, VA successfully deployed an integrated PDMP solution into the electronic health record. The integrated PDMP solution enables querying PDMPs from within the Veteran's patient record with the click of a button, providing greater efficiency while supporting safe prescribing of controlled substances. The integrated PDMP solution fulfills a key milestone for VA,

[d] See the OSI toolkit materials from the VHA Pain Management, Opioid Safety, and Prescription Drug Monitoring Program Office, available at: https://www.va.gov/PAINMANAGEMENT/Opioid_Safety_Initiative_OSI.asp

meeting the requirements of the MISSION Act Section 134, and enables VA to participate in a robust network of State-based PDMPs.

In addition to expanding opioid safety measures in VA, CARA promoted greater access to pain care for Veterans including full implementation of the stepped care model for pain management and designated interdisciplinary pain teams at all VA facilities. Moreover, CARA requires each facility to have a pain management team and to expand integrative health modalities. The pain management team evaluates and provides follow-up as needed for Veterans with complex pain conditions.

Also in 2016, the same year as CARA, the CDC released a guideline for prescribing opioids for chronic pain,(17) followed by the 2017 publication of the VA/DoD CPG for Opioid Therapy for Chronic Pain, which specifically recommended against initiation of long-term opioids for chronic pain.

To further enhance risk mitigation, VHA policy since 2018 has required interdisciplinary team review and care coordination for Veterans who are receiving opioid medication and are estimated to be at very high risk for overdose/suicide based on the Stratification Tool for Opioid Risk Mitigation (STORM). Updated daily, STORM utilizes predictive analytics to estimate a "risk score" of adverse outcomes (e.g., suicide-related events, overdose, overdose death) from variables in the VA medical record for all patients with an opioid prescription. It displays this information along with documentation of recommended risk mitigation strategies and non-opioid pain treatments.(89)

As part of the CARA legislation, the VHA also began requiring the establishment of large-scale piloting of the Whole Health model of care, to shift chronic pain care from a disease-focused "find-it, fix-it" model to one driven by patients' personal health goals, to foster patient self-management and to improve well-being.(90) Survey data from pilot participants demonstrated those who used Whole Health services reported greater improvements in perceptions of care, engagement in health care and self-care, life meaning and purpose, pain, and perceived stress.(20) There were also greater improvements in opioid use among Veterans using the Whole Health model compared to those with no Whole Health model use.(20)

Also mandated within CARA was convening of a task force to review best practices for pain management and make recommendations on addressing gaps and inconsistencies. As a result, the Pain Management Best Practices Inter-Agency Task Force (Task Force) was convened by the U.S. Department of Health and Human Services (HHS), in conjunction with DoD, VA, and the Office of National Drug Control Policy. The Task Force was composed of 29 members representing federal agencies as well as non-federal experts from a broad range of stakeholders. The Task Force was the largest federal and civilian group to review the evidence and provide guidelines on this topic. The Task Force recognized the unintended consequences of risk mitigation strategies recommended by the 2016 CDC guidelines, such as forced opioid tapers and patient abandonment, which were due in part to the misapplication or misinterpretation of the guideline. The Task Force recommended increased collaboration, reduced administrative burden, improved access to care, addressing stigma, and enhancing education, innovation, and research.(91, 92)

To address the increased concern related to mounting harms of forced and non-standardized tapering strategies, attention has turned to assessing and addressing the risks of various tapering strategies. One observational study of 509 VHA patients who were all discontinued from long-term opioid therapy evaluated for the presence of suicidal ideation and suicidal self-directed violence.(93) Within the 12

months following opioid discontinuation, close to 10% of Veterans experienced suicidal ideation, and 2.4% had suicidal self-directed violence. The presence of PTSD and psychotic disorders were associated with increased risk.(93) Another observational study reported that death from suicide or overdose increased after discontinuation of opioids.(94) Consistent with this, in 2019, the authors of the 2016 CDC guideline and the U.S. Department of Health and Human Services (HHS) both issued commentary advising against abrupt tapering or sudden discontinuation of opioids.(95, 96)

In 2018, recognizing the urgent need to improve access to MOUD, the VHA implemented the Stepped Care for Opioid Use Disorder Train the Trainer (SCOUTT) Initiative to facilitate access to MOUD in VHA non-SUD-specialty care settings, in particular in primary care, pain specialty, and general mental health clinics, along with two VHA-funded implementation research projects to facilitate implementation and evaluation of the SCOUTT Initiative.(97) Several educational and consultation initiatives serve to complement and support the national implementation of SCOUTT, including the Buprenorphine in VA (BIV) initiative, the Medication Addiction Treatment in VA (MAT-VA) initiative, and the National TeleMental Health Center SUD Telehealth Program (NTMHC-SUD).(97) The goal of these programs is to educate, advise, and mentor VHA providers to assess and mitigate opioid-related risks (BIV and MAT-VA) and to provide direct-to-Veteran consultation for complex SUD-related clinical presentations (NTMHC-SUD) to improve access to quality MOUD care across the VHA.

In keeping with these initiatives, in 2019, the VHA's Health Services Research and Development convened the 15th State-of-the-Art conference, titled *Effective Management of Pain and Addiction: Strategies to Improve Opioid Safety* to determine a research agenda focused on the remaining challenges to the delivery of high-quality pain management and OUD care in the VHA. The resulting research agenda relates to managing OUD, long-term opioids for pain, and the treatment of co-occurring pain and SUD. The highest priority topics were implementation studies for expanding access to MOUD, research on tapering programs for patients prescribed long-term opioids, and larger trials of behavioral and exercise/movement interventions for pain among patients with SUD.(98)

In early 2021, HHS published the *Practice Guidelines for the Administration of Buprenorphine for Treating Opioid Use Disorder*[e] to expand access to MOUD by exempting physicians from certain certification requirements needed to prescribe buprenorphine for OUD treatment.

Moreover, the MHS has seen a significant decline in opioid prescriptions as a primary tool for pain management. The decline in opioid prescriptions highlights the success of the Defense Health Agency's (DHA) training and education programs aimed at reducing the risks linked to opioids.(99) The most dramatic decline in recent years was reported among ADSMs, but military health data shows reductions in opioid prescriptions across the entire MHS including among non-active duty beneficiaries both under age 65 and ages 65 and over.(99) To reduce the risks of addiction and potentially fatal overdoses, the MHS has implemented a comprehensive effort to curb the prescribing of opioids in favor of other effective pain management strategies. Among ADSMs from April 2017 to July 2021, military health data shows a 69% decline in prescriptions filled for opioids at a strength of 50 morphine milligrams equivalent (MME) per day or more.(99) For non-active duty beneficiaries under the age of 65, the decline for the same period was

[e] Available at: https://www.federalregister.gov/public-inspection/2021-08961/practice-guidelines-for-the-administration-of-buprenorphine-for-treating-opioid-use-disorder

47%. Further, for non-active duty beneficiaries 65 or older, the decline was 32%, according to data from the MHS information platform.(99) The MHS is also reporting fewer opioid prescriptions for people who are co-prescribed opioids and benzodiazepines.(99) Finally, long-term opioid use among MHS beneficiaries (defined as taking opioids 90 days or more out of the past 180 days) has also declined.(99)

III. Scope of this Guideline

This CPG is based on published clinical evidence and related information available through April 9, 2021. It is intended to provide general guidance on best evidence-based practices (see Appendix A for additional information on the evidence review methodology). This CPG is not intended to serve as a standard of care. This CPG is intended to aid practitioners in understanding the state of evidence on the use of opioids for chronic pain. The use of guidelines must always be in the context of a health care provider's clinical judgment in the care of a particular patient. Guidelines may be viewed as a tool to aid a practitioner in making evidence-based clinical decisions.

A. Guideline Audience

This CPG is intended for use by VA and DoD PCPs and other clinicians, including physicians, nurse practitioners, physician assistants, physical therapists, nurses, psychologists, dietitians, pharmacists, social workers, and others, involved in the healthcare team caring for patients prescribed opioids for chronic pain. Additionally, this CPG is intended for community-based clinicians involved in the care of Service Members, beneficiaries, or Veterans prescribed opioids for chronic pain.

B. Guideline Population

The patient population of interest for this CPG is adults who are eligible for care in the VA or DoD healthcare delivery systems and those who receive care from community-based clinicians with chronic pain or acute pain who are on or being considered for prescription opioid therapy. It includes Veterans and Service Members as well as their beneficiaries. Recommended interventions in this CPG are applicable regardless of care setting, unless otherwise indicated, for any patient in the VA and DoD healthcare system.

IV. Highlighted Features of this Guideline

A. Highlights in this Guideline Update

The current document is an update to the 2017 VA/DoD Opioids CPG. The following significant updates make it important that providers review this version of the CPG:

- Updated algorithm (modified from four modules to three; condensed 2017 Modules C and D to a single module [Module C] on Maintaining, Tapering, Discontinuing, or Switching from Full Agonist Opioids)
- Added four new recommendations; reviewed and replaced 12 recommendations; deleted seven recommendations
- Used more rigorous application of GRADE methodology

The pace of clinical research on long-term and short-term use of opioids for pain conditions continues to grow every year. This CPG includes recommendations on the following key topics:

- Behavioral health assessment in all patients, including assessing all patients with chronic pain for co-occurring behavioral health conditions prior to opioid initiation and periodically during treatment with opioids
- Screening patients with acute pain for pain catastrophizing when opioids are being considered
- The use of pre-operative opioid and pain management education for patients
- The use of buprenorphine instead of full agonist opioids for patients receiving daily opioids for chronic pain

As noted above, the methodology used in developing this CPG has been updated since the prior versions and reflects a more rigorous application of the methodology than previous iterations, which are detailed in Appendix A. The result is a refined CPG that includes methodologically rigorous, evidence-based recommendations for the treatment of patients with chronic pain and limited recommendations for patients with acute pain.

B. Components of the Guideline

The 2022 VA/DoD Opioids CPG is the fourth update to this CPG. It provides clinical practice recommendations for the care of patients with chronic pain or acute pain who are on or being considered for prescribed opioids (see Recommendations). In addition, the Algorithm incorporates the recommendations in the context of the flow of patient care. This CPG also includes Research Priorities, which list areas the Work Group identified as needing additional research.

To accompany this CPG, the Work Group also developed toolkit materials for providers and patients, including a provider summary, patient summary, and pocket card. These can be found at https://www.healthquality.va.gov/.

V. Guideline Development Team

The VA Evidence Based Practice, Office of Quality and Patient Safety, in collaboration with the Clinical Quality Improvement Program, Defense Health Agency, identified the following four clinicians to serve as Champions (i.e., leaders) of this CPG's Work Group: Dr. Friedhelm Sandbrink and Dr. Jennifer Murphy from the VA and Dr. Christopher Spevak and CDR Melanie Johansson from the DoD.

The Work Group comprised individuals with the following areas of expertise: pain and addiction medicine, pain and addiction psychiatry, clinical psychology, pharmacy, nursing, social work, complementary and integrative health, physical therapy, case management, behavioral medicine, and primary care. See Table 1 for a list of Work Group members.

This CPG Work Group, led by the Champions, was tasked with:

- Determining the scope of the CPG
- Crafting clinically relevant key questions (KQs) to guide the systematic evidence review

- Identifying discussion topics for the patient focus group and considering the patient perspective
- Providing direction on inclusion and exclusion criteria for the systematic evidence review and the assessment of the level and quality of evidence
- Developing evidence-based clinical practice recommendations, including determining the strength and category of each recommendation

The Lewin Team, including The Lewin Group, ECRI, Sigma Health Consulting, and Duty First Consulting, was contracted by the VA to help develop this CPG.

Table 1. Guideline Work Group and Guideline Development Team

Organization	Names*
Department of Veterans Affairs	**Jennifer Murphy, PhD (Champion)**
	Friedhelm Sandbrink, MD (Champion)
	Jamie Clinton-Lont, AGPCNP-BC
	Ellen L. Edens, MD, MPE
	Franz Macedo, DO
	Mitchell Nazario, PharmD
	Juli Olson, DC, DACM
	Sanjog Pangarkar, MD
	Matthew Prince, PT, DPT, OCS
	Donna Endsley Real, MPH, LCSW
Department of Defense	**CDR Melanie Johansson, MD, FACEP (Champion)**
	Christopher Spevak, MD, MPH, JD (Champion)
	MAJ Nicole H. Brown, DPT, OCS, SCS, FPS
	Kathryn Gillespie, MSN, JD, RN, CNL
	MAJ Raquel Giunta, PharmD, BCPS
	COL Samuel Preston, DO
	CAPT David Riegleman, MD
	Evan Steil, MD, MBA, MHA, FAAFP
VA Evidence Based Practice, Office of Quality and Patient Safety Veterans Health Administration	Eric Rogers, PhD, FNP-BC
	James Sall, PhD, FNP-BC
	René Sutton, BS, HCA
Clinical Quality Improvement Program Defense Health Agency	Lisa Jones, BSN, RN, MHA, CPHQ
	Elaine Stuffel, MHA, BSN, RN
	Kathryn Gillespie, MSN, JD, RN, CNL
The Lewin Group	Clifford Goodman, PhD
	Erika Beam, MS
	Ben Agatston, JD, MPH
	Charlie Zachariades, MSc
	Andrea Dressel, BS
	Estee Welo, BA

Organization	Names*
ECRI	James Reston, PhD, MPH
	Kelley Tipton, MPH
	Allison Hedden-Gross, MS, MLS
Sigma Health Consulting	Frances M. Murphy, MD, MPH
	James Smirniotopoulos, MD
Duty First Consulting	Mary Kate Curley, BA
	Kate Johnson, BA
	Rachel Piccolino, BA
	Richa Ruwala, BA

*Additional contributor contact information is available in Appendix H

VI. Summary of Guideline Development Methodology

The methodology used in developing this CPG follows the *Guideline for Guidelines*, an internal document of the VA/DoD EBPWG updated in January 2019 that outlines procedures for developing and submitting VA/DoD CPGs.(100) The *Guideline for Guidelines* is available at https://www.healthquality.va.gov/. This CPG also aligns with the NAM's principles of trustworthy CPGs (e.g., explanation of evidence quality and strength, the management of potential conflicts of interest [COI], interdisciplinary stakeholder involvement, use of systematic review, and external review).(101) Appendix A provides a detailed description of the CPG development methodology.

A. Evidence Quality and Recommendation Strength

The Work Group used the GRADE approach to craft each recommendation and determine its strength. Per the GRADE approach, recommendations must be evidence-based and cannot be made based on expert opinion alone. The GRADE approach uses the following four domains to inform the strength of each recommendation (see Determining Recommendation Strength and Direction):(102)

- Confidence in the quality of the evidence
- Balance of desirable and undesirable outcomes
- Patient values and preferences
- Other considerations, as appropriate, e.g.:
    - Resource use
    - Equity
    - Acceptability
    - Feasibility
    - Subgroup considerations

Using these four domains, the Work Group determined the relative strength of each recommendation (*Strong* or *Weak*). The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the

framework above, which incorporates the four domains.(103) A *Strong* recommendation generally indicates *High* or *Moderate* confidence in the quality of the available evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar patient values and preferences, and understood influence of other implications (e.g., resource use, feasibility).

In some instances, there is insufficient evidence on which to base a recommendation for or against a particular therapy, preventive measure, or other intervention. For example, the systematic evidence review may have found little or no relevant evidence, inconclusive evidence, or conflicting evidence for the intervention. The manner in which this is expressed in the CPG may vary. In such instances, the Work Group may include among its set of recommendations a statement of insufficient evidence for an intervention that may be in common practice even though it is not supported by clinical evidence, and particularly if there may be other risks of continuing its use (e.g., high opportunity cost, misallocation of resources). In other cases, the Work Group may decide to not include this type of statement about an intervention. For example, the Work Group may remain silent where there is an absence of evidence for a rarely used intervention. In other cases, an intervention may have a favorable balance of benefits and harms but may be a standard of care for which no recent evidence has been generated.

Using these elements, the Work Group determines the strength and direction of each recommendation and formulates the recommendation with the general corresponding text (see Table 2).

Table 2. Strength and Direction of Recommendations and General Corresponding Text

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend …
Weak for	We suggest …
Neither for nor against	There is insufficient evidence to recommend for or against …
Weak against	We suggest against …
Strong against	We recommend against …

It is important to note that a recommendation's strength (i.e., *Strong* versus *Weak*) is distinct from its clinical importance (e.g., a *Weak* recommendation is evidence-based and still important to clinical care). The strength of each recommendation is shown in the Recommendations section.

This CPG's use of GRADE reflects a more rigorous application of the methodology than previous iterations. For instance, the determination of the strength of the recommendation is more directly linked to the confidence in the quality of the evidence on outcomes that are critical to clinical decision-making. The confidence in the quality of the evidence is assessed using an objective, systematic approach that is independent of the clinical topic of interest. Therefore, recommendations on topics for which it may be inherently more difficult to design and conduct rigorous studies (e.g., randomized controlled trials [RCTs]) are typically supported by lower quality evidence and, in turn, *Weak* recommendations. Recommendations on topics for which rigorous studies can be designed and conducted may more often be *Strong* recommendations. Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(104, 105) This stricter standard provides a consistent approach to determining recommendation strengths. For additional information on GRADE or CPG methodology, see Appendix A.

B. Categorization of 2017 Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current. Except for an original version of a new CPG, this typically requires revision of a CPG's previous versions based on new evidence or as scheduled subject to time-based expirations.(106) For example, the U.S. Preventive Services Task Force (USPSTF) has a process for monitoring the emergence of new evidence that could prompt an update of its recommendations, and it aims to review each topic at least every five years for either an update or reaffirmation.(107)

Recommendation categories were used to track how the previous CPG's recommendations could be reconciled. These categories and their corresponding definitions are similar to those used by the National Institute for Health and Care Excellence (NICE, England).(108, 109) Table 3 lists these categories, which are based on whether the evidence supporting a recommendation was systematically reviewed, the degree to which the previous CPG's recommendation was modified, and whether a previous CPG's recommendation is relevant in the updated CPG.

Additional information regarding these categories and their definitions can be found in Recommendation Categorization. The 2022 CPG recommendation categories can be found in Recommendations. Appendix G outlines the 2017 VA/DoD Opioids CPG's recommendation categories.

Table 3. Recommendation Categories and Definitions[a]

Evidence Reviewed	Recommendation Category	Definition
Reviewed[b]	New-added	New recommendation
	New-replaced	Recommendation from previous CPG was carried forward and revised
	Not changed	Recommendation from previous CPG was carried forward but not changed
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted
Not reviewed[c]	Not changed	Recommendation from previous CPG was carried forward but not changed
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted

[a] Adapted from the NICE guideline manual (2012) (108) and Garcia et al. (2014) (109)

[b] The topic of this recommendation was covered in the evidence review carried out as part of the development of the current CPG

[c] The topic of this recommendation was not covered in the evidence review carried out as part of the development of the current CPG

Abbreviation: CPG: clinical practice guideline

C. Management of Potential or Actual Conflicts of Interest

Management of COIs for the CPGs is conducted as described in the *Guideline for Guidelines*.(100) Further, the *Guideline for Guidelines* refers to details in the VHA Handbook 1004.07 Financial Relationships between VHA Health Care Professionals and Industry (November 2014, issued by the VHA National Center for Ethics in Health Care),(70) as well as to disclosure statements (i.e., the standard disclosure form that is completed at least twice by CPG Work Group members and the guideline development team).(100) The disclosure form inquires regarding any relevant financial and intellectual interests or other relationships with, e.g., manufacturers of commercial products, providers of commercial services, or other commercial

interests. The disclosure form also inquires regarding any other relationships or activities that could be perceived to have influenced, or that give the appearance of potentially influencing, a respondent's contributions to the CPG. In addition, instances of potential or actual COIs among the CPG Work Group and the guideline development team were also subject to random web-based identification via standard electronic means (e.g., Centers for Medicare & Medicaid Services Open Payments and/or ProPublica).

No COIs were identified among the CPG Work Group or the guideline development team. If an instance of potential or actual COI had been reported, it would have been referred to the VA and DoD program offices and reviewed with the CPG Work Group Champions. The VA and DoD program offices and the CPG Work Group Champions would have determined whether, and if so, what, further action was appropriate (e.g., excusing Work Group members from selected relevant deliberations or removal from the Work Group). Disclosure forms are on file with the VA Office of Quality and Patient Safety and are available upon request.

D. Patient Perspective

When developing a CPG, consideration should be given to patient perspectives and experiences, which often vary from those of providers.(104, 110) Focus groups can be used to help collect qualitative data on patient perspectives and experiences. VA and DoD Leadership arranged a virtual patient focus group on February 11, 2021. The focus group aimed to gain insights into patients prescribed opioids for chronic pain of potential relevance and incorporate these into the CPG as appropriate. Topics discussed included the patients' priorities, challenges they have experienced, information they have received regarding their care, and the impacts of their care on their lives.

The patient focus group comprised a convenience sample of five people. There were two males and three females. All five participants were Veterans who received care from the VA health system. The Work Group acknowledges this convenience sample is not representative of all patients prescribed opioids for chronic pain within the VA and DoD healthcare systems and, thus, findings are not generalizable and do not comprise evidence. For more information on the patient focus group methods and findings, see Appendix E. Patient focus group participants were provided the opportunity to review the final draft and provide additional feedback.

E. External Peer Review

The Work Group drafted, reviewed, and edited this CPG using an iterative process. For more information, see Drafting and Finalizing the Guideline. Once the Work Group completed a near-final draft, they identified experts from the VA and DoD healthcare systems and outside organizations generally viewed as experts in the respective field to review that draft. The draft was sent to those experts for a 14-business-day review and comment period. The Work Group considered all feedback from the peer reviewers and modified the CPG where justified, in accordance with the evidence. Detailed information on the external peer review can be provided by the VA Office of Quality and Patient Safety.

F. Implementation

This CPG and algorithm are designed for adaptation by individual healthcare providers with consideration of unique patient considerations and preferences, local needs, and resources. The algorithm serves as a tool to prompt providers to consider key decision points in the care for a patient who is on or being

considered for prescribed opioids for chronic pain. The Work Group submits suggested performance metrics for the VA and DoD to use when assessing the implementation of this CPG. Robust implementation is identified in VA and DoD internal implementation plans and policies. Additionally, implementation would entail wide dissemination through publication in the medical literature, online access, educational programs, and, ideally, electronic medical record programming in the form of clinical decision support tools at the point of care.

VII. Approach to Care in Department of Veterans Affairs and Department of Defense

A. Patient-centered Care

Guideline recommendations are intended to consider patient needs and preferences. Guideline recommendations represent a whole/holistic health approach to care that is patient-centered, culturally appropriate, and available to people with limited literacy skills and physical, sensory, or learning disabilities. VA/DoD CPGs encourage providers to use a patient-centered, whole/holistic health approach (i.e., individualized treatment based on patient needs, characteristics, and preferences). This approach aims to treat the particular condition while also optimizing the individual's overall health and well-being.

Regardless of the care setting, all patients should have access to individualized evidence-based care. Patient-centered care can decrease patient anxiety, increase trust in clinicians, and improve treatment adherence.(111, 112) A whole/holistic health approach (https://www.va.gov/wholehealth/) empowers and equips individuals to meet their personal health and well-being goals. Good communication is essential and should be supported by evidence-based information tailored to each patient's needs. An empathetic and non-judgmental approach facilitates discussions sensitive to gender, culture, ethnicity, and other differences.

B. Shared Decision Making

This CPG encourages providers to practice shared decision making, which is a process in which providers and patients consider clinical evidence of benefits and risks as well as patient values and preferences to make decisions regarding the patient's treatment.(113) Shared decision making was emphasized in *Crossing the Quality Chasm,* an Institute of Medicine (IOM) (now NAM) report in 2001 (114) and is inherent within the whole/holistic health approach. Providers must be adept at presenting information to their patients regarding individual treatments, expected risks, expected outcomes, and levels and/or settings of care, especially where there may be patient heterogeneity in risks and benefits. The VHA and MHS have embraced shared decision making. Providers are encouraged to use shared decision making to individualize treatment goals and plans based on patient capabilities, needs, and preferences.

C. Patients with Co-occurring Conditions

Co-occurring conditions can modify the degree of risk, impact diagnosis, influence patient and provider treatment priorities and clinical decisions, and affect the overall approach to the use of opioids in the management of chronic pain. Many Veterans, Service Members, and their families have one or more co-occurring conditions. Because chronic pain is sometimes accompanied by co-occurring conditions, it is often best to make decisions about use of opioids in the management of chronic pain collaboratively with

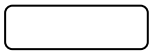
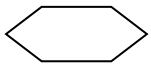
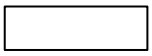
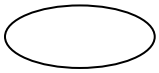
other care providers. Some co-occurring conditions may require early specialist consultation to determine any necessary changes in treatment or to establish a common understanding of how care will be coordinated. This may entail reference to other VA/DoD CPGs (e.g., for Major Depressive Disorder [MDD],[f] SUD,[g] and Suicide[h]).

VIII. Algorithm

This CPG's algorithm is designed to facilitate understanding of the clinical pathway and decision making process used in managing patients prescribed opioids for chronic pain. This algorithm format represents a simplified flow of the use of opioids in the management of chronic pain and helps foster efficient decision making by providers. It includes:

- An ordered sequence of steps of care
- Decisions to be considered
- Recommended decision criteria
- Actions to be taken

The algorithm is a step-by-step decision tree. Standardized symbols are used to display each step, and arrows connect the numbered boxes indicating the order in which the steps should be followed.(115) Sidebars provide more detailed information to assist in defining and interpreting elements in the boxes.

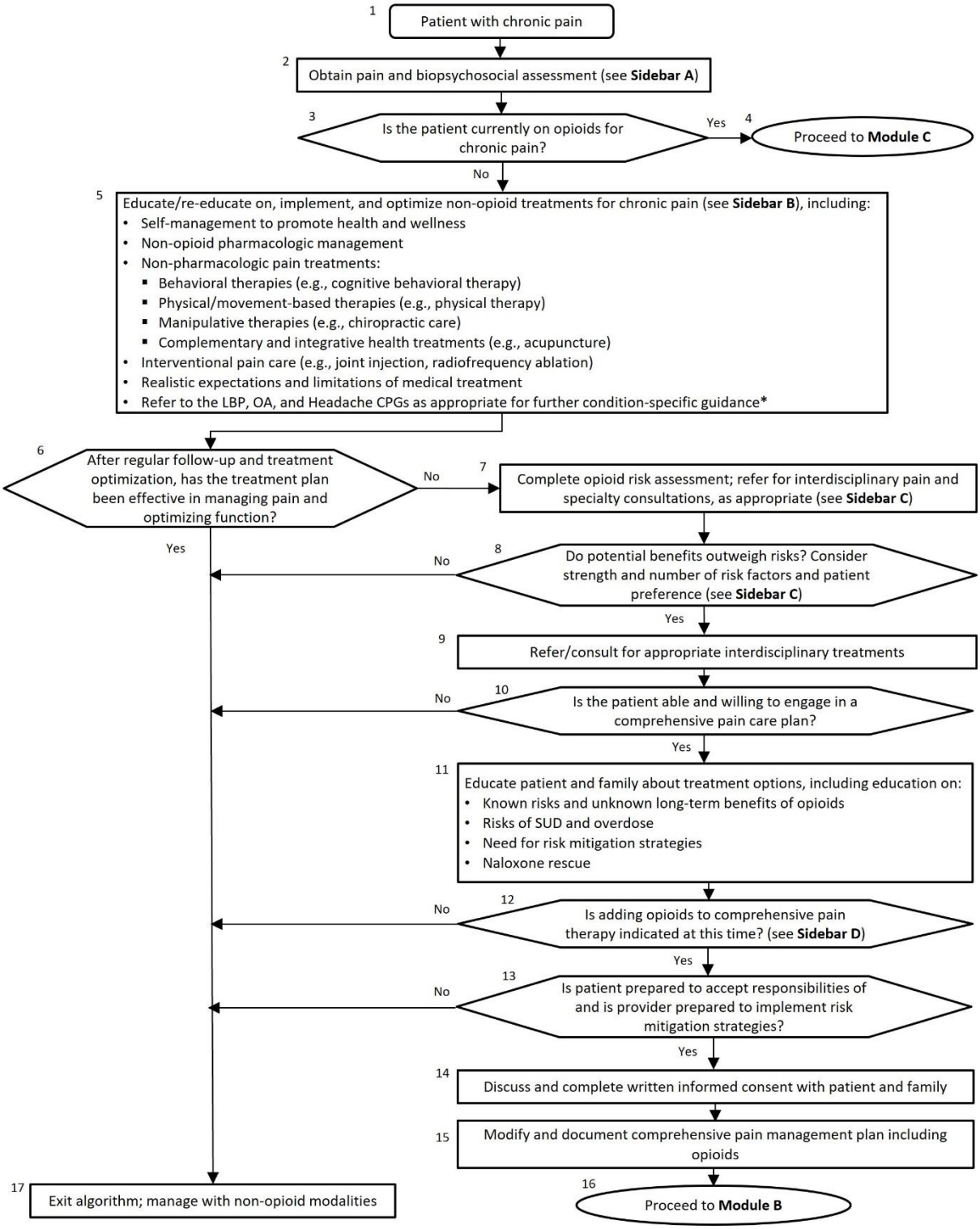
Shape	Description
	Rounded rectangles represent a clinical state or condition
	Hexagons represent a decision point in the process of care, formulated as a question that can be answered "Yes" or "No"
	Rectangles represent an action in the process of care
	Ovals represent a link to another section within the algorithm

Appendix J contains alternative text descriptions of the algorithm.

[f] See the VA/DoD CPG for the Management of Major Depressive Disorder, available at: https://www.healthquality.va.gov/
[g] See the VA/DoD CPG for the Management of Substance Use Disorders, available at: https://www.healthquality.va.gov/
[h] See the VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide, available at: https://www.healthquality.va.gov/

A. Module A: Determination of Appropriateness for Opioids for Chronic Pain

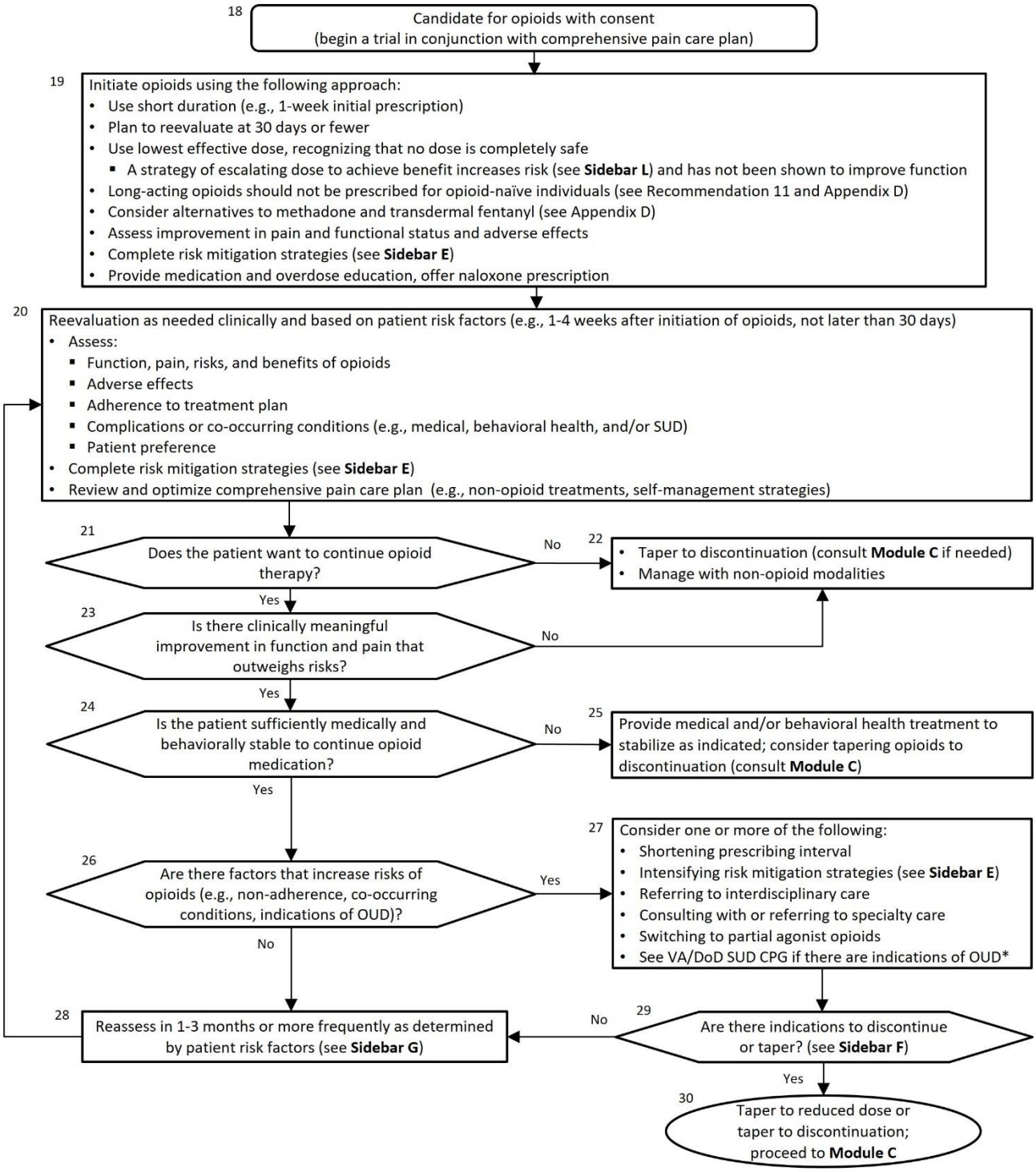
Note: Non-pharmacologic and non-opioid pharmacologic treatments are preferred for chronic pain



* Other VA/DoD CPGs are available here: https://www.healthquality.va.gov/

Abbreviations: CPGs: VA/DoD Clinical Practice Guidelines; LBP: low back pain; OA: osteoarthritis; SUD: substance use disorders

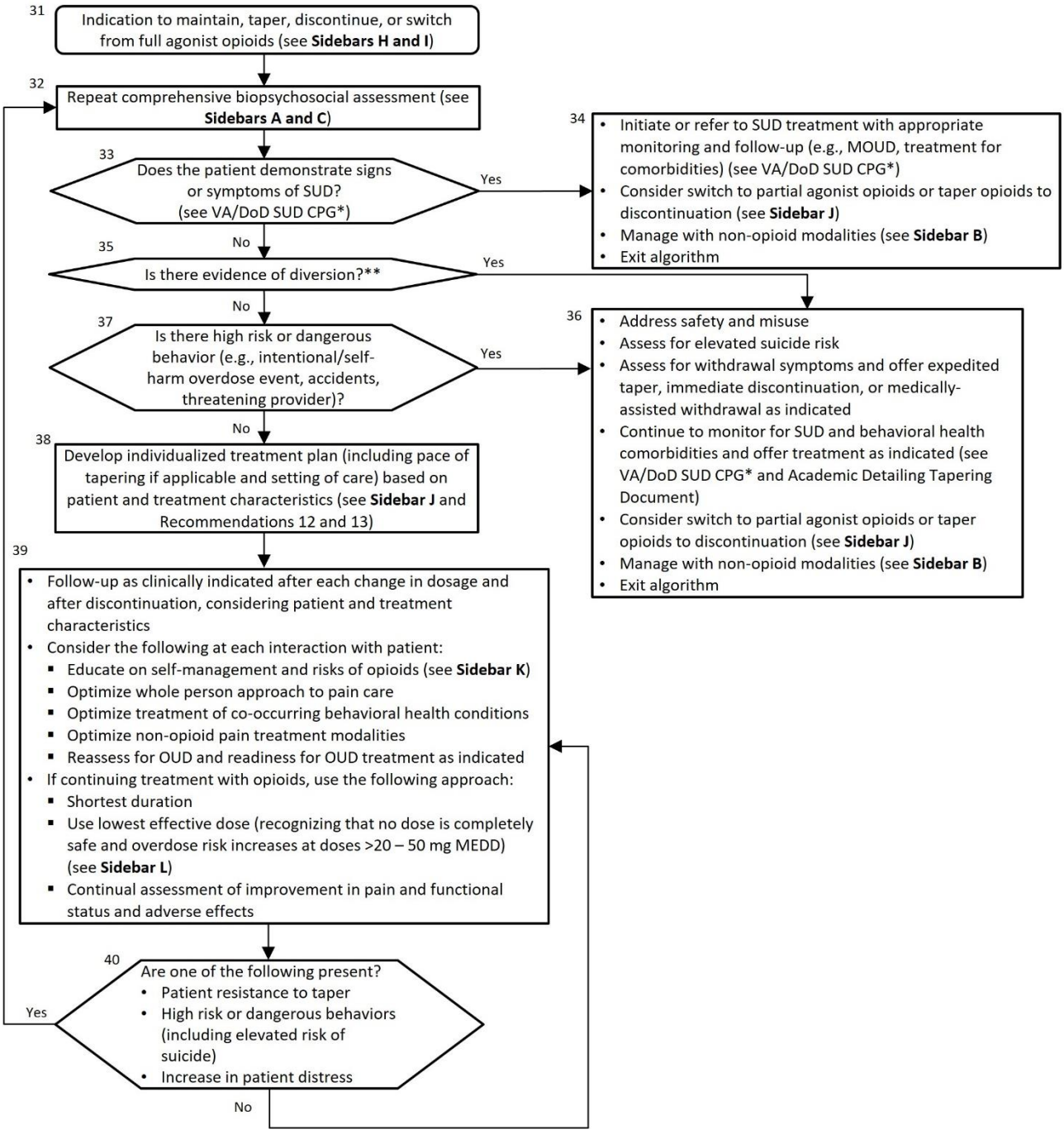
B. Module B: Initiation of Treatment with Opioids



* VA/DoD SUD CPG is available here: https://www.healthquality.va.gov/

Abbreviations: OUD: opioid use disorder; SUD: substance use disorders; VA/DoD SUD CPG: VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders

C. Module C: Maintaining, Tapering, Discontinuing, or Switching from Full Agonist Opioids



* VA/DoD SUD CPG is available here: https://www.healthquality.va.gov/

** According to the CDC, drug diversion is when prescription medicines are obtained or used illegally

Abbreviations: MEDD: morphine equivalent daily dose; mg: milligram(s); MOUD: medication for opioid use disorder; OUD: opioid use disorder; SUD: substance use disorders; VA/DoD SUD CPG: VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders

Sidebar A: Components of Pain/Biopsychosocial Assessment

- Conduct a pain assessment (e.g., information about the onset of pain, location, duration, exacerbating factors, relieving factors, whether there is radiation [location of the radiation and what triggers the radiation], 24 hour pain pattern, quality of pain)
- Assess history of previous treatments and effect on pain
- Assess impact of pain on daily functioning and quality of life (e.g., pain interference, family, education, work, community, social activities, sleep quality)
- Assess patient's functional goals
- Evaluate psychological/behavioral factors, including suicide risk,[a] that may affect treatment (e.g., pain avoidance, pain catastrophizing)
- Evaluate social factors that may affect treatment (e.g., employment, homelessness)
- Assess current and past co-occurring conditions (medical and behavioral health comorbidities)
- Conduct physical exam
- Confirm diagnosis (review previous diagnostic studies)
- Consider consultations and referrals
- Patient beliefs and understanding of:
  - The cause of their pain
  - Their treatment preferences
  - The perceived efficacy of various treatment options

For patients already on prescribed opioids, see Module C.

[a] See the VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide, available at: https://www.healthquality.va.gov/

Sidebar B: Non-opioid Treatments for Chronic Pain

- Rehabilitation and manipulative therapies (e.g., provided by physical therapists, occupational therapists, chiropractors)
- Pharmacologic therapy (e.g., over-the-counter medications, non-opioid prescription pain medications)
- Interventional procedures (e.g., trigger point injections, joint injections, acupuncture)
- Psychological and behavioral interventions (e.g., motivational interviewing, CBT)
- Complementary and integrative treatments (e.g., yoga, tai chi)

Abbreviations: CBT: cognitive behavioral therapy

Sidebar C: Opioid Risk Assessment

Examples of contraindications to initiating opioids for chronic pain:

- SUD, not in remission
- Elevated suicide risk[a]
- Concomitant use of benzodiazepines

If patient is already on prescribed opioids, is there evidence of OUD, such as:

- Self-escalating dose
- Early refills
- Difficulty tapering
- Cravings
- Continued use despite medical or psychological consequences
- Interpersonal or social problems related to opioid use

Screening tools and predictive models (repeat as clinically indicated). Examples include:

- RIOSORD
- STORM

[a] See the VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide, available at: https://www.healthquality.va.gov/

Abbreviations: OUD: opioid use disorder; RIOSORD: Risk Index for Overdose or Serious Opioid-induced Respiratory Depression; STORM: Stratification Tool for Opioid Risk Mitigation; SUD: substance use disorders

Sidebar D: Consideration Checklist for Prescribing Opioids for Chronic Pain

- Risks do not outweigh potential functional benefits
- Patient has a condition that is:
  - Causing severe chronic pain
  - Interfering with function and quality of life
  - Failing to adequately respond to indicated non-pharmacologic and non-opioid pharmacologic therapy
- Clear and measurable functional goals are established
- Patient is willing and able to access adequate follow-up for prescribed opioids
- PDMP and UDT are concordant with expectations (no aberrant behavior)
- Patient is fully informed and consents to treatment with opioids

Abbreviations: PDMP: prescription drug monitoring program; UDT: urine drug testing

Sidebar E: Risk Mitigation Strategies

- UDT
- PDMP
- Informed consent
- OEND
- Provider follow-up (in-person or video-based) with frequency determined by risk

Abbreviations: OEND: overdose education and naloxone distribution; PDMP: prescription drug monitoring program; UDT: urine drug testing

Sidebar F: Considerations for Tapering, Dosage Reduction, and Discontinuation

- Patient preference
- Patient characteristics and needs
- Lack of clinically meaningful improvement in functional goals (review treatment goals at onset of treatment)
- Concomitant use of medications that increase risk of overdose
- Co-occurring medical or behavioral health conditions, including SUD, that increase risk
- Patient non-compliance with opioid safety measures and opioid risk mitigation strategies
- Patient non-participation in a comprehensive pain care plan
- Higher dosage which increases risk of adverse events (see **Sidebar L**)
- Pain condition not effectively treated with opioids (e.g., back pain with normal MRI; fibromyalgia)
- Improvement in the underlying pain condition being treated
- Significant side effects
- Experiences overdose or other serious adverse events
- Diversion

Abbreviations: MRI: magnetic resonance imaging

Sidebar G: Factors That May Indicate Need for More Frequent Follow-up

- Non-adherence to comprehensive pain care plan (e.g., attendance at appointments)
- Unexpected UDT and PDMP results
- Non-adherence to opioid prescription (e.g., using more than prescribed and/or running out early)
- Higher risk medication characteristics (e.g., higher-dose opioids [see **Sidebar L**], combination of opioids and benzodiazepines)
- Patients with co-occurring medical and behavioral health conditions, including SUD, that increase risk for adverse outcomes

Abbreviations: PDMP: prescription drug monitoring program; SUD: substance use disorders; UDT: urinary drug testing

Sidebar H: Factors Requiring Immediate Attention and Possible Discontinuation or Switch to Safer Regimen

- Untreated SUD
- Unstable other behavioral health disorder
- Medical condition that acutely increases opioid risks (e.g., compromised or worsening cognitive or cardiopulmonary status, acute liver or renal disease)
- Other factors that acutely increase risk of overdose:
  - Recent overdose
  - Current sedation
  - Concomitant medications (e.g., benzodiazepines) and/or alcohol use
- Acutely elevated suicide risk[a]
- Diversion

[a] See the VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide, available at: https://www.healthquality.va.gov/

Abbreviations: SUD: substance use disorders

Sidebar I: Considerations During Reassessment

Risks

- Increase in all-cause mortality
- Increased risk of overdose (including overdose death)
- Increased risk of developing OUD
- Risk of developing or worsening:
  - Depression
  - Falls
  - Fractures
  - Sleep disordered breathing
  - Worsening pain
  - Motor vehicle accidents
  - Hypogonadism
  - Prolonged pain
  - Nausea
  - Constipation
  - Dry mouth
  - Sedation
  - Cognitive dysfunction
  - Immune system dysfunction
  - Reduction in function
  - Reduction in quality of life

Benefits

- Modest short-term improvement in pain
- Possible short-term improvement in function

If risks outweigh benefits, consider tapering, discontinuing, or switching from full agonist opioids (see Module C, Box 36).

Abbreviations: OUD: opioid use disorder

Sidebar J: Tapering Treatment

- Safety permitting, a gradual taper rate (consider a 5-20% reduction every 4 weeks or longer, adjust or pause as needed) allows time for neurobiological, psychological, and behavioral adaptations
- Tapering plans should be individualized based on patient goals and concerns, treatment characteristics, and safety considerations
- The VHA PBM Academic Detailing Service offers example tapers for opioids in their *Opioid Taper Decision Tool: A VA Clinicians Guide*. Examples are provided for four taper rates: slowest, slower, fast, and rapid tapers.
- When there are concerns regarding risks of tapering (e.g., unmasked OUD, exacerbation of underlying behavioral health conditions), consider interdisciplinary services that may include behavioral health, specialty SUD, primary care, specialty pain care, and complementary and integrative health interventions
- Provide patient education to address concerns that may negatively impact taper (e.g., inability for adequate follow-up, inability to provide adequate treatment for co-occurring medical and behavioral health conditions, including SUD, address anxiety concerns)

Patient and treatment characteristics to consider when determining tapering strategy:

- Opioid dose
- Duration of therapy
- Type of opioid formulation
- Psychiatric, including SUD, and medical comorbidities
- Other patient risk factors (e.g., non-adherence, high-risk medication-related behavior, strength of social support, coping)
- Response/tolerance to prior tapers (e.g., withdrawal symptoms)
- Level of engagement in non-pharmacologic pain treatments
- Access to facilities and/or telehealth for monitoring and follow up

Abbreviations: OUD: opioid use disorder; PBM: Pharmacy Benefits Management; SUD: substance use disorders; VHA: Veterans Health Administration

Sidebar K: Talking Points for Providers When Recommending Changes to Patients Currently on Opioids

In the context of motivational interviewing and shared decision making:

- "Evidence shows that the best treatments for chronic pain are options such as behavioral interventions, rehabilitation therapies, and non-opioid medications."
- "Science has demonstrated that long-term opioid use can lead to multiple problems including loss of pain-relieving effects, increased pain, unintentional death, OUD, and problems with sleep, mood, hormonal dysfunction, and immune dysfunction. I am concerned about your health and safety."
- "While opioids were prescribed to you, we now understand in general that the risks outweigh the benefits when opioids are used long-term. Let's work on reducing your dosage of opioids and discuss other treatment options."

Abbreviations: OUD: opioid use disorder

Sidebar L: Risks of Prescription Opioid Overdose and Overdose Death at Selected Morphine Equivalent Daily Dose Intervals

Study	Main outcome measure	Expression of risk	MEDD (mg)				
			0	1 to 19	20 to <50	50 to <100	>100
Turner and Liang (2015)[a,e] (116)	All overdose	AOR (95% CI)	1	0.80 (0.50-1.27)	1.54 (1.23-1.94)	2.08 (1.61-2.69)	4.34 (3.37-5.57)
Zedler et al. (2014)[a,b,c,e] (117)	All overdose	OR (95% CI)	–	1	1.5 (1.1-1.9)	2.2 (1.5-3.2)	4.1 (2.6-6.5)
Bohnert et al. (2011)[a,c,f] (118)	Unintentional overdose death	HR (95% CI)	–	1	1.88 (1.33-2.67)	4.63 (3.18-6.74)	7.18 (4.85-10.65)
Bohnert et al. (2011)[b,c,f] (118)	Unintentional overdose death	HR (95% CI)	–	1	1.74 (0.69-4.35)	6.01 (2.29-15.78)	11.99 (4.42-32.56)
Dunn et al. (2010)[a,e] (119)	All overdose	HR (95% CI)	0.19 (0.05-0.68)	1	1.19 (0.40-3.60)	3.11 (1.01-9.51)	11.18 (4.80-26.03)
Ilgen et al. (2016)[a,c,d] (120)	Overdose with suicidal intent	HR (95% CI)	–	1	1.59 (1.12-2.27)	1.74 (1.09-2.76)	2.09 (1.22-3.56)

[a] Chronic non-cancer pain

[b] Chronic cancer pain

[c] Study conducted in U.S. Veterans

[d] Intentional overdose

[e] Drug overdose per ICD-9-CM codes

[f] Overdose death

Abbreviations: AOR: adjusted odds ratio; 95% CI: 95% confidence interval; HR: hazard ratio; MEDD: morphine equivalent daily dose; mg: milligram(s); OR: odds ratio

IX. Recommendations

The following evidence-based clinical practice recommendations were made using a systematic approach considering four domains as per the GRADE approach (see Summary of Guideline Development Methodology). These domains include: confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient values and preferences, and other implications (e.g., resource use, equity, acceptability).

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Initiation and Continuation of Opioids		1.	We recommend against the initiation of opioid therapy for the management of chronic non-cancer pain (for non-opioid treatments for chronic pain, see the VA/DoD CPGs for Low Back Pain, Headache, and Hip and Knee Osteoarthritis).[c]	Strong against	Reviewed, New-replaced
		2.	We recommend against long-term opioid therapy, particularly for younger age groups, as age is inversely associated with the risk of opioid use disorder and overdose.	Strong against	Reviewed, New-replaced
		3.	We recommend against long-term opioid therapy, particularly for patients with chronic pain who have a substance use disorder (refer to the VA/DoD CPG for the Management of Substance Use Disorders).[d]	Strong against	Reviewed, New-replaced
		4.	For patients receiving medication for opioid use disorder, there is insufficient evidence to recommend for or against the selection of any one of the following medications over the other for the management of their co-occurring chronic pain: methadone, buprenorphine, or extended-release naltrexone injection. Treat the opioid use disorder according to the VA/DoD CPG for the Management of Substance Use Disorders.[d]	Neither for nor against	Reviewed, New-replaced
		5.	For patients receiving daily opioids for the treatment of chronic pain, we suggest the use of buprenorphine instead of full agonist opioids due to lower risk of overdose and misuse.	Weak for	Reviewed, New-added
		6.	We recommend against the concurrent use of benzodiazepines and opioids for chronic pain (refer to Recommendation 10 in the VA/DoD CPG for the Management of Substance Use Disorders[d] for further guidance related to tapering one or both agents).	Strong against	Reviewed, Amended

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Dose, Duration, and Taper of Opioids	*Dose and Duration*	7.	If prescribing opioids, we recommend using the lowest dose of opioids as indicated by patient-specific risks and benefits.	Strong for	Reviewed, Amended
		8.	If considering an increase in opioid dosage, we recommend reevaluation of patient-specific risks and benefits and monitoring for adverse events including opioid use disorder and risk of overdose with increasing dosage.	Strong for	Reviewed, New-replaced
		9.	When prescribing opioids, we recommend the shortest duration as indicated.	Strong for	Reviewed, New-replaced
		10.	After initiating opioid therapy, we recommend reevaluation at 30 days or fewer and frequent follow-up visits, if opioids are to be continued.	Strong for	Reviewed, New-replaced
		11.	We recommend against prescribing long-acting opioids: • For acute pain • As an as-needed medication • When initiating long-term opioid therapy	Strong against	Reviewed, Amended
	Tapering	12.	We suggest a collaborative, patient-centered approach to opioid tapering.	Weak for	Reviewed, New-replaced
		13.	There is insufficient evidence to recommend for or against any specific tapering strategies.	Neither for nor against	Reviewed, New-replaced
Screening, Assessment, and Evaluation		14.	We recommend assessing risk of suicide and self-directed violence when initiating, continuing, changing, or discontinuing long-term opioid therapy (refer to the VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide[e] for guidance on intervention timing and strategies).	Strong for	Reviewed, New-replaced
		15.	For patients with chronic pain, we recommend assessing for behavioral health conditions, history of traumatic brain injury, and psychological factors (e.g., negative affect, pain catastrophizing) when considering long-term opioid therapy, as these conditions are associated with a higher risk of harm.	Strong for	Reviewed, New-added
		16.	For patients with acute pain when opioids are being considered, we suggest screening for pain catastrophizing and co-occurring behavioral health conditions to identify those at higher risk for negative outcomes.	Weak for	Reviewed, New-added
		17.	For patients on opioids, we suggest ongoing reevaluation of the benefits and harms of continued opioid prescribing based on individual patient risk characteristics.	Weak for	Reviewed, New-replaced
Risk Mitigation		18.	We suggest urine drug testing for patients on long-term opioids.	Weak for	Reviewed, New-replaced
		19.	We suggest interdisciplinary care that addresses pain and/or behavioral health problems, including substance use disorders, for patients presenting with high risk and/or aberrant behavior.	Weak for	Not reviewed, Amended
		20.	We suggest providing patients with pre-operative opioid and pain management education to decrease the risk of prolonged opioid use for post-surgical pain.	Weak for	Reviewed, New-added

[a] For additional information, see Determining Recommendation Strength and Direction

[b] For additional information, see Recommendation Categorization and Appendix D

[c] Other VA/DoD CPGs are available at: https://www.healthquality.va.gov/

[d] See the VA/DoD CPG for the Management of Substance Use Disorders, available at: https://www.healthquality.va.gov/

[e] See the VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide, available at: https://www.healthquality.va.gov/

A. Initiation and Continuation of Opioids

Recommendation

1. We recommend against the initiation of opioid therapy for the management of chronic non-cancer pain (for non-opioid treatments for chronic pain, see the VA/DoD CPGs for Low Back Pain, Headache, and Hip and Knee Osteoarthritis[i]).
   (Strong against | Reviewed, New-replaced)

Discussion

Evidence from SRs of RCTs suggests that the use of opioids for the management of chronic pain is mixed, and the balance between the risks versus benefits is questionable in whether it will result in a meaningful benefit for the patient while also increasing adverse events (AEs) as compared to controls. The Work Group, in their review of the impact of opioids on underlying pain conditions (e.g., worsening of pain/opioid-induced hyperalgesia), considered findings related to the following outcomes: pain (pain severity, pain interference, chronification of pain), functional status, QoL, and serious AEs.

Busse et al. (2018) was the largest and most comprehensive SR included in the systematic evidence review.(121) It encompassed over 26,000 patients from 96 RCTs and found that, in patients with chronic non-cancer pain (CNCP), prescribed oral or transdermal opioids provided small and not clinically significant improvements in pain and physical functioning compared to non-opioid controls.(121) In 87 trials, patients in an opioid group had an average follow up of only 60 days (interquartile range [IQR]: 30-84 days). Such a short average follow-up can be seen as a significant limitation of this SR. It is also important to note that 79% of these trials received industry funding, 12% did not specify funding type, and only 9% reported no industry funding.(121)

Huang et al. (2019) and Ma et al. (2016), both SRs with 3 and 11 RCTs respectively, found treatment with opioids was associated with no improvement in pain, pain severity, or functional status in patients with cancer-related pain.(122, 123)

However, there was some evidence suggesting opioids can improve pain severity and functional status, particularly for those with musculoskeletal pain, including chronic low back pain (124) and osteoarthritis (OA).(125, 126) Sommer et al. (2020) and Derry et al. (2016) found treatment with opioids was associated with some improvement for those with non-cancer neuropathic pain.(127, 128) However, this relief and improved function must be weighed against the known risks associated with opioids (see below). The evidence for QoL was limited and included only three studies (124, 125, 127) with mixed results in terms of impact and clinical relevance.

Overall, the evidence for serious AEs did not differ between opioid and placebo groups for the SRs included in the evidence review.(124, 125, 127) The SRs included in the evidence had a maximum follow up of one to six months. Thus, the Work Group considered findings of non-controlled, observational studies that examined opioid misuse, dosage, overdose, and opioid-related mortality.(120, 129-134) The evidence from observational studies indicated that serious AEs can occur with long-term opioid use. At least two observational studies showed that a higher dose of opioids prescribed to individuals increased

[i] Other VA/DoD CPGs are available at: https://www.healthquality.va.gov/

the risk of being treated for OUD.(132, 134) Three retrospective studies found that higher doses of opioids resulted in increased risk of fatal overdoses, both intentional and unintentional.(120, 129, 130) The Work Group noted that observational studies often followed patients for much longer than the average of one to six months, which was the case for the SRs included in this evidence review. This analysis over an extended period of time provides insight on serious AEs for long-term opioid use for more than six months.

Consistently, the use of opioids for six months or less did not show evidence of serious AEs but did show a level of harm when measuring AEs. As noted in Huang et al. (2019), a major limitation of the SRs is the assumption that all types of opioids and dosing are equivalent.(122) The evidence from one SR and meta-analysis of five RCTs suggests that serious AEs did not differ between opioid and placebo groups at limited follow-up periods of four and 12 weeks in patients with non-cancer neuropathic pain.(127) Evidence from another SR using data from six RCTs also suggests no difference between groups for serious AEs at four and 15 weeks in patients with low back pain.(124) Finally, an SR and meta-analysis of data from 13 RCTs found no difference in serious AEs between groups at four and 24 weeks in patients with OA.(125) One study suggests serious AEs occurred more often with tramadol than with placebo at one and 12 week follow-ups among patients with OA.(126)The are several factors to take into consideration regarding AEs. Busse et al. (2018) suggests a level of harm associated with adding opioids to a non-opioid therapy regime.(121) At follow-ups between one and six months, AEs such as vomiting, nausea, constipation, and dizziness were more likely to occur in patients receiving opioids than in patients receiving placebo. Also, Busse et al. (2018) excluded patients at the highest risk of poor outcomes.(121) Sixty-nine trials excluded patients with current or prior SUD and 45 trials excluded patients with diagnosed behavioral health disorders or patients who were taking a psychotropic medication.

It is important to make considerations for certain subsets of patients, including those experiencing acute pain conditions, acute pain conditions who also have chronic pain, or an acute exacerbation of a chronic pain condition. These patients should be treated according to best medical evidence for the acute condition, including opioids, if clinically appropriate. In these cases, a short-term opioid prescription may be appropriate. Evidence for the use of opioids for acute pain is not addressed in this CPG.

Overall, the quality of the body of evidence for this recommendation was low. Limitations of the SRs and RCTs included poor clarity around randomization and allocation procedures, high attrition, and lack of blinding.(122, 124-127) Overall, the SRs had follow-up periods of less than six months, with some 60 days or less. This limited the ability to determine if serious AEs such as opioid overdose or addiction can result from use of opioids long-term. Limitations of the observational studies included inability to account for all potential confounding variables in the analyses.(120, 129-131, 133) However, the Work Group determined that despite limitations of the evidence base, the potentials risk of serious harms due to opioid therapy for chronic pain relatively outweigh the potential for benefit, particularly in light of the lack of high-quality evidence that long-term use of opioids greatly improves pain, function, and/or QoL, or that any temporary benefit, if present at all, is maintained in the long run. The Work Group also considered findings of studies from the 2017 VA/DoD Opioids CPG for this recommendation.(117, 118, 135)

Busse et al. (2018) found moderate to low quality evidence suggesting that opioids were associated with similar improvements in pain and physical functioning compared with nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants, and synthetic cannabinoids.(121) Busse et al. (2018) also found that opioids were associated with small improvements in pain but not physical functioning compared with

anticonvulsants.(121) These results were restricted to treatment lasting one to six months and may not apply to individuals with SUD or other behavior health disorders, to those involved in litigation, or to those receiving disability benefits.

At the time of this evidence review, no studies were found that compared opioid treatment head-to-head with a non-opioid, non-pharmacologic intervention besides usual care. Studies of this nature may prove beneficial and future RCTs that evaluate such comparisons are needed. Further studies may help determine which patients are most likely to benefit from a specific non-pharmacologic therapy (physical, psychological, and/or pain rehabilitation) or non-opioid pharmacologic therapies alone or as part of a multimodal approach earlier in the course of treatment.

There is some variation in patient preference, as some patients may prefer pharmacologic therapies or treatment with opioids. As evidenced from the patient focus group (Appendix E) and clinician experiences, there is a recent paradigm shift in patient values, leading patients to be more open to discussions of a full range of treatment options that include a whole/holistic health approach. The opioid epidemic spurred a cultural shift among clinicians in the acceptability of using opioids to treat pain, particularly chronic pain. Therefore, both clinicians and patients may think differently about asking for opioids and may be more willing to accept an alternative to opioids. Education may increase patient trust in non-opioid treatments, with the knowledge that opioids are still an option.

The Work Group systematically reviewed evidence related to this recommendation (120-133) and considered the assessment of the evidence put forth in the 2017 VA/DoD Opioids CPG.(117, 118, 135) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including indirectness (e.g., did not study VA/DoD population specifically, mean age was relatively high), methodological concerns regarding RCTs including lack of clarity around randomization and allocation procedures, high attrition, and lack of blinding.(124-127) The evidence also showed limitations regarding dosing effect (all types of opioids being considered equivalent to one another) and study duration (mostly short-term).(123, 127, 128) The potential benefits of adding opioids to a non-opioid therapy pain care plan did not result in clinically significant improvements in outcomes. Potential catastrophic harms of long-term opioids such as AEs (124-127) and serious AEs (e.g., opioid misuse, overdose, and opioid-related mortality) (120, 129, 130, 132, 134) outweighed potential benefits of improved pain severity and functional status for those with chronic low back pain, OA, and neuropathic pain. Patient values and preferences were somewhat varied because patients have different levels of willingness to consider alternative options for pain relief given known risks of opioids. Considering GRADE guidelines: 15, which states, "A strong recommendation may be warranted…when low quality evidence suggests benefit in a life-threatening situation," the Work Group decided upon a *Strong against* recommendation.(136)

Recommendation

2. We recommend against long-term opioid therapy, particularly for younger age groups, as age is inversely associated with the risk of opioid use disorder and overdose.
   (Strong against | Reviewed, New-replaced)

Discussion

Age should be considered in the risk-benefit determination for initiating and continuing long-term use of opioids, as it is inversely correlated with OUD and overdose. In the 2017 VA/DoD Opioids CPG, the Work Group chose 30 years as a clinically reasonable threshold to recommend against long-term use of opioids based on two studies which reported the highest risk of OUD and overdose were in patients aged 18 – 30 years.(118, 137) After reviewing the current literature, no specific age cutoff was chosen for this guideline update, as the Work Group determined there was not enough evidence to support a certain age at which there was any statistically significantly increase in OUD or overdose. Rather, the studies examined illustrated that age is inversely correlated with the risk of adverse health outcomes.(130, 138-141)

Evidence from ten studies (one SR, six retrospective cohort studies, and three population-based observational studies) suggests younger adults treated with opioids long-term are at increased risk of OUD, drug overdose, and opioid misuse.(118, 130, 132, 137-143) Seven of the ten studies provided moderate quality evidence,(118, 130, 132, 137, 141-143) while three provided low quality evidence.(138-140) Evidence from seven other studies, most of which provided low quality evidence, did not find an association between younger age and opioid overdose death or opioid misuse.(117, 120, 129, 131, 133, 144, 145) Of these, two studies with low quality evidence found a higher risk of overdose death in patients aged 45-54 years (117, 129) and one study with moderate quality evidence found that age was associated with a higher risk of inappropriate opioid prescribing.(145)

The body of evidence for increased risk of OUD and overdose in young patients on opioids long-term is consistent and profound. Papadomanolakis-Pakis et al. (2021) found that young adults (age 18 – 24) had a higher risk of treated OUD, and senior citizens (age 65+) had a lower risk of treated OUD than other age groups.(132) In addition, Liang et al. (2016) further illustrated that older age lowers the risk of drug overdose.(130) Edlund et al. (2014) found that, compared to patients ≥65 years old, patients 18 – 30 years old carried 11 times the risk of OUD and overdose.(137) Patients 31 – 40 years old carried five times the risk of OUD and overdose compared to those who were ≥65 years old.(137) Bohnert et al. (2011) found that, compared to patients 18 – 29 years old, those who were 30 – 39 years old had roughly half the risk of developing OUD or overdose (hazard ratio [HR]: 0.56, 95% CI: 0.27-1.17).(118) Compared to patients 18 – 29 years old, those who were ≥70 years old had a far lesser risk (nearly 1/17) of developing OUD or overdose (HR: 0.06, 95% CI: 0.02, 0.18).(118)

Younger patients may also be at a higher risk of opioid misuse, though there is conflicting evidence. In a prospective cohort of 192 patients, Martel et al. (2020) showed that age was not associated with opioid misuse.(131) This contrasted with findings from other studies. An SR of twelve observational studies, by Cragg et al. (2019), indicated younger age was indeed associated with opioid misuse (OR: 2.19; 95% CI: 1.81 to 2.64).(138) Turner et al. (2014) showed that patients aged 45 – 64 were significantly less likely to have an aberrant urine drug test (UDT) (detection of a non-prescribed opioid, non-prescribed benzodiazepine, illicit drug, or tetrahydrocannabinol [THC]) in comparison to patients aged 20 – 44.(143)

Thus, due to the inconsistencies in the evidence, opioid misuse was not included in the recommendation with regard to patient-centered adverse health outcomes.

There is large variability in patient preferences regarding the recommendation against long-term use of opioids for younger adults. Some may interpret the recommendation to limit opioid use by age as arbitrary and potentially discriminatory when taken out of context; however, there is neurophysiologic rationale explaining the relationship between age and OUD and overdose. Studies in other areas (e.g., use of different substances) indicate that developing brains are at increased risk of abnormalities and addiction when exposed to substance use early in life.(146-149) Notwithstanding, younger age is not an absolute contraindication to the use of opioids. There may be some situations in which the benefits of long-term use of opioids outweigh the risks of OUD and overdose. Hospitalized patients recovering from battlefield injuries, for example, are known to have less chronic pain, depression, and posttraumatic stress disorder (PTSD) when their pain is aggressively managed starting soon after injury.(150) In addition, patients may prefer not to taper opioids due to risk of withdrawal symptoms and temporary increase of pain (see Recommendations 12 and 13 on tapering). Implications of this recommendation can be burdensome as it may increase the frequency of visits and number of referrals to align with the patient focus group's importance of continuity and coordination of care across treatment settings.

The Work Group systematically reviewed evidence related to this recommendation (120, 129-133, 138, 144, 145) and considered the assessment of the evidence put forth in the 2017 VA/DoD Opioids CPG.(117, 118, 137, 139-143) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's overall confidence in the quality of the evidence was low. The body of evidence had some limitations including inability to adjust for all potential confounders in the analysis and small sample size.(117, 118, 120, 129-133, 137-145) The potential catastrophic harms of long-term use of opioids in younger adults (e.g., OUD and overdose) outweighed the potential benefits. Patient values and preferences were largely varied because some patients prefer opioid therapy and are reluctant to taper off opioids. The implications of increased resources required if tapering must also be considered. Considering GRADE guidelines: 15, which states, "A strong recommendation may be warranted…when low quality evidence suggests benefit in a life-threatening situation," the Work Group decided upon a *Strong against* recommendation.(136)

Recommendation

3. We recommend against long-term opioid therapy, particularly for patients with chronic pain who have a substance use disorder (refer to the VA/DoD CPG for the Management of Substance Use Disorders[j]).
   (Strong against | Reviewed, New-replaced)

Discussion

Opioids carry a significant risk for overdose, death, OUD, and opioid misuse, especially among patients with SUD. The recommendation against long-term opioids for patients with SUD is supported by 13 studies (one SR, 11 retrospective case cohort studies, and one case cohort study).(116, 118, 120, 130, 132, 137, 138, 140, 145, 151-154) The quality of evidence for specific outcomes varies from very low to moderate quality; however, the body of evidence is supportive of this recommendation due to the catastrophic risks

[j] See the VA/DoD CPG for the Management of Substance Use Disorders, available at: https://www.healthquality.va.gov/

stated above. Refer to the VA/DoD CPG for the Management of Substance Use Disorders (specifically Appendix B) for additional information on the clinical pharmacology and safety of medications for AUD and SUD, as this is outside the scope of this CPG.[k]

Multiple studies investigated the serious risks of overdose and death. A large study of 206,869 patients receiving care in a health maintenance organization (HMO) who received opioid prescriptions and who had a diagnosis of an alcohol or drug use disorder were found to have a significantly higher risk of overdose.(116) The VHA's National Patient Care Database case cohort study of 154,684 patients also found that patients diagnosed with SUD and CNCP had a significantly elevated risk of overdose death (HR: 2.53, 95% CI: 1.99-3.22) compared to patients with no SUD diagnosis.(118) This association is supported not only by Liang et al. (2016), which showed that alcohol use disorder (AUD) or SUD (other than AUD) significantly increased the risk of overdose (OR: 5.95, 95% CI: 4.33-8.06 in women and OR 4.69, 95% CI: 3.24-6.68 in men), but also by Carey et al. (2018) which associated measures of opioid misuse with higher risk of overall mortality, opioid overdose, and death within thirty days of overdose.(130, 151)

Another study used a VHA database to review the outcomes of patients who had been prescribed chronic short-acting or long-acting opioids.(154) This study found that patients who received chronic short-acting or long-acting opioids and who were diagnosed with SUD had an increased risk of suicide attempts compared to those without an SUD diagnosis (OR: 2.42, standard error [SE]: 0.035 for chronic short-acting for patients with drug use disorder; OR: 2.83, SE: 0.057 for chronic long-acting for patients with drug use disorder; OR: 1.99, SE: 0.033 for chronic short- acting for patients with AUD; OR: 1.87, SE: 0.056 for chronic long-acting for patients with AUD). Ilgen et al. (2016) added evidence to show that SUD is not only associated with an increased risk of suicide attempts, but heightens the risk of death by intentional overdose (HR 2.00, 95% CI: 1.44-2.78).(120)

Two large retrospective cohort studies by Edlund et al. (2014) and Papadomanolakis-Pakis et al. (2021) studies found that patients diagnosed with AUD had higher rates of OUD (OR: 3.22, 95% CI: 1.79-5.80 and OR: 3.62, 95% CI: 2.59-5.06, respectively).(132, 137) Moreover, Huffman et al. (2015) found that the presence of a lifetime history of SUD for patients with CNCP was associated with 28 times increased odds of therapy for opioid addiction compared to patients with CNCP without a lifetime history of SUD (OR: 28.58, 95% CI: 10.86-75.27).(140) The SR conducted by Cragg et al. (2019) illustrated an increased risk of opioid misuse in patients with current or previous substance use (OR: 3.55, 95% CI: 2.62-4.82) as well as illicit drug use history (OR: 4.21, 95% CI: 2.31-7.65).(138) In a retrospective cohort study using de-identified Oregon Medicaid claims data (from 2010 to 2014), Abraham et al. (2020) also showed that OUD was associated with a higher risk of inappropriate opioid prescriptions after 12 months (adjusted odds ratio [AOR]: 2.36, 95% CI: 2.22-2.51).(145) Using the Nationwide Emergency Department (ED) Sample to examine overdoses from opioids leading to ED visits among patients with cancer in the U.S., Jairam et al. (2020) found that the risk of opioid-related ED visits increases for patients diagnosed with SUD (OR: 3.54, 95% CI: 3.28-3.82).(152) In addition, Landsman-Blumberg et al. (2017) showed a higher risk of injury (AOR 1.32, 95% CI: 1.02-1.71) in patients with alcohol use or dependence who were prescribed opioids.(153)

Despite the lack of evidence of efficacy of long-term opioid use and the considerable evidence of significant harms of overdose, death from overdose, and increased risk of suicide, the Work Group agreed

[k] See the VA/DoD CPG for the Management of Substance Use Disorders, available at: https://www.healthquality.va.gov/

that SUD cannot be considered an absolute contraindication to long-term opioid use, as each patient's case should be treated individually. Instead, SUD should be deemed a relative contraindication, as the increased likelihood for catastrophic risks outweigh the potential modest benefit of prescribing long-term opioid therapy in this population. The need for increased specialty care treatment and consultation for patients with SUD and chronic pain was also considered in this recommendation. Furthermore, buprenorphine is commonly used in this setting and is discussed in detail in the following section.

The Work Group systematically reviewed evidence related to this recommendation (120, 130, 132, 138, 145, 151-153) and considered the assessment of the evidence put forth in the 2017 VA/DoD Opioids CPG.(116, 118, 137, 140, 154) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including the inability to account for all potential confounding variables in the analyses. The potential catastrophic risks of long-term use of opioids for chronic pain in patients with untreated SUD outweighed the potential benefits of modest pain improvement. Patient values and preferences were somewhat varied because patients with SUD still require pain relief, and the increased resource burden to identify and treat patients with SUD cannot be ignored. Considering GRADE guidelines: 15, which states, "A strong recommendation may be warranted…when low quality evidence suggests benefit in a life-threatening situation," the Work Group decided upon a *Strong against* recommendation.(136)

Recommendation

4. For patients receiving medication for opioid use disorder, there is insufficient evidence to recommend for or against the selection of any one of the following medications over the other for the management of their co-occurring chronic pain: methadone, buprenorphine, or extended-release naltrexone injection. Treat the opioid use disorder according to the VA/DoD CPG for the Management of Substance Use Disorders.[I]
   (Neither for nor against | Reviewed, New-replaced)

Discussion

Opioid use disorder is associated with premature death from opioid overdose and other medical complications such as acquired immunodeficiency syndrome (AIDS), hepatitis C, and sepsis. On average, OUD carries a 40 – 60% 20-year mortality rate.(155) Therefore, individuals with OUD are at high risk for premature death, not only from opioid overdose, but from other causes. Thus, providing first-line treatment for OUD is important to save lives as well as to improve the QoL of patients.

The recent VA/DoD SUD CPG recommends either methadone or buprenorphine/naloxone as first line and suggests (with a lower strength of evidence) extended-release naltrexone when treating OUD. Occasionally, however, the presence of chronic pain will lead a prescriber to choose one of these medications over another. Given this, the systematic evidence review assessed the comparative effectiveness of the three medications indicated to treat OUD (methadone, buprenorphine, and extended-release naltrexone) in the treatment of chronic pain in patients with OUD. The systematic evidence review returned a single RCT related to this topic, looking at extended-release naltrexone and buprenorphine/naloxone.(156) There were no studies found that addressed the use of methadone. In

[I] See the VA/DoD CPG for the Management of Substance Use Disorders, available at: https://www.healthquality.va.gov/

developing the current recommendation, the Work Group also considered evidence from the 2017 VA/DoD Opioids CPG.(157, 158)

In the RCT by Latif et al. (2019), 159 opioid-dependent patients from an outpatient clinic were initially identified for the study.(156) After completing an individually-adapted inpatient detoxification program, patients were randomized to receive either extended-release naltrexone (XR-NTX) or buprenorphine/naloxone (BP-NLX) for 12 weeks. By the end of the trial, 143 patients partially completed the study, and only 105 of the patients completed through the randomized part of the trial. The trial showed pain outcomes did not significantly worsen among patients switching from daily opioid use to either long-acting naltrexone or buprenorphine/naloxone for reduced or no pain at 12 weeks, based on reports with the Visual Analogue Scale (VAS), Present Pain Inventory (PPI), Affective Pain Score (AP), and SP (sensory pain).(156) Among participants with a pain condition that had persisted at least three months prior to the study, the percentage reporting no pain slightly increased from weeks 4 (55 of 136 patients, or 40%) to 12 (53 of 105 patient, or 50%), but did not reach statistical significance. Latif et al. (2019) provided very low quality evidence, with serious limitations including risk of bias (patients with severe chronic pain were not encouraged to participate), low rate of study retention, and imprecision.(156)

In the Prescription Opioid Abuse Treatment Study (POATS), a multicenter RCT by Weiss et al. (2014), patients with prescription OUD were provided a four-week taper using buprenorphine/naloxone to discontinuation plus two regimens of outpatient counseling.(157) Those who did not achieve successful outcomes after the buprenorphine taper in phase one were invited to participate in phase two consisting of 12 weeks of treatment using buprenorphine/naloxone followed by taper to discontinuation. During both phases, patients were randomized to receive a manualized, physician-delivered psychosocial intervention known as Standard Medical Management or Standard Medical Management plus manually-driven opioid drug counseling delivered by a trained therapist. Only 6.6% of patients achieved a successful outcome after tapering in phase one, with no difference between the groups. In phase two, while taking buprenorphine/naloxone, 49% of patients achieved a successful outcome, again with no difference between the groups. Eight weeks after tapering again, 8.6% of patients achieved a successful outcome. This suggests that MOUD with moderate dose buprenorphine/naloxone and brief, structured counseling by the prescribing physician can be successful for about half of selected patients with prescription OUD, whereas withdrawal management alone, even with close weekly follow-up and counseling, is successful for less than 10% of patients.(157)

The SR and meta-analysis by Dennis et al. (2015) involved a review of 14 articles with a total of 3,128 patients.(158) The authors evaluated the impact of CNCP on substance use behaviors, physical health, psychological symptoms, and social functioning outcomes. They also evaluated whether any specific MOUD demonstrated superiority or benefit for patients with comorbid OUD and pain. Due to large variations in the definitions and measurements of outcomes across the studies, there was insufficient data for a comprehensive meta-analysis. The authors chose a qualitative summary for most outcomes, and, when there were similar measures and outcomes, quantitative analysis was performed (in no cases were more than three studies analyzed). The authors also noted there were significant bias concerns, and some outcome definitions were inconsistent even within studies. The authors found that chronic pain had no effect on illicit opioid consumption (pooled odds ratios [pOR]: 0.70; 95% CI 0.41-1.17,) but it did increase the risk of illicit non-opioid consumption (pOR: 0.57; 95% CI 0.41-0.79). Moreover, the presence of chronic

pain in patients on MOUD was associated with an increased risk of having comorbid psychiatric symptoms (pOR 2.18; 95% CI 1.6-2.9). The authors noted the review did not demonstrate that the presence of chronic pain affected any of the outcomes for patients on buprenorphine or buprenorphine/naloxone.(158)

Although the quality of the evidence in these studies was low to very low, none indicated that the presence of chronic pain is reason to withhold MOUD.(157) Additionally, there is insufficient evidence to lead prescribers to choose one MOUD over another on the basis of the presence of chronic pain. Rather, treat the OUD according to current clinical guidelines for OUD. Patient preference regarding MOUD may vary widely and is influenced by many potential barriers to care, including stigma toward diagnosis and treatment, distance to an opioid treatment program (required to prescribe methadone), cost of certain medications, availability of buprenorphine/naloxone prescribers, and insurance coverage. Patients in rural settings and minorities are disproportionately limited in their choices of MOUD.(159)

The Work Group systematically reviewed evidence related to this recommendation (156) and considered the assessment of the evidence put forth in the 2017 VA/DoD Opioids CPG.(157, 158) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including a small number of studies, unclear randomization, unaddressed biases, and confounders in the analysis. The potential benefits of using MOUD in patients with OUD with or without pain (e.g., improved treatment retention, decreased overdose, improved mortality) outweighed the potential harms. Patient values and preferences were largely varied because of stigma and differing levels of monitoring required for each medication, availability, and access. Thus, the Work Group decided upon a *Neither for nor against* recommendation, while strongly recommending that patients with OUD be offered MOUD according to current guidelines (refer to the VA/DoD CPG for the Management of Substance Use Disorders[m]).

Recommendation

5. For patients receiving daily opioids for the treatment of chronic pain, we suggest the use of buprenorphine instead of full agonist opioids due to lower risk of overdose and misuse. **(Weak for | Reviewed, New-added)**

Discussion

As noted in the discussion for Recommendation 1, the evidence for opioid prescribing for chronic pain, based on a large SR that included 96 studies, suggests a significant but small benefit for pain and physical functioning compared to placebo.(121) There is no clear benefit when compared to non-opioid analgesic medication such as NSAIDs.(121) While this SR included several studies on buprenorphine (in transdermal and buccal formulations), it reports the outcomes in the aggregate for all included studies and not for each opioid medication specifically.(121) Additionally, the majority of included studies excluded patients with current or prior SUD and half excluded patients who had a diagnosed behavioral health disorder or were taking a psychotropic medication. Two of the 96 trials reported rates of accidental opioid overdose. Among 254 participants in a study of buprenorphine, there were no accidental overdoses. Among 191 patients in a trial of extended-release hydrocodone, there was one accidental overdose with respiratory arrest.

[m] See the VA/DoD CPG for the Management of Substance Use Disorders, available at: https://www.healthquality.va.gov/

The limited information in this large study is complemented by Petzke et al. (2020), which reviewed the use of opioids for low back pain and included four studies with buprenorphine (two each with buprenorphine transdermal [maximum 20 ug/h] and buprenorphine buccal [maximum 1,800 ug/d]).(124) Here again, most studies excluded higher risk patients, especially those with a previous or current SUD. Additionally, Sommer et al. (2020) reviewed the use of opioids for neuropathic pain and included one buprenorphine transdermal trial (maximum 40 ug/h).(127) Similarly, these studies provide low to very low quality evidence to suggest minor benefit from opioids, but also do not provide data on buprenorphine specifically. Any potential benefit from opioids in carefully selected patients (many of the included studies excluded patients with behavioral health comorbidities, specifically SUD) and in the short-term (duration of included studies was 4 – 15 weeks) is likely outweighed by the risks, in particular the grave concerns of overdose and OUD associated with long-term use (see discussion for Recommendation 1). Moreover, these risks are clearly correlated with duration and dosage of opioids (see Recommendations 7 – 10).

Two network meta-analyses included a separate analysis on buprenorphine compared to other opioids. Boya et al. (2021) evaluated a variety of opioid analgesics used in the management of chronic low back pain.(160) The authors compared pain reduction with buprenorphine to pain reduction with other opioids (hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, tramadol, and tapentadol), in most cases showing no difference. Low quality evidence from Boya et al. (2021) favors buprenorphine over tramadol for 30% reduction in pain.(160) The authors note that many of the included studies did not report the duration of chronic low back pain, previous use of opioid analgesics, or response to previous interventions. In general, given the complex nature of chronic low back pain and the narrowly defined inclusion criteria in the included clinical trials, generalizability to other populations and chronic pain conditions is limited. Freynhagen et al. (2021) compared tapentadol to a variety of other opioids, including buprenorphine, in chronic pain treatment.(161) They provided low quality evidence favoring buprenorphine for the outcome of any adverse effect.(161)

Several studies have evaluated the use of buprenorphine as an analgesic, including several SRs that were not included in the evidence base. However, these studies were consistent in their findings. An SR by Cote et al. (2014) reported some analgesic benefit in 10 trials and noted potential advantages including increased efficacy for the following situations: for neuropathic pain, in the elderly, in those with renal impairment, in those with less immunosuppression, and most notably for the ceiling effect on respiratory depression resulting in lower risk for overdose.(162) A more recent meta-analysis and SR by Lazaridou et al. (2020), also not included in the evidence base for this recommendation, evaluated the effects of buprenorphine on chronic pain outcomes.(163) Lazaridou et al. (2020) included five studies in a chronic pain population with OUD and nine studies in a chronic pain population without OUD.(163) This meta-analysis revealed a beneficial effect on pain intensity overall, with a larger effect size in chronic pain patients without OUD (moderate to large mean effect size) versus those with OUD (small effect size).(163)

The Work Group also identified an SR of 25 RCTs involving five buprenorphine formulations (intravenous, sublingual buprenorphine with and without naloxone, buccal, and transdermal delivery system [TDS]) in patients with chronic pain.(164) The primary outcome of this SR was analgesic efficacy as assessed by change in pain scores (visual analog and numeric rating scales) comparing buprenorphine to other analgesic or placebo management. Of the 25 included RCTs, 14 demonstrated clinically significant benefit in the management of chronic pain using buprenorphine. Of these, however, only three had active

analgesic agents as the comparator while 11 trials compared buprenorphine to placebo. The greatest amount of data available was for transdermal buprenorphine, with a dose ranging from 5 – 70 mcg/hour. While 10 of 15 studies of TDS showed a significant reduction in pain against a comparator, only one of the 10 reported efficacy when compared to another opioid (60 mg SR morphine per day).(165) The authors conclude there was a paucity of evidence for the other formulations of buprenorphine. However, this SR was not included in the systematic evidence review and, therefore, does not inform the strength of evidence for this recommendation.(164)

While the Work Group found insufficient evidence regarding the comparative effectiveness of buprenorphine and other full agonist opioids for the management of chronic pain, because of its superior safety profile as a partial agonist at the mu opioid receptor, there is reason to consider buprenorphine a first line agent in adults with chronic pain compared to scheduled dosing of moderate to high dose full agonist opioids. Buprenorphine is a Schedule III opioid analgesic with unique pharmacologic properties, including partial agonist activity with very high binding affinity for the μ-opioid receptor. This limit on effects at the upper end of the dose response curve is the mechanism underlying the superior safety profile of buprenorphine compared to full mu opioid agonists with respect to 1) respiratory depression even in non-dependent individuals (166, 167) and 2) fatal overdose when not combined with other sedating medications.(168) Additionally, excluding those who are opioid-naïve, buprenorphine is less likely to cause euphoriant effects and is a first-line treatment for OUD. Therefore, the Work Group determined that the benefits outweighed the harms for this recommendation. This recommendation should be weighed against the paucity of evidence in patients who are opioid-naïve or who are taking guideline-concordant low or intermittent dosing of full opioid agonists. Lethal overdose with buprenorphine is possible in opioid-naïve individuals or when it is taken in combination with CNS depressants such as benzodiazepines or alcohol. Similar to other opioids, it should be used with caution in such contexts.(169) Nonetheless, given the known risks of moderate to high does full agonist therapy and the intrinsic ceiling effect on respiratory depression that buprenorphine provides, the Work Group determined that a specific recommendation should be made based on its benefit compared to moderate to high dose long-term opioid therapy for the critical outcomes of overdose, addiction, and mortality, despite the limited evidence identified on buprenorphine's analgesic efficacy compared to other full agonist opioids by the systematic evidence review.

There is large variation in patient preference regarding this treatment. Buprenorphine is a Schedule III medication, with less stringent refill requirements and allowing for more flexibility in monitoring. However, buprenorphine is also indicated for the treatment of OUD, and some patients find the association between the medication and OUD treatment to be limiting. Furthermore, access to buprenorphine is not equitably distributed and is notably underutilized in rural settings (170) and among ethnic/racial minorities.(159) Finally, providers face multiple barriers to prescribing buprenorphine, for both chronic pain and for OUD, in their practice setting.(171, 172) Many U.S. counties have no physicians able to prescribe buprenorphine for OUD. Though a specialized license is not required to prescribe buprenorphine for the management of chronic pain, many practice settings restrict use to prescribers with specialized waivers, even for off-label formulations, including current VA guidance.

The Work Group systematically reviewed evidence related to this recommendation.(121, 124, 127, 160, 161) Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the

quality of the evidence was low. The body of evidence had some limitations including lack of evidence on the comparative effectiveness of buprenorphine and other full agonist opioids for the management of chronic pain. The benefits of treatment with buprenorphine (e.g., superior safety profile) outweighed the potential harms (e.g., possible overdose in opioid-naïve individuals or when taken in combination with CNS depressants). Patient values and preferences were largely varied. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

6. We recommend against the concurrent use of benzodiazepines and opioids for chronic pain (refer to Recommendation 10 in the VA/DoD CPG for the Management of Substance Use Disorders for further guidance related to tapering one or both agents[n]).
   (Strong against | Reviewed, Amended)

Discussion

The Work Group determined that the harms outweigh the benefits for the concurrent use of benzodiazepines and opioids. There is moderate quality evidence that the concurrent use of benzodiazepines with prescription opioids increases risk of overdose and overdose death.(130) In a retrospective cohort study, the adjusted OR for drug overdose was highest for individuals on long-term opioids for chronic pain (without anxiety or PTSD) who also received concurrent long-term benzodiazepine therapy.(116)

There may be some variation in patient preference regarding concurrent use of benzodiazepines and opioids because some patients who have been taking both medications may want to continue. Benzodiazepines should not be started in patients being treated with opioids, and patients already on benzodiazepines should not be started on long-term opioids. For situations in which there is concurrent benzodiazepine and opioid use, there is serious risk for unintentional overdose death, and a risk-benefit evaluation should be heavily weighed for tapering versus continuing one or both agents.

Once initiated, benzodiazepines can be challenging to discontinue due to symptoms related to benzodiazepine dependence, exacerbations of PTSD, and/or anxiety.(173) The abrupt discontinuation of benzodiazepines should be avoided, as it can lead to serious adverse effects including seizures and death. For patients currently on opioids and benzodiazepines, tapering of one or both medications should be considered when risks exceed benefits, and providers should consider obtaining a specialty consultation, as appropriate (refer to the VA/DoD CPG for the Management of Substance Use Disorders[o]). Caution should be used if initiating benzodiazepines for Veterans with PTSD who have co-occurring pain due to their difficulty in tapering and/or discontinuing. The VA/DoD CPG for the Management of Posttraumatic Stress Disorder and Acute Stress Reaction recommends against benzodiazepines for the prevention of PTSD and cautions against their use in treatment of PTSD.[p]

The Work Group systematically reviewed evidence related to this recommendation (130) and considered the assessment of the evidence put forth in the 2017 VA/DoD Opioids CPG.(116) Therefore, this is a

[n] See the VA/DoD CPG for the Management of Substance Use Disorders, available at: https://www.healthquality.va.gov/
[o] See the VA/DoD CPG for the Management of Substance Use Disorders, available at: https://www.healthquality.va.gov/
[p] See the VA/DoD CPG for the Management of Posttraumatic Stress Disorder and Acute Stress Reaction, available at: https://www.healthquality.va.gov/

Reviewed, Amended recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including a limited amount of new data on this topic. The potential harms of concurrent use of benzodiazepines and opioids, including unintentional overdose death, outweighed the potential benefits. Patient values and preferences were somewhat varied because some patients prefer to remain on both medications. Considering GRADE guidelines: 15, which states, "A strong recommendation may be warranted…when low quality evidence suggests benefit in a life-threatening situation," the Work Group decided upon a *Strong against* recommendation.(136)

B. Dose, Duration, and Taper of Opioids

a. Dose and Duration

Recommendation

7. If prescribing opioids, we recommend using the lowest dose of opioids as indicated by patient-specific risks and benefits.
   (Strong for |Reviewed, Amended)
8. If considering an increase in opioid dosage, we recommend reevaluation of patient-specific risks and benefits and monitoring for adverse events including opioid use disorder and risk of overdose with increasing dosage.
   (Strong for |Reviewed, New-replaced)

Discussion

There is low to moderate quality evidence supporting an association between opioid dose and risk for opioid misuse, development of OUD, and overdose death.(120, 129, 130, 132-134) One retrospective cohort study provided low quality evidence that MEDD was independently associated with opioid misuse behavior (HR, 1.003; 95% CI, 1.002-1.004; p<.001) among patients taking opioids for cancer pain.(133) A large retrospective cohort study in opioid naïve individuals prescribed opioids for non-cancer pain provided moderate quality evidence that there is dose-related risk for developing an OUD.(132) Compared to patients on an average daily dose of <20 MME, higher average daily doses at initiation were associated with greater risk of developing an OUD; patients on 20–50 MME (HR 1.11, 95% CI: 1.02, 1.21) had a lower risk than those prescribed > 200 MME (HR 4.15, 95% CI: 2.89, 5.97).(132) Another retrospective cohort study in the VHA evaluated the potential harmful effects of opioid dose escalation among patients with CNCP.(134) The study provided moderate quality evidence that the risk for the composite measure of subsequent SUD (including opioid, non-opioid, and alcohol) was higher among the opioid dose escalator group as compared to the maintainers (OR=1.31, 95% CI: 1.22, 1.41).(134)

New evidence supports previous findings reported in the 2017 VA/DoD Opioids CPG (116-119) indicating that risk of prescription opioid overdose and overdose death exists even at low opioid dosage levels and increases with increasing doses. A retrospective cohort study among Washington Medicaid patients with non-cancer pain provided low quality evidence that, compared with patients at doses 1–19 mg/d, the risk of opioid overdose death significantly increased at 50–89 mg/d of MEDD (about 2.3 times to approximately 5 times the risk in those on ≥200 mg/d MEDD).(129) Ilgen et al. (2016) also demonstrated an association between increased risk for intentional overdose with higher prescribed opioid doses in a retrospective case-cohort study in the Department of Veterans Affairs (see Table 4).(120) Table 4

illustrates the association between the MEDD and the risk of prescription opioid overdose and overdose death from other studies reported in the 2017 VA/DoD Opioids CPG.

Table 4: Risks of Prescription Opioid Overdose and Overdose Death at Selected Morphine Equivalent Daily Dose Intervals

Study	Main outcome measure	Expression of risk	MEDD (mg)				
			0	1 to 19	20 to <50	50 to <100	>100
Turner and Liang (2015)[a,e] (116)	All overdose	AOR (95% CI)	1	0.80 (0.50-1.27)	1.54 (1.23-1.94)	2.08 (1.61-2.69)	4.34 (3.37-5.57)
Zedler et al. (2014)[a,b,c,e] (117)	All overdose	OR (95% CI)	–	1	1.5 (1.1-1.9)	2.2 (1.5-3.2)	4.1 (2.6-6.5)
Bohnert et al. (2011)[a,c,f] (118)	Unintentional overdose death	HR (95% CI)	–	1	1.88 (1.33-2.67)	4.63 (3.18-6.74)	7.18 (4.85-10.65)
Bohnert et al. (2011)[b,c,f] (118)	Unintentional overdose death	HR (95% CI)	–	1	1.74 (0.69-4.35)	6.01 (2.29-15.78)	11.99 (4.42-32.56)
Dunn et al. (2010)[a,e] (119)	All overdose	HR (95% CI)	0.19 (0.05-0.68)	1	1.19 (0.40-3.60)	3.11 (1.01-9.51)	11.18 (4.80-26.03)
Ilgen et al. (2016)[a,c,d] (120)	Overdose with suicidal intent	HR (95% CI)	–	1	1.59 (1.12-2.27)	1.74 (1.09-2.76)	2.09 (1.22-3.56)

[a] Chronic non-cancer pain

[b] Chronic cancer pain

[c] Study conducted in U.S. Veterans

[d] Intentional overdose

[e] Drug overdose per ICD-9-CM codes

[f] Overdose death

Abbreviations: AOR: adjusted odds ratio; 95% CI: 95% confidence interval; HR: hazard ratio; MEDD: morphine equivalent daily dose; mg: milligram(s); OR: odds ratio

The evidence suggests that both the initiation of opioids in the opioid naïve patient (132) and opioid dose escalation in patients on chronic opioids (120, 133, 134) are associated with risks including opioid misuse, development of OUD, and overdose. Further, these risks were observed in both cancer (133) and non-cancer pain patients on opioids.(120, 132, 134)

The Work Group systematically reviewed evidence related to Recommendation 7 (120, 129, 130, 132-134) and considered the assessment of the evidence put forth in the 2017 VA/DoD Opioids CPG.(116-119, 140, 174) Therefore, this is a *Reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was low, but the adverse outcomes related to this recommendation are potentially catastrophic. The body of evidence had some limitations (e.g., multivariate analysis could not adjust for all potential confounders and the true incidence of OUD was underestimated since they only captured OUD that was treated with methadone or buprenorphine/naloxone). The potential benefits of opioid dose reduction or tapering to discontinuation outweighed the potential harms related to opioid misuse, the development of treated OUD, and the risk for overdose death. There is some variation in patient values and preferences regarding this recommendation. The Work Group noted that patients that have been on high dose opioids for some time may be hesitant to reduce their dose. The tapering process also presents some inherent challenges to both patients and some providers. Considering GRADE guidelines: 15, which

states, "A strong recommendation may be warranted…when low quality evidence suggests benefit in a life-threatening situation," the Work Group decided upon a *Strong for* recommendation for Recommendation 7.(136)

The Work Group systematically reviewed evidence related to Recommendation 8 (120, 129, 130, 132-134) and considered the assessment of the evidence put forth in the 2017 VA/DoD Opioids CPG.(116-119, 140, 174) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was low, but the adverse outcomes related to this recommendation are potentially catastrophic (in the form of OUD and/or drug overdose). The body of evidence had some limitations (e.g., multivariate analysis could not adjust for all potential confounders and the true incidence of OUD was underestimated since they only captured OUD that was treated with methadone or buprenorphine/naloxone). The potential benefits of prescribing the lowest opioid dosage outweighed the potential harms. Patients should be reevaluated for patient-specific risks and benefits and monitored for AEs including OUD and overdose if an increase in the opioid dose is contemplated. Generally, higher doses are associated with greater harms. Patient values and preferences were somewhat varied because there is some variation in patients who have already been on higher doses of opioids. Considering GRADE guidelines: 15, which states, "A strong recommendation may be warranted…when low quality evidence suggests benefit in a life-threatening situation," the Work Group decided upon a *Strong for* recommendation for Recommendation 8.(136)

Recommendation

9. When prescribing opioids, we recommend the shortest duration as indicated.
   (Strong for |Reviewed, New-replaced)
10. After initiating opioid therapy, we recommend reevaluation at 30 days or fewer and frequent follow-up visits, if opioids are to be continued.
    (Strong for |Reviewed, New-replaced)

Discussion

Evidence suggests that a longer duration of opioids is associated with a higher risk of being treated for OUD and a higher risk of fatal opioid overdose.(129, 132, 137, 140, 142)

A large retrospective cohort study by Papadomanolakis-Pakis et al. (2021) provided moderate quality evidence that a higher total days' supply of opioids was associated with a higher risk of being treated for OUD.(132) This study, comprised of opioid-naïve individuals who initiated prescription opioids for non-cancer pain, investigated the time to treated OUD with a maximum follow-up of 57 months. The incidence of treated OUD within the study period was 86 cases per 100,000 person-years, but the authors noted that the prevalence of treated OUD was likely lower than OUD in general. In addition to dosage, a higher total days' supply of opioids was associated with a higher risk of treated OUD. Compared to a total supply of 1 – 2 days, individuals who received 11 – 29 days of opioids had a higher risk for treated OUD (HR 1.55, 95% CI: 1.33, 1.80). Risk increased further with ≥30 days of opioids (HR 2.19, 95% CI: 1.82, 2.63). Of note, no such association was documented for a supply from 3 – 10 days.(132)

A retrospective cohort study by Garg et al. (2017) assessed the critical outcome of opioid overdose deaths in relation to the duration of treatment with opioids.(129) This study, which was conducted among

Medicaid patients with non-cancer pain, found that patients with 31 – 89 cumulative days of opioid use were four times more likely to have an opioid-related death than patients with ≤30 cumulative days of use (aHR 4.3, 95% CI: 2.7, 6.9). Risks increased further for 90 – 179 days (aHR 7.2, 95% CI: 4.6, 11.4) and 181 – 365 days (aHR 14.0, 95% CI: 9.0, 21.7). At >730 cumulative days of opioid use, the risk of opioid overdose death was over 20 times the risk in patients with ≤30 days of use (aHR 23.7, 95% CI: 13.9, 40.5).(129)

Prior to initiating opioids as part of a comprehensive pain care plan, an individualized assessment of potential opioid-related harms relative to potential benefits must be completed. After initiating opioids, subsequent follow-up visits allow for the review and adjustment of the pain care plan, including the use of opioids if continuation is indicated. The Work Group recommends reevaluation and initial follow-up at 30 days or fewer, as clinically indicated, if opioids are to be continued. This timeline was chosen based on the significantly increased risk for OUD and fatal overdose with opioid use extending beyond 30 days, as documented in the above studies.(129, 132)

Regarding frequent follow-up visits, Im et al. (2015) found that, for patients receiving opioid therapy, more frequent follow-up visits after new prescriptions were associated with a decreased risk of suicide attempt, as compared to patients receiving opioid therapy in facilities with less frequent follow-up visits.(175)

At follow-up visits, a clinician should reexamine the rationale for continuing the patient on opioids. Follow-up visits increase the impact of risk mitigation strategies and enhance the delivery of comprehensive, biopsychosocial pain care. The frequency of visits thereafter should be based on risk stratification. Clinicians should account for changes in co-occurring conditions, diagnoses/medications, and functional status when conducting the risk/benefit analysis for opioids. Alcohol use, pregnancy, nursing of infants, and lab abnormalities may change the risk/benefit calculus for long-term opioids. Ongoing opioid prescribing practices usually include patient education documented by informed consent, UDT, and checking state PDMPs, and may include pharmacy review and naloxone prescribing. A clinician should also be mindful of signs of diversion during follow-up and reevaluation. The longer the patient is on opioids, the greater the potential for change in patient status and development of opioid-related harms.

There is some variability in patient preferences regarding these treatment recommendations. Patients may prefer continuation or dosage escalation of opioids upon follow-up visits that may not be clinically indicated or justified. The burden related to resource utilization and feasibility of 30-day follow-up, or sooner in patients with elevated risks, may be challenging for the provider and/or the patient. Patient focus group participants noted that frequent visits can be burdensome, and higher dosage may require more labor-intensive risk mitigation and monitoring strategies. While some of the follow-up evaluations may be done by telehealth to reduce the need for travel, opioid prescribing laws and regulations (including federal and state regulations) and risk mitigation strategies (such as UDT) may require in-person visits.

These recommendations are well aligned with the 2016 CDC guideline for opioids that recommended reevaluating harms versus benefits within one to four weeks of starting opioids or at any dose change, and at least every three months or more frequently if needed for patients on stable dosages.(17) The 2016 CDC guideline was undergoing an update at the time of development of this CPG.

The Work Group systematically reviewed evidence related to both Recommendations 9 and 10 (129, 132) and considered the assessment of the evidence put forth in the 2017 VA/DoD Opioids CPG.(137, 140, 142)

Therefore, these are *Reviewed, New-replaced* recommendations. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations (e.g., the true incidence of OUD was likely underestimated since they only captured treated OUD).(129) Regarding Recommendation 9, the potential benefits of prescribing for the shortest duration as indicated outweighed the potential harms related to resource utilization and feasibility. Patient values and preferences were somewhat varied for Recommendation 9, with some patients preferring pharmacologic therapy and requesting continuation or escalation. Regarding Recommendation 10, the potential benefits of reevaluation at 30 days or fewer and frequent follow-up visits outweighed the potential burden related to resource utilization and feasibility. Patient values and preferences were somewhat varied for Recommendation 10, due to limited feasibility of frequent follow-up and reevaluation in some patients. Considering GRADE guidelines: 15, which states, "A strong recommendation may be warranted…when low quality evidence suggests benefit in a life-threatening situation," the Work Group decided upon *Strong for* recommendations.(136)

Recommendation

11. We recommend against prescribing long-acting opioids:
    - For acute pain
    - As an as-needed medication
    - When initiating long-term opioid therapy

    (Strong against | Reviewed, Amended)

Discussion

Long-acting opioids should not be used for the treatment of acute pain, on an as-needed (prn) basis, or during initiation of long-term prescribed opioids due to the potentially catastrophic harms of OUD, overdose, and death.

Moderate quality evidence from one large retrospective cohort study, by Papadomanolakis-Pakis et al. (2021), indicated that long-acting opioids increased the risk of being treated for OUD over short-acting opioids.(132) Higher doses were also associated with higher non-medical opioid use behavior. Garg et al. (2017) provided low quality evidence that patients taking long-acting and schedule II short-acting opioid formulations simultaneously were 4.7 times more likely to die of an overdose than patients using non-schedule II opioids alone.(129)

Furthermore, the FDA has added the following warnings to extended-release opioid preparations: "Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve [extended-release opioid preparations] for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. [Extended-release opioid preparation] is not indicated as an as-needed (prn) analgesic."(176)

In general, however, no single opioid or opioid formulation is preferred over the others. There is limited evidence regarding the comparative effectiveness and safety of various opioid formulations (different opioids are discussed further in Recommendations 4 and 5). The current systematic evidence review identified two network meta-analyses,(160, 161) five RCTs,(177-181) two retrospective cohort

studies,(129, 132) and one SR related to this recommendation.(138) There were no studies meeting search criteria that addressed immediate-release/short-acting opioids versus extended-release/long-acting opioids. There is a lack of head-to-head comparison and inadequate follow-up in the studies. Placebo-controlled trials rather than head-to-head trials lead to, at best, indirect comparison between formulations. The Work Group also considered two studies from the previous systematic evidence review, Pedersen et al. (2014) and Yu et al. (2014).(182, 183)

Inoue et al. (2018) compared other routes of administration and provided low quality evidence for the outcomes of interest, demonstrating no difference between routes of administration.(179)

Individuals may have a better response, degree of safety, or tolerability depending on medication characteristics and patient preferences. Additional information for use when deciding on appropriate pharmacologic treatment of pain for a specific patient can be found in Appendix D.

The Work Group systematically reviewed evidence related to this recommendation (129, 132, 138, 160, 161, 177-181) and considered the assessment of the evidence put forth in the 2017 VA/DoD Opioids CPG.(182, 183) Therefore, this is a *Reviewed, Amended* recommendation. The Work Group's overall confidence in the quality of the evidence was very low; however, one study provided moderate quality evidence for several of the critical outcomes (Papadomanolakis-Pakis et al. [2021]).(132) The body of evidence had some limitations including its scope because there were no studies meeting search criteria that addressed immediate-release/short-acting opioids versus extended-release/long-acting opioids. There was also a lack of head-to-head comparison and inadequate follow-up in some studies. The potential harms of long-acting opioid use (especially in acute pain settings and as an as-needed medication) include OUD, overdose, and death, and these potentially catastrophic outcomes outweighed any possible benefit. Patient values and preferences were somewhat varied because some patients may desire or request opioids for acute pain or on an as-needed basis, whereas others do not prefer continued treatment with opioids. Considering GRADE guidelines: 15, which states, "A strong recommendation may be warranted…when low quality evidence suggests benefit in a life-threatening situation," the Work Group decided upon a *Strong against* recommendation.(136)

b. Tapering

Recommendation

12. We suggest a collaborative, patient-centered approach to opioid tapering.
    (Weak for |Reviewed, New-replaced)
13. There is insufficient evidence to recommend for or against any specific tapering strategies.
    (Neither for nor against |Reviewed, New-replaced)

Discussion

The Work Group suggests that providers take a collaborative and patient-centered approach to tapering, if the decision is made to taper. Collaborative tapering strategies may include dose reduction or opioid discontinuation. The confidence in the quality of the evidence for the critical outcome of serious AEs was low, whereas the confidence in the quality of the evidence for the important outcomes pain, QoL, function, and other AEs ranged from low to very low. These ratings were primarily due to limitations in the studies that included lack of blinding of participants, providers, or outcome assessors; uncertainty around

attrition, outcome reporting, and adherence to treatment; and differential baseline demographics between treatment groups.

One RCT compared motivational interviewing-opioid taper to usual care,(184) and one SR with 12 RCTs compared patient- or clinician-focused opioid de-prescribing interventions to usual care.(185) Findings from both studies suggest a benefit of patient-focused opioid de-prescribing interventions for disability.(184, 185) Matheison et al. (2020) provided low quality evidence for the reduction of pain and improvement in QoL and function.(185) Hah et al. (2020) demonstrated non-inferiority of the taper versus usual care in pain, QoL, function, and other AEs with low to very low quality evidence.(184) The Work Group also considered the assessment of the evidence put forth in the 2017 VA/DoD Opioids CPG; however, no evidence was carried forward.

The Work Group noted that the benefits of a collaborative, patient-centered approach to tapering outweighed the harms. A potential benefit is risk reduction for overdose, OUD, and other AEs. There were no direct harms identified when effective patient collaboration was employed. However, there are potential harms of forced tapering, in particular forced rapid tapering, which can destabilize patients, precipitating opioid withdrawal which may be accompanied by worsening pain, loss of function, increased suffering, worsening depression, increased suicidal ideations and attempts, and use of other substances. These potential harms can be mitigated by using gradual patient-centered tapering strategies. Tapering may be best tolerated at a rate of decrease that is slow enough to avoid withdrawal symptoms. If OUD is suspected at any point while treating a patient with chronic pain, appropriate treatment for OUD should be initiated. Please refer to the HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics for more information.

Discussions around tapering should include the patient, family and/or caregivers, and the provider. Regarding use of a collaborative, patient-centered approach to tapering, patient values and preferences were similar, as most patients prefer this type of approach. Patient focus group participants noted that they value a whole/holistic health approach to their care that focuses not only on pain symptoms but improving overall function and QoL (see Appendix E). They also described the importance of continuity of care and coordination of care between their providers within and across treatment settings. All providers can and should be able to take a patient-centered, collaborative approach with a focus on the patient's goals, capabilities, prior treatments, and preferences. Providers should encourage patients to discuss previous experiences and/or successes or difficulties with the cessation or tapering of opioids. There are some potential harms associated with tapering (particularly for patients with long-term, high dose use of opioids), but these harms may be mitigated by taking a collaborative approach. Use of partial agonist therapy may be a helpful strategy for tapering in some patients. The Work Group also notes that even if this approach means more time spent with a patient up front, it will likely save time in the end.

Regarding tapering, there is large variability in patient preferences. Some patients may be hesitant, frightened, or not respond well to tapering; others have a strong desire to stop taking opioids. The patient focus group participants noted opioids can be important for pain management in the immediate post-surgical period, but continued treatment with opioids was not preferred (see Appendix E). The patient focus group participants also expressed a need for medications that may be stronger than over-the-counter medications yet are not opioids. In addition, tapering can be burdensome and time-consuming to

the patient because it requires frequent visits. Further, there may be limited access to patient-centered tapering programs, and not all providers have adequate training to guide patients through an opioid taper.

The Work Group systematically reviewed evidence related to Recommendation 12.(184, 185) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including lack of blinding, uncertainty around attrition, and uncertainty around adherence to treatment. The potential benefits of a collaborative, patient-centered approach to opioid tapering (e.g., improved outcomes related to serious AEs) outweighed the potential harms (no direct harms were identified when effective patient collaboration was employed). Patient values and preferences were similar because most patients appreciate a patient-centered, collaborative approach. Thus, the Work Group decided upon a *Weak for* recommendation.

The Work Group systematically reviewed evidence related to Recommendation 13.(184, 185) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including lack of blinding, uncertainty around attrition, and uncertainty around adherence to treatment. The potential benefits of opioid tapering outweighed the potential harms of opioid withdrawal. Patient values and preferences were largely varied because some patients may be hesitant or not respond well to tapering, whereas others want to stop taking opioids. Thus, the Work Group decided upon a *Neither for nor against* recommendation. The Work Group recommends future research on this topic.

C. Screening, Assessment, and Evaluation

Recommendation

14. We recommend assessing risk of suicide and self-directed violence when initiating, continuing, changing, or discontinuing long-term opioid therapy (refer to the VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide for guidance on intervention timing and strategies[q]).
    (Strong for | Reviewed, New-replaced)

Discussion

Opioid medications are potentially lethal, and an assessment of current suicide risk should be made across the continuum of care. Visits during which long-term opioid therapy is being initiated, continued, changed, or discontinued can serve as touch points to assess a patient's individual risk of suicide and self-directed violence, which is not static across their continuum of care. The VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide recommends restricting the availability of lethal means for patients considered to be at intermediate or high acute risk of suicide (determined by presence and severity of suicidal ideation, level of intention to act, existence of risk factors, limited or absent protective factors, etc.) and views suicidality as a relative contraindication for long-term opioids.[r] Accordingly, suicidality is considered to be an important risk factor for long-term opioid use.

[q] See the VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide, available at: https://www.healthquality.va.gov/

[r] See the VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide, available at: https://www.healthquality.va.gov/

Studies (not included in the current systematic evidence review) have consistently shown that chronic pain conditions are associated with increased risk of suicide, and there is a correlation between pain severity and suicide risk.(186-193) A large retrospective cohort study also suggests an association between prescribed opioids and suicide risk among Veterans receiving long-term opioids for CNCP.(120) Suicide risk is not static, and many factors influence an individual's risk of suicide at any given point in time, as noted in the VA/DoD Suicide Risk CPG.[s] Recent literature indicates specific populations including those with psychotic disorders, mood disorders, pain disorders, headache, pain, neuropathy, and a cancer diagnosis may be at elevated risk.(120) Thus, ongoing assessment of suicide risk is important regardless if initiating, maintaining, changing, or terminating long-term use of opioids.

Both escalation of opioid dose and discontinuation of opioid prescription have shown increased risk of adverse events. Hayes et al. (2020) reviewed a cohort of Veterans who were prescribed opioids for CNCP and found an association between dose escalation and increased risks of SUD and opioid-related adverse outcomes, including self-directed harm.(134) Oliva et al. (2020) concluded that Veterans were at greater risk of death from overdose or suicide after discontinuing opioid treatment.(94) This risk increased the longer patients had been taking opioids prior to discontinuation. Although this study was not included in the systematic evidence review and therefore is not considered when determining the recommendation strength, its relevance to the VA/DoD population warrants attention. Although studies evaluating the association between opioid discontinuation and risk of suicide/self-directed violence were not captured by the systematic evidence review, Oliva et al. (2020) demonstrates the potential of catastrophic harm resulting from abrupt discontinuation.(94) Considering GRADE guideline: 15, which states, "A strong recommendation may be warranted…when low quality evidence suggests benefit in a life-threatening situation," (136) the Work Group decided to include provider interactions during which long-term opioid therapy is being discontinued as another touch point to assess a patient's risk of suicide and self-directed violence.

Individual assessment of the risk of suicide and self-directed violence is recommended when initiating, continuing, changing, or discontinuing long-term opioid therapy. The Columbia-Suicide Severity Rating Scale (C-SSRS) screener is a widely accepted instrument, validated for the outpatient setting. The C-SSRS, though it takes relatively longer to complete compared to other tools, provides clinicians information which will inform the need for additional behavioral health assessment and support. The C-SSRS provides clinicians with current and historic suicide-related information. If the C-SSRS screener is positive, it should be promptly followed by a comprehensive suicide risk evaluation. Clinicians should consider alternatives to long-term opioids when a patient endorses suicidal ideation and should weigh historic suicide behaviors when assessing risk.

Some patients on long-term opioids who suffer from chronic pain and co-occurring OUD, depression, and/or personality disorders may threaten suicide when providers recommend discontinuation of opioids. However, continuing long-term opioids to "prevent suicide" in someone with chronic pain is not recommended as this increases overall risk due to presence of lethal means. In such cases, it is essential to involve behavioral health providers to assess, monitor, and treat a patient who becomes destabilized because of a medically appropriate decision to taper or cease long-term use of opioids. Clinicians should

[s] See the VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide, available at: https://www.healthquality.va.gov/

consider offering buprenorphine as a bridging strategy to support gradual titration of long-term opioids (titration off opioids or tapering to reduced dose), to help relieve distress surrounding opioid tapering.

Further research is needed to identify strategies for safely managing patients at elevated risk of suicide who demand or require opioids or become further destabilized during tapering.

The Work Group systematically reviewed evidence related to this recommendation (120, 134) and considered the assessment of the evidence put forth in the 2017 VA/DoD Opioids CPG.(175) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations. The potential benefits of identifying the catastrophic risk of suicide and/or OUD outweighed the burden of assessment. Patient values and preferences were somewhat varied because some patients dislike screening and subsequent evaluation. Considering GRADE guidelines: 15, which states, "A strong recommendation may be warranted…when low quality evidence suggests benefit in a life-threatening situation," the Work Group decided upon a *Strong for* recommendation.(136)

Recommendation

15. For patients with chronic pain, we recommend assessing for behavioral health conditions, history of traumatic brain injury, and psychological factors (e.g., negative affect, pain catastrophizing) when considering long-term opioid therapy, as these conditions are associated with a higher risk of harm.
    (Strong for | Reviewed, New-added)

Discussion

The Work Group recommends assessing for comorbid behavioral health conditions due to the severity of potential harm of no assessment and the relatively low costs. The evidence review assessed associated risks when a comorbid behavioral health diagnosis was present with a concurrent opioid prescription. The behavioral health conditions reviewed for this recommendation included anxiety, depression, psychotic disorders, and SUD (see Recommendation 3). Though the Work Group recommends assessment for all behavioral health disorders in patients prescribed opioid medications to ensure adequate treatment and support for comorbid behavioral health conditions, the individual behavioral health diagnoses reviewed are provided below so clinicians formulating a treatment strategy can weigh the strength of evidence to assess risks and benefits of behavioral health screening with their knowledge of the patient and clinical judgment. The recommendation to assess for behavioral health conditions when considering long-term opioid therapy applies to both the initiation and continuation of long-term opioid therapy. Although a risk for harm has been associated with opioid tapering and discontinuation, the evidence review for this recommendation did not address opioid tapering or discontinuation.

Anxiety Disorders

The evidence supporting screening for anxiety disorders is mixed. An SR of 11 observational studies associates anxiety with a higher risk of opioid misuse.(138) However, two subsequent studies with a similarly low strength of evidence did not find associated AEs in opioid prescribed populations and comorbid anxiety. Specifically, a large retrospective cohort study did not find an increased risk of OUD in those with comorbid anxiety disorder.(132) Likewise, a large retrospective case-cohort study found that

anxiety disorders were not associated with a higher risk of intentional overdose.(120) Clinicians must weigh indications to screen for anxiety disorders in light of the low confidence in the quality of this evidence. There are several validated screening instruments for anxiety in the outpatient, primary care setting. The two-item Generalized Anxiety Disorder scale (GAD-2) is a validated tool which is easily completed in the outpatient setting. Other tools available based on clinician familiarity and comfort include the Hamilton Anxiety Scale (HAM-A), Hospital Anxiety and Depression Scale (HADS), Covi Anxiety Scale, Clinical Anxiety Scale (CAS), State-Trait Anxiety Inventory (STAI), Generalized Anxiety Disorder Questionnaire-IV (GAD-Q-IV), and World Health Organization Composite International Diagnostic Interview Short-Form (CIDI-SF).

Depression

An SR of 12 observational studies indicates patients with comorbid depression are at a higher risk of opioid misuse (OR: 2.30; 95% CI: 1.92 to 2.77).(138) Because the strength of evidence is moderate, the Work Group strongly recommends screening for depression and referring when indicated before initiating chronic opioid therapy. There are several validated screening tools acceptable in the outpatient setting to include the 2- and 9-item Patient Health Questionnaire (PHQ-2, PHQ-9) as well as the Beck Depression Inventory (BDI) and Zung Depression Scale (ZDS). The PHQ-2 is often a first-line tool in outpatient clinics because it is relatively short and easy to administer.[t]

Mood Disorders

Though depression is a mood disorder, the literature reviewed combined depression with other mood disorders. Mood disorders represent a spectrum of disorders, including depression, bipolar disorder, and mood disorders not otherwise specified. Like depression alone, the relative confidence in the quality of evidence for mood disorders is moderate, indicating a general consistency within this classification of condition. All studies reviewed indicated some level of risk associated with comorbid mood disorders and any opioid prescription. Specifically, one large retrospective cohort study found that mood disorders were associated with a higher risk of treated OUD (adjusted HR: 1.77; 95% CI 1.13 to 2.77, p=0.0125).(132) Additionally, one very large cohort study reported mood disorders were associated with a higher risk of opioid-related emergency department visits.(152) Another large retrospective case-cohort study found that depression/bipolar/mood disorders not otherwise specified were associated with a higher risk of death by intentional overdose.(120) As discussed in the previous section, the Work Group recommends screening for depression prior to consideration of long-term opioids. Clinicians should consider screening for mood disorders such as bipolar disorder based on clinical judgment with referral when indicated before prescribing opioids for long-term treatment.

Posttraumatic Stress Disorder

The evidence for screening for PTSD prior to prescribing opioids directs clinical attention toward opioid misuse. One SR of five observational studies found that PTSD was associated with a higher prevalence of opioid misuse.(138) However, a large retrospective case-cohort study found that PTSD was not associated with a higher risk of death by intentional overdose.(120) Though there is not adequate evidence of increased mortality in the population with PTSD, screening for PTSD may provide clinicians with

[t] See the VA/DoD CPG for the Management of Major Depressive Disorder, available at: https://www.healthquality.va.gov/

information to better tailor treatment for these patients. Common, validated screening instruments for use in the outpatient setting include the Primary Care PTSD screen (PC-PTSD) or the PTSD Checklist (PCL).[u]

Psychotic Disorders

The Work Group recommends screening for psychotic disorders based on one large retrospective case-cohort study, which found that psychotic disorders were associated with a higher risk of intentional overdose (HR: 2.41; 95% CI: 1.50 to 3.87).(132) Though the overall strength of this evidence is low, when taken into aggregate with other studies (refer to Other Behavioral Health Diagnoses or Disorders), psychosis and psychotic-spectrum conditions (schizophrenia) may correlate with increased morbidity. Therefore, the Work Group recommends screening for psychotic disorders before initiating opioids. Clinical interview is the best method of screening for thought disorders. Assessing for paranoia, hallucinations, or disorganized thinking is an important aspect of a clinician's assessment of mental capacity. If there are concerns regarding a patient's perceptions of reality, medical work-up and referral to psychiatric services for comprehensive assessment is indicated prior to prescribing opioid medications.

Traumatic Brain Injury

Based on moderate quality evidence provided by one large retrospective cohort study, TBI was associated with an increased risk of opioid overdose among Veterans (adjusted HR: 3.22; 95% CI: 2.13 to 4.89).(194) Because of the relatively common diagnosis of TBI in the military population, often subclinical or by history, clinicians are strongly encouraged to screen for TBI prior to considering long-term opioids. History of concussive event with associated mental, emotional, or physical symptoms should result in additional evaluation and tailored counseling regarding the risks and benefits of treatment prior to prescribing opioid medications in the concussed population.[v]

Self-harm

The Work Group recommends screening for history of self-harm based on one large retrospective case-cohort study indicating a history of deliberate self-harm was associated with a higher risk of treated OUD (adjusted HR: 2.20; 95% CI: 1.18 to 4.11, p=0.0131).(132) Due to other potentially mortal outcomes associated with individuals who display self-directed harm, it is highly recommended providers screen for a history of self-harm during clinical interview before considering long-term opioids.

Insomnia

The evidence review did not result in a recommendation for or against assessment for insomnia in the long-term opioids population. A retrospective cohort study in the VHA found that compared to 1-30 days of opioid analgesic use, 31-90 days of use was associated with a new depressive episode in those without (HR = 1.20; 95 percent CI: 1.12-1.28) but not with insomnia (HR = 1.06; 95 percent CI: 0.86-1.32).(195) Results showed a stronger effect of chronic (>90 days) opioid analgesic use in those with insomnia (HR = 1.59; 95 percent CI: 1.27-1.98) compared to those without (HR = 1.31; 95 percent CI: 1.21-1.42). However,

[u] See the VA/DoD CPG for the Management of Posttraumatic Stress Disorder and Acute Stress Reaction, available at: https://www.healthquality.va.gov/

[v] See the VA/DoD CPG for the Management and Rehabilitation of Post-Acute Mild Traumatic Brain Injury, available at: https://www.healthquality.va.gov/

all stratum-specific effects were not significantly different (p = 0.136).(195) Clinicians should assess for insomnia and sleep disorders routinely in the pain population and treat and refer as indicated.

Psychological Factors of Clinical Relevance

Negative affect, described as the presence of anxiety or depression based on The Hospital Anxiety and Depression Scale (HADS), and pain catastrophizing, described as the significance with which a patient displays pain magnification, rumination, and helplessness based on the Pain Catastrophizing Scale (PCS), are associated with a higher risk of using illegal or unauthorized substances.(131) The same study also indicated those with pain catastrophizing were more likely to run out of their opioid medication early. Similarly, another prospective cohort study indicated pain catastrophizing (indicated by the Coping Strategies Questionnaire (CSQ) pain catastrophizing subscale) was associated with suicidal ideation and behavior.(196) Though the strength of evidence is low for these studies, the Work Group recommends screening for pain catastrophizing, depression, and anxiety prior to initiating long-term opioids due to the risk of potential catastrophic harms associated with these psychological factors.

Other Behavioral Health Diagnoses or Disorders

This category is a collection of studies combining behavioral health diagnoses in a cohort. The research provides a mixed picture regarding the potential risk of long-term opioids in those with comorbid mental illness, with the prevailing finding of increased risk overall. For example, one large retrospective cohort study provided moderate quality evidence that depression or psychotic disorder was associated with a higher risk of drug overdose in both women and men.(130) Conversely, a large retrospective cohort study provided low quality evidence that schizophrenia and other behavioral disorders were not associated with an increased risk of treated OUD.(132) Furthermore, one SR found that any behavioral health diagnosis was associated with a higher risk of opioid misuse.(138) Another large retrospective cohort study found that psychiatric disorders were associated with a higher risk of inappropriate opioid prescriptions within a 12-month follow-up.(145) Due to the relatively low risk of screening for behavioral health disorders with the benefit of reducing misuse and comorbidity, the Work Group recommends screening for behavioral health diagnoses and psychological factors before initiating long-term opioids.

There is some variability in patient preferences regarding assessment and screening. The Work Group acknowledges that increased screening may result in higher referrals to behavioral health providers, availability for whom is already critically low in some areas. Furthermore, some patients may associate their psychological or behavioral health symptoms with their chronic pain and become frustrated when there is consideration that those symptoms may be from another etiology. Care must be taken regarding patients' feelings, stigma, and possible legal/criminal justice issues surrounding behavioral health services. Cultural sensitivity as well as patient preference may guide clinicians on how to best screen for or approach behavioral health with their patients. The ability of the patient to afford additional services or attend recurrent therapy due to logistic considerations should also be weighed before recommending treatment of comorbid behavioral health conditions. Virtual behavioral health services are an opportunity to support patients with a behavioral health referral who are unable or unreliably able to access in-person behavioral health assessment, though they must be willing to engage in services through a virtual platform. Ultimately, it is better for providers to know about underlying behavioral health comorbidities than to initiate long-term opioids without this clinical knowledge. This understanding allows providers to comprehensively weigh the risks and the benefits with the patient.

The Work Group systematically reviewed evidence related to this recommendation.(120, 130-132, 138, 145, 152, 194, 196) Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including its composition of primarily retrospective cohort studies of varying strength. The potential benefits of screening for behavioral health conditions (e.g., improved outcomes of reduction of opioid misuse, reduced overdose, and reduction in suicidal death) outweighed the potential harms (e.g., increased utilization of potentially strained behavioral health system and patient discomfort with a behavioral health diagnosis). Patient values and preferences were largely varied because some patients may carry stigma regarding behavioral health diagnoses. Although the Work Group's confidence in the quality of the evidence was very low, the adverse outcomes related to forgoing assessment are potentially catastrophic (in the form of OUD, drug misuse, and/or drug overdose), in support of a *Strong for*. Considering GRADE guidelines: 15, which states, "A strong recommendation may be warranted…when low quality evidence suggests benefit in a life-threatening situation," the Work Group decided upon a *Strong for* recommendation.(136)

Recommendation

16. For patients with acute pain when opioids are being considered, we suggest screening for pain catastrophizing and co-occurring behavioral health conditions to identify those at higher risk for negative outcomes.
    (Weak for | Reviewed, New-added)

Discussion

Evidence suggests that patients with acute pain and co-occurring behavioral health conditions are at increased risk for opioid dependence, overdose, mortality, and potentially obtaining inappropriate prescriptions. Shah et al. (2017) found that in a retrospective cohort study of over 600,000 patients undergoing urological surgery who are prescribed postoperative opioids, those with a history of depression were at an increased risk (OR: 2.41) of opioid dependence or overdose.(197) In a retrospective matched cohort study of over 13,000 trauma patients compared with 70,000 non-trauma patients, Von Oelreich et al. (2020) found that risk of mortality was increased with a history of psychiatric comorbidity (HR: 1.47) or substance use (HR: 2.06) (psychiatric comorbidity was defined as the presence of a diagnosis in ICD-10 groups F20 – F99 and substance abuse as a diagnosis in F10 – F19).(198) In a retrospective population-based study evaluating over 15,000 opioid-naïve patients undergoing surgical management of facial fracture, Lapidus et al. (2020) found that comorbidities such as prior substance use (OR: 1.504) and behavioral health disorder (OR: 1.504) were found to be significantly associated with obtaining potentially inappropriate prescriptions.(199) In a retrospective cohort study of over 68,000 patients, Abraham et al. (2020) found that in patients diagnosed with acute pain who were prescribed opioids, a history of a psychiatric disorder (OR: 1.83), OUD (OR: 2.17), non-opioid drug use disorder (OR: 1.10), or combination of alcohol or drug use disorder (OR: 1.30) was associated with increased risk of filling inappropriate opioid prescriptions.(145)

Two smaller prospective cohort studies demonstrated that catastrophizing or anticipation of pain lasting longer than one week was associated with persistent pain.(200, 201)

In reviewing the retrospective studies evaluating the association between co-occurring behavioral health conditions and negative outcomes, the Work Group determined there were no other specific harms studied outside of those outlined above.

There is likely large variability regarding patient preferences in being screened for co-occurring behavioral health conditions and/or catastrophizing. Some patients will be resistant to screening, while others may feel it is a routine part of care. For patients within the DoD, there are potential career implications for positive screening for co-occurring behavioral health conditions. The minor burdens associated with screening are related to resource utilization, with providers being required to take more time to complete screening and the necessity to follow-up on positive screens/results. The Work Group determined that the benefits of reducing mortality, overdose, opioid dependence or inappropriate prescriptions outweighs the potential burdens.

The Work Group systematically reviewed evidence related to this recommendation.(145, 197-201) Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including most studies being retrospective or retrospective cohort studies (145, 197-199) related to evaluation of co-occurring behavioral health conditions and their association with negative outcomes. Additionally, none of the studies evaluated the impact of treatment for co-occurring behavioral health conditions and potential for reduced risk. The studies evaluating catastrophizing (200, 201) had small sample sizes which was a limitation as well. The potential benefits of screening for co-occurring behavioral health conditions or catastrophizing and thereby potentially reducing risk of mortality, overdose, opioid dependence or potentially inappropriate prescriptions outweighed the potential burdens which the group felt to be small. Patient values and preferences were largely varied because some patients may be resistant to screening, subgroups such as DoD patients may be concerned about career implications for positive screening while other patients may have no concerns regarding the screening questions. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

17. For patients on opioids, we suggest ongoing reevaluation of the benefits and harms of continued opioid prescribing based on individual patient risk characteristics.
    (Weak for | Reviewed, New-replaced)

Discussion

Evidence points to a variety of factors that elevate risk in opioid users. Ongoing reassessment of patients is useful for clinical decision making in balancing the risks and benefits in a patient-centered model.

Although previous versions of this guideline have suggested reevaluation at specific intervals, there is no evidence that a particular interval is more safe or effective in managing outcomes from opioids. Although standards of care, such as follow-up within 30 days of initiation of opioid medication and three-month intervals for continued opioid prescription, lack verification in the current literature as being superior to any other timeframe, the Work Group believes that these timeframes are reasonable as standards of care. Moreover, ongoing reevaluation and monitoring is reasonable based on the known risks and standards of

care. Any potential gain due to monitoring should be weighed against the burdens on the patient and health care system.

To understand how risk factors can be mitigated, the Work Group looked at associations between demographic factors and opioid-related factors with any time points or intervals shown to mitigate risks for adverse outcomes. Risks of harm may be elevated at certain age points (see Recommendation 2), gender, (129, 132, 138, 144) socioeconomic status, (132, 144) dose (see Recommendations 7 and 8), (120, 129, 130, 132-134) opioid formulation, (129, 132, 138, 202) and with use of other prescriptions (see Recommendation 6).(129, 130, 132, 138)

Risk factors may lead to the critical outcomes of OUD, non-medical opioid use, inappropriate opioid prescription, drug overdose, opioid misuse, fatal opioid overdose, or death by intentional overdose.(120, 129-133, 138, 144, 145) As potential outcomes from these events can be catastrophic, the harms of failing to identify risk factors are significant.

To discover changes in an individual patient's risk factors, periodic reassessment is reasonable, but no evidence exists to identify the appropriate time frame for reassessment and clinical decision making that balances risks and benefits of continued opioid therapy. The timeframe for reassessment should be individualized based on individual patient risks. The Work Group proposes utilizing the CDC guidance of reevaluation every 90 days as a starting point, although some patients may need more frequent reevaluation of risks and benefits. This may capture changes within an individual's health presentation or lifestyle that would identify a risk not previously known or present (for example, a newly diagnosed behavioral health condition or evidence of SUD). See Module A in the algorithm for more information on reassessment. When considering assessment and reevaluation, pain is not identified as a fifth vital sign in this CPG.

Some variability is expected among patients in terms of their acceptance of follow up for ongoing evaluation of risk. Additional appointments may be appreciated by some or a nuisance to others. The burden of attending in-person appointments may be challenging but telehealth opportunities may provide a method of reducing that burden for a subset of the patient population. Other implications include increased use of provider time for reassessments, concern about the geographically underserved including those with unstable housing, transportation, or technology (for telehealth). Some high risk populations may require more frequent follow up.

In balancing the risks and benefits of this recommendation, the Work Group feels the benefits of periodic reassessment slightly outweigh the risks, as the risks of not completing periodic reassessment are substantial and could lead to potentially catastrophic outcomes. These factors affected the strength of this recommendation.

The Work Group systematically reviewed evidence related to this recommendation.(120, 129-134, 138, 144, 145, 202) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had limitations including applicability (there are a lack of studies to directly answer the question about appropriate periodicity of reassessment to mitigate risk). The potential harms of OUD, non-medical opioid use, inappropriate opioid prescription, drug overdose, opioid misuse, fatal opioid overdose, and death by intentional overdose (120,

129-133, 138, 144, 145) were weighed against patient and provider burden for reassessment. Patient values and preferences were somewhat varied due to stigma and burden associated with periodic reassessment, including additional appointments. Thus, the Work Group decided upon a *Weak for* recommendation.

D. Risk Mitigation

Recommendation

18. We suggest urine drug testing for patients on long-term opioids.
    (Weak for | Reviewed, New-replaced)

Discussion

We suggest urine drug testing (UDT) for patients on long-term opioids to decrease the risk of self-directed violence. The Work Group acknowledges that standard of care includes many risk mitigation strategies, despite the insufficient evidence confirming their usefulness. For most risk mitigation strategies, predictive modeling, and risk assessment tools, little evidence exists to suggest improved safety for patients on long-term opioids or those who are being considered for opioids for chronic pain. The Work Group sought to find studies that investigated the effectiveness or comparative effectiveness of informed consent, risk assessment instruments, pill counts or limited pills per prescription, use of abuse deterrent formulations, diversion prevention interventions, pharmacogenetic testing, random call-backs, monitoring for aberrant or high risk behaviors, or naloxone prescription to improve outcomes, but evidence was lacking for most strategies.

There is moderate quality evidence carried forward from the 2017 VA/DoD Opioids CPG that intensive monitoring helps mitigate suicide risk among patients on long-term opioid therapy. Im et al. (2015) found moderate quality evidence of an association, at the facility-level, between increased drug screens and fewer suicide attempts.(175) In addition, patients on long-acting opioids within the facilities providing more follow-up after new prescriptions were associated with decreased risk of suicide attempt (OR: 0.2, 95% CI: 0.0-0.7).(175)

Several studies from the current evidence review focused on comparing the effectiveness of opioid management plans with motivational interviewing and various educational programs. Low to moderate quality evidence was available for opioid management plans (which included various combinations of care management, patient education, counseling, use of risk tools, opioid treatment agreements), motivational interviewing, and attention control psychoeducation (ACP) (opioid-focused phone sessions to review care plan, continue opioid tapers, order non-opioid pain medications, alcohol breath and urine drug screens, and/or placed referrals for non-pharmacological pain care, and evaluate pain and assess opioid addiction), and collaborative care practices.(203-206) These were delivered through nurse educators,(205) pharmacists,(203, 206) PCPs,(204) and psychologist care managers.(204) Opioid pain management plans resulted in no difference versus treatment as usual in physical function,(203) early refills,(205, 207) Current Opioid Misuse Measure (COMM)(205), or discontinuation of opioid prescription.(205)

A study by Borsari et al. (2021) compared two approaches: collaborative care motivational interviewing (CCMI) with ACP in a Veteran population.(204) Both arms included additional education through PCP, opioid safety education, SMART goal development (those goals which are specific, measurable, achievable,

relevant, and time-bound), and a personalized health plan and encouragement to engage in complementary and integrative health modalities. The CCMI arm consisted of four additional 20-30 minute sessions with case managers (clinical psychologists, postdoctoral fellows, or psychology research staff) to work on progress toward SMART goals. The ACP sessions were shorter but followed the same time periods delivered by the same staff. Both the CCMI and ACP groups showed reduction in COMM score (Cohen's d= 0.33-0.50) and addiction behavior checklist (ABC) (Cohen's d=0.82-0.90), but no significant differences were found between the two arms in the aberrant behaviors of positive alcohol breathalyzer testing or urine drug screen.(204)

In a small pilot study (n=32) by Cochran et al. (2019), Brief Motivational Intervention-Medication Therapy Management (BMI-MTM), which included medication therapy management (MTM), brief motivational interviewing (BMI), patient navigation, and naloxone training and referral, was favored over standard medical counseling for aberrant behavior at three months (ITT: AOR=0.13; 95% CI=0.05, 0.35, p<0.001. NUMSESS: AOR=0.05; 95% CI=0.01, 0.25; p<0.001).(206) Both interventions were pharmacist-led with BMI-MTM including up to eight weekly telephone navigation sessions of 30-45 minutes duration.(206)

Liebschutz et al. (2017) examined education oriented toward opioid prescribers in a safety-net primary care practice.(207) Academic detailing (a quality-oriented approach that helps providers make appropriate clinical decisions, based on the best available safety, efficacy, and cost-effectiveness data), an electronic registry, and nurse care management were provided to a random sample of physicians. While this intervention showed the prescribers were more likely to provide guideline-concordant care (65.9% vs 37.8%; p<.001; AOR, 6.0; 95% CI, 3.6-10.2), there was no difference found in early refill rates among the two groups.(207)

Due to the lack of conclusive evidence identified regarding the clinical utility of predictive models and screening tools for risk mitigation by the systematic evidence review, the Work Group did not make a specific recommendation on these topics. Predictive models aggregate risk factors to help identify individuals who are at increased risk for serious AEs. These models can be used to inform tools and other activities to help prevent or minimize these negative outcomes. Given the likelihood of provider variability in screening and evaluation, these models and tools can aid providers in recognizing and minimizing risk in a standardized fashion.

Regarding UDT, there was some variation in the values and preferences of patients, which mostly centered around patient perceptions of monitoring and increased frequency of visits to providers. Some patients may welcome monitoring and more frequent UDT to show their appropriate use of prescription opioids, while others may resist monitoring or struggle to make frequent appointments. The emergence of increased telehealth infrastructure may be of some benefit for those interventions that do not require in person visits (e.g., pill counts, UDT). There is concern for certain rural populations and their access to personnel with experience in risk mitigation strategies and resources. Another implication is resource use, as Thapa et al. (2021) noted that pharmacist-led opioid management plans were more costly.(203)

The Work Group systematically reviewed evidence related to this recommendation (203-207) and considered the assessment of evidence put forth in the 2017 VA/DoD Opioids CPG.(175) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including small sample sizes and a lack of evidence on

many of the interventions that are typically considered part of risk mitigation strategies.(203-206) The potential benefits of risk mitigation strategies (some improvement in aberrant behaviors and COMM and ABC scores as well as decreased risk of suicide attempt) (175, 204, 206) were balanced with the potential harms of utilizing risk mitigation strategies, such as time and stigma. Patient values and preferences were somewhat varied because of stigma and level of effort associated with increased monitoring and appointment frequency. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

19. We suggest interdisciplinary care that addresses pain and/or behavioral health problems, including substance use disorders, for patients presenting with high risk and/or aberrant behavior. **(Weak for |Not reviewed, Amended)**

Discussion

Chronic pain frequently co-occurs with a range of behavioral health conditions (including SUD and subclinical substance use, depression, anxiety, and suicidal thinking), which in turn may complicate the management of each condition and contribute to overall functional decline. A variety of high-risk medication-related behaviors (e.g., taking more than prescribed, running out early, problematic findings on urine tests) may suggest the presence of a co-occurring disorder, including SUD. Other factors including co-use of other prescribed controlled substances and difficulty engaging in multimodal treatment plans or attending regular clinic appointments can add to the challenge of safely providing opioids in the primary care setting. Chronic pain is a complex human experience influenced by physical, psychological, spiritual, social, and systemic/structural factors. Interdisciplinary care, defined by IASP as an "integrated team with ongoing care coordination and strong communication with aligned goals for the patient," that addresses these influences is helpful for all patients with chronic pain. Interdisciplinary care is particularly important when chronic pain is accompanied by co-occurring conditions, impaired function, or psychosocial vulnerabilities.

The Work Group did not review this topic in the current systematic evidence review, but considered the assessment of the evidence put forth in the 2017 VA/DoD Opioids CPG.(208, 209) Low quality evidence supports the benefits of providing brief behavioral interventions and close monitoring to patients at high risk for unsafe prescription opioid use. In 2010, Jamison et al. (2010) randomized patients at high risk for aberrant opioid use to receive either highly structured monitoring and motivational counseling (high-risk experimental) or standard care (high-risk control).(208) A group determined to be at low-risk for unsafe opioid use was used as the low-risk control group. After six months, the high-risk experimental (26.3%) and low-risk control groups (25.0%) had similarly low rates of aberrant medication use as measured by the Drug Misuse Index and compared to the high-risk control group (73.7%). A retrospective chart review of 195 patients by Meghani et al. (2009), which was carried forward from the 2010 VA/DoD Opioids CPG, found that high-risk medication-related behaviors were resolved in 45.6% of patients managed in a pharmacist-run opioid renewal clinic that was supported by a multidisciplinary pain management team, though the confidence in the quality of the evidence was low.(209)

Therefore, the previous recommendation was brought forward and amended based upon the strength of evidence from the 2017 VA/DoD Opioids CPG evidence review. The Work Group notes that the benefits of

interdisciplinary care for patients with chronic pain and co-occurring behavioral health conditions outweigh the harms.

Though referring patients with co-occurring behavioral health conditions to interdisciplinary care teams staffed by pain and behavioral health providers (including addiction medicine/psychiatry) is ideal, it is not accessible to all patients and in all settings. In such cases, multidisciplinary care (i.e., multiple disciplines co-managing a patient) with care coordination between pain care and other specialty care, including SUD specialty care, may be utilized. Chronic pain in general, and long-term use of opioids in particular, requires consideration of all aspects of a patient's life. If resources do not exist to address co-occurring behavioral health conditions, including SUDs, or if the patient declines to participate, treatment with long-term use of opioids should be reconsidered.

Research is needed to identify the efficacy and feasibility, including the relative benefits/costs, of providing interdisciplinary care to patients at high risk for poor outcomes when prescribed opioids long-term.

Many patients may value or even prefer interdisciplinary care, yet others might decline additional appointments and/or being treated by behavioral health providers. Interdisciplinary care may require upfront costs from systems of care, including more personnel resources. Conversely, any upfront costs might save the system resources over time given better coordination of care, a greater ability to address comorbidities in real time, and fewer inappropriate consults. Access to interdisciplinary care is unlikely to be evenly distributed—particularly in rural settings or when multiple appointments and co-pays disproportionately burden those with lower income. Accessing interdisciplinary pain programs via telehealth in such circumstances could be considered.

The Work Group considered the assessment of the evidence put forth in the 2017 VA/DoD Opioids CPG.(208, 209) Therefore, this is a *Not reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including finding only two studies, both of low quality, suggesting benefits of intensive monitoring and brief counseling in lowering high-risk medication-taking behaviors.(208, 209) The potential benefits of interdisciplinary care for patients with chronic pain and co-occurring behavioral health conditions, including SUD, outweighed the potential harms (e.g., appointment burden, potential cost to both the patient and system). Patient values and preferences have some variation because, while many patients might prefer interdisciplinary care, others might decline additional appointments or meeting with behavioral health providers. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

20. We suggest providing patients with pre-operative opioid and pain management education to decrease the risk of prolonged opioid use for post-surgical pain.
    (Weak for | Reviewed, New-added)

Discussion

Low to moderate quality evidence supports the use of pre-operative opioid and pain management education as a risk mitigation strategy to decrease the risk of prolonged opioid use in post-surgical settings. Cheesman et al. (2020) performed a moderate quality RCT with three year follow-up comparing brief pre-operative pain management and opioid education to a control group within an arthroscopic

rotator cuff repair setting of opioid naïve patients.(210) The pre-operative education group showed a significant decrease in critical outcomes of requested opioid prescription refills and prolonged opioid use at both short-term and over two year follow-up periods. Findings from multiple studies utilizing pre-operative opioid and pain management education within different post-surgical populations consistently showed non-inferiority in important short term outcomes of average and total pain scores.(210-214) Pre-operative education utilized in the trials reviewed included pain management education on the use of multi-modal pain regimens such as NSAIDs, acetaminophen, and non-pharmacologic strategies for the . management of pain.(210, 213, 214) Many of the trials showed that pre-operative opioid and pain management education led to better engagement in multi-modal pain regimens;(211, 213) however, one study with only a five day follow-up period showed no difference.(212) Stepan et. al (2021) provided pre-operative education and perioperative reinforcement in the form of a laminated card with their discharge instructions, which summarized the pre-operative education.(174) Perioperative reinforcement of pre-operative education may be a helpful strategy to enhance patient retention of pre-operative education. The Work Group believes these types of pain management strategies are important in successfully controlling pain post-surgically while reducing opioid consumption.

In considering this recommendation, the Work Group determined the benefits of reducing the need for prolonged opioids significantly outweighed the burdens required by healthcare professionals to provide pre-operative opioid and pain management education. The Work Group determined there are no direct harms related to education of patients. In most trials, the education was not longer than seven minutes, which the Work Group believed was feasible for real-world implementation; however, subgroup considerations such as literacy, culture, and language barriers may impact this. There are likely to be similar values, as most patients would be accepting of brief education provided in an acute setting and findings from some trials reviewed showed no difference in satisfaction surveys.(213) While not directly impacting the strength or direction of our recommendation, the Work Group is aware of a recent SR (215) which found that education interventions were more successful when they were directly related to opioid use compared to education interventions related solely to post-operative expectations.

The Work Group systematically reviewed evidence related to this recommendation.(210-215) Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including short-term follow-up, limited number of studies, varied post-surgical populations, and the focus on opioid naïve patients in some trials.(210-214) The potential benefits of pre-operative opioid and pain management education (e.g., decrease in prolonged opioid use, decrease in need for opioid refills) outweighed the potential harms (which the Work Group determined to be very low to non-existent for education). Patient values and preferences were similar because the Work Group expects most patients would be accepting of being provided education from healthcare providers within an acute setting. Thus, the Work Group decided upon a *Weak for* recommendation.

X. Research Priorities

During the development of this CPG, the Work Group identified areas in which well-designed studies, preferably in the population of interest (military/Veteran), are needed. These include areas that require stronger evidence to support current recommendations as well as those that require evidence to inform new recommendations for future CPGs. After assessing the currently available evidence, the Work Group identified the following important topics for future research:

A. Prescribing Practices

- Comparative effectiveness and safety of long-acting versus short-acting opioids, particularly morbidity and mortality, including OUD, overdose, and opioid-induced hyperalgesia
- Comparative effectiveness of dosing regimens and safety, particularly morbidity and mortality
- Provider prescribing preferences based on patient satisfaction surveys
- Equivalency of various opioids and formulations
- Comparative effectiveness and risks of regimen type, dosing, and dosing approach
- Use of buprenorphine for pain

B. Tapering Approaches

- Comparative effectiveness and risks of opioid tapering strategies and schedules, including switching to partial agonist therapy
- Tapering strategies in patients without OUD that include conversion to buprenorphine followed by tapering
- Tapering strategies and schedules for co-prescribed benzodiazepines/opioids
- Examination of non-pharmacologic approaches that may improve opioid tapering outcomes
- Benefits of predictive modeling and screening tools for predicting risks or success of tapering

C. Management of Patients On and Being Considered for Opioids

- Benefits of periodic reevaluation and risk mitigation strategies for patient safety (e.g., informed consent, risk assessment instruments, UDT, pill counts or limited pills per prescription, use of abuse-deterrent formulations, diversion prevention interventions, pharmacogenetic testing, random call-backs, monitoring for aberrant or high risk behaviors, naloxone prescription to improve outcomes)
- Intervals and timing of periodic reevaluation for improving patient safety
- Benefits of predictive modeling and screening tools for initiation and continuation of opioid prescribing in patients with acute pain
- Benefits of predictive modeling and screening tools for continuation of opioid prescribing in patients with chronic pain
- Benefits of predictive modeling and screening tools for various subpopulations

- Comparative effectiveness of opioids versus non-opioid interventions (both pharmacologic and non-pharmacologic) for pain
- Promising interdisciplinary pain care practices with and without opioid prescribing
- Social-environmental, behavioral, psychological, and other factors that affect the transition from short-term to chronic opioid use

D. Intersection of OUD

- Outcomes related to the transition to chronic opioid use in patients with comorbid AUD versus OUD
- Medication treatment for OUD in patients with co-occurring OUD and chronic pain
- Treatment strategies that concurrently address pain and OUD to improve patient outcomes
- Treatment of pain in patients with co-occurring OUD and acute or chronic pain

Future studies focusing on outcomes of interest, including serious AEs and QoL, are needed. Additionally, future research that incorporates diverse demographics (e.g., race, gender) to represent the population is required.

Appendix A: Guideline Development Methodology

A. Developing Key Questions to Guide the Systematic Evidence Review

To guide this CPG's systematic evidence review, the Work Group drafted 12 KQs on clinical topics of the highest priority for the VA and DoD populations. The KQs followed the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework, as established by the Agency for Healthcare Research and Quality (AHRQ) (see Table A-1).

Table A-1. PICOTS (216)

PICOTS Element	Description
Population or Patients	Patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-occurring conditions, and other patient characteristics or demographics.
Intervention or Exposure	Treatment (e.g., drug, surgery, lifestyle changes), approach (e.g., doses, frequency, methods of administering treatments), or diagnostic /screening test used with the patient or population.
Comparator	Treatment(s) (e.g., placebo, different drugs) or approach(es) (e.g., different dose, different frequency, standard of care) that are being compared with the intervention or exposure of interest described above.
Outcomes	Results of interest (e.g., mortality, morbidity, QoL, complications). Outcomes can include short, intermediate, and long-term outcomes.
Timing, if applicable	Duration or follow-up of interest for the particular patient intervention and outcome to occur (or not occur).
Setting, if applicable	Setting or context of interest. Setting can be a location (e.g., primary, specialty, inpatient care) or type of practice.

Abbreviation: PICOTS: population, intervention, comparison, outcome, timing, and setting

Due to resource constraints, all KQs of interest to the Work Group could not be included in the systematic evidence review. Thus, the Work Group selected the 12 highest priority KQs for inclusion in the systematic evidence review (see Table A-2).

Using the GRADE approach, the Work Group rated each outcome on a 1 – 9 scale (7 – 9, critical for decision making; 4 – 6, important, but not critical, for decision making; and 1 – 3, of limited importance for decision making). Critical and important outcomes were included in the evidence review (see Outcomes); however, only critical outcomes were used to determine the overall quality of evidence (see Determining Recommendation Strength and Direction).

a. Population(s)

- Key Question 1: Standard population
- Key Question 2:
  - Standard population
  - Adults with chronic pain being considered for prescribed opioids
- Key Question 3: Adults with chronic pain, subgroups for patients with:
  - SUD (including OUD)
  - Co-occurring behavioral/mental health conditions

    - Co-occurring medical conditions
- Key Questions 4, 5, 7, and 11: Standard population, subgroups for patients with:
    - SUD (including OUD)
    - Co-occurring behavioral/mental health conditions
    - Co-occurring medical conditions
- Key Question 6:
    - Standard population
    - Adults with chronic pain being considered for prescribed opioids
    - Subgroups for patients with:
        - SUD (including OUD)
        - Co-occurring behavioral/mental health conditions
        - Co-occurring medical conditions
    - Patients being considered for prescribed opioids include:
        - Patients who have not responded to non-opioid therapy for chronic pain for a long period of time
        - Patients who have used prescribed opioids for 3 or more months
- Key Question 8 and 9: Adults prescribed opioids for acute pain
- Key Question 10: Adults with chronic pain
- Key Question 12: Patients with OUD

b. Interventions

- Key Question 1: One of the following co-occurring medical or behavioral/mental health conditions
    - Active pursuit of compensation
    - Anxiety
    - Bipolar disorder
    - Centralized pain conditions (e.g., fibromyalgia)
    - Chronic obstructive pulmonary disease
    - Cognitive impairment
    - Depression
    - Headache
    - Gastrointestinal motility problems (e.g., toxic megacolon, gastrointestinal pain syndromes, narcotic bowel syndrome)
    - Functional abdominal pain
    - Immune status changes

- Impulse control disorder
- Inability to participate in comprehensive treatment plan
- Incarceration (history of)
- Multiple sclerosis
- Hepatic, renal, or pulmonary disease
- Suspected opioid misuse (e.g., overdose, early refills, diversion, taking more than prescribed)
- Osteoporosis
- High pain catastrophizing
- Fear avoidance behaviors
- Poor pain self-efficacy
- Personality disorders
- Poor social functioning
- PTSD
- Psychotic disorders
- Sleep disorders
- SUDs (current or history of)
- Other addiction behaviors
- Stress
- Suicidality
- Traumatic brain injury
- Use of medical marijuana or cannabidiol (CBD)
- Use of kratom
- QT prolongation

- Key Question 2: Comparison groups that vary by dosage and length of opioid use, other factors
  - Dose
  - Formulation
  - Duration
  - Mechanism of action (full versus partial opioid)
  - Different regimens (e.g., scheduled, continuous, as-needed)
  - Age
  - Gender
  - Race

  - Marital status
  - Healthcare utilization
  - Diversion considerations
  - Marijuana use
  - Depression
  - Anxiety
  - Catastrophizing
  - Comorbidities (e.g., PTSD)
  - Co-prescriptions
  - Socioeconomics
- Key Question 3: Prescribed opioids
- Key Question 4:
  - Immediate-release/short-acting opioid drugs
  - Transdermal patches, buccal, sublingual, or intrathecal pumps
  - Abuse deterrent formulations
  - Tramadol and other dual-mechanism opioids
  - Buprenorphine
  - Methadone
  - One prescribing regimen (e.g., PRN use)
- Key Question 5: Prescribed opioids plus medications with CNS effects (prescribed and over the counter)
  - Benzodiazepines
  - CNS depressants and antidepressants (e.g., serotonin–norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants [TCAs])
  - Antiepileptics
  - Gabapentinoids
  - Non-opioid analgesics (e.g., ketamine)
  - Stimulants
  - Muscle relaxers
  - Cannabinoids (e.g., medical marijuana, CBD)
  - Z-drugs (e.g., hypnotics for sleep)
  - Kratom
  - Seroquel
  - Diphenhydramine and antihistamines

- Key Question 6: Risk mitigation strategy
    - Naloxone rescue with one form of naloxone
    - Informed consent
    - Written informed consent (previously called contracts)
    - Risk assessment instruments (e.g., Opioid Risk Tool; Screener and Opioid Assessment for Patients with Pain [SOAPP]; Screening Instrument for Substance Abuse Potential; Diagnosis, Intractability, Risk, Efficacy; Prescription Drug Use Questionnaire Self-Report; COMM; Pain Medication Questionnaire; Pain Assessment and Documentation Tool; ABC; and Cut down, Annoyed, Guilty, and Eye-opener)
    - Opioid management plans
    - Patient education
    - UDT
    - PDMP
    - Monitoring instruments (e.g., SOAPP, STORM, RIOSORD score, PHQ-9, DAST-10)
    - More frequent monitoring
    - Pill counts
    - Limited amounts of pills per prescription fill
    - Use of abuse –deterrent formulations
    - Diversion prevention interventions (e.g., properly securing drugs, medication take back programs, public health education)
    - Pharmacogenetic testing
    - Random call-backs
    - Compliance with other therapies
    - Case management
    - Periodic check of state databases
    - Needle exchange programs
    - Monitoring for aberrant or high-risk behaviors
- Key Question 7: One tapering strategy or schedule
    - Pharmacotherapy
    - Non-pharmacological options (e.g., complementary and integrative health, psychotherapies, behavioral health interventions, education)
    - Changes to pharmacotherapy (e.g., switching to buprenorphine)
    - Buprenorphine assisted taper
    - Rapid detox through ketamine

- Key Question 8: Factors potentially associated with transition to chronic opioid use
    - Chronic distress in daily life (e.g., housing insecurity/homelessness, unemployment, financial stress/poverty, divorce)
    - Psychological factors (e.g., comorbid depression, SUD, PTSD, smoking, or other behavioral health conditions)
    - TBI
    - Fear avoidance behaviors
    - Adverse childhood events
    - Social-environmental factors (e.g., rurality)
    - Passive coping behaviors
    - Emotional factors
    - Personality factors
    - Failed treatments
    - High pain catastrophizing
    - Pain severity
    - Tissue damage
    - Nociceptive versus neuropathic pain
    - High disability/impairment rating
    - Worker's compensation
- Key Question 9: Risk mitigation strategies
    - Naloxone rescue with one form of naloxone
    - Informed consent
    - Written informed consent (previously called contracts)
    - Risk assessment instruments
    - Opioid management plans
    - Patient education
    - UDT
    - PDMP
    - Monitoring instruments
    - More frequent monitoring
    - Pill counts
    - Use of abuse –deterrent formulations

- Diversion prevention interventions (e.g., properly securing drugs, medication take back programs, public health education)
- Pharmacogenetic testing
- Random call-backs
- Compliance with other therapies (also engagement, participation, and adherence)
- Case management
- Periodic check of state databases
- Needle exchange programs

- Key Question 10:
  - Prescribed opioids
  - Opioid dosage
  - Opioid regimen type
  - Opioid formulation
- Key Question 11:
  - Screening tools
    - STORM
    - RIOSORD
    - Others
  - Screening for risk factors
    - Impulse control disorder
    - Suicidal depression
    - Bipolar disorder
    - Anxiety
    - Stress
    - Catastrophizing
    - Poor social functioning
    - Polypharmacy
  - Predictive analytics
- Key Question 12:
  - Methadone
  - Buprenorphine
  - Naltrexone

c. Comparators

- Key Question 1: No co-occurring medical or behavioral/mental health condition
- Key Question 2: Comparison groups that vary by dosage and length of opioid use, other factors
- Key Question 3: Non-opioid therapy (including placebo) or other pain management strategies:
    - Standard set of non-opioid medications
    - Physical (e.g., physical therapy)
    - Exercise
    - Ultrasound stimulation
    - Chiropractic
    - Osteopathic manipulation therapy (also known as spinal manipulative therapy), spinal mobilization, joint mobilization
    - Behavioral/mental health (e.g., cognitive behavioral therapy, assertive community treatment, mindfulness-based stress reduction, mindfulness, dialectical behavioral therapy)
    - Interventional
    - Complementary and integrative approaches, including:
        - Acupuncture/dry needling
        - Biofeedback/neurofeedback
        - Clinical hypnosis
        - Massage therapy
        - Meditation
        - Relaxation techniques (e.g., deep breathing/diaphragmatic breathing, visualization, muscle relaxation, guided imagery)
        - Tai Chi/Qigong
        - Yoga
- Key Question 4:
    - Extended-release/long-acting opioid drugs or combination short and long-acting drugs (need to specify)
    - Other route of administration/delivery alternatives
    - Non abuse-deterrent formulations
    - Other opioids
    - No use of buprenorphine
    - No use of methadone
    - Different prescribing regimen (e.g., around the clock use)

- Key Question 5: Prescribed opioids alone
- Key Question 6: No risk mitigation strategy or other mitigation strategy
- Key Question 7: Different tapering strategy or schedule; maintenance of current tapering strategy or schedule; opioid maintenance
- Key Question 8: Different level of exposure to a potential risk factor
- Key Question 9: No risk mitigation strategy or other mitigation strategy
- Key Question 10: No use of screening or predictive analytics
- Key Question 12: Other interventions listed in previous column

d. Outcomes

- Key Question 1
  - Critical outcomes:
    - SUD (including OUD) and related events
    - Serious AEs
  - Important outcomes:
    - Other AEs
    - Pain (pain severity, pain interference, chronification of pain)
    - Function
    - Engagement in multimodal care (including non-opioid therapy for pain) and retention
- Key Question 2
  - Critical outcomes:
    - Misuse or OUD
    - Overdose
- Key Question 3
  - Critical outcomes:
    - SUD (including OUD) and related events
    - Serious AEs
    - Pain (pain severity, pain interference, chronification of pain)
    - Function
  - Important outcomes:
    - Other AEs
    - QoL
    - Engagement in multimodal care (including non-opioid therapy for pain) and retention

- Key Question 4 and 5
  - Critical outcomes:
    - Serious AEs
    - Pain (pain severity, pain interference, chronification of pain)
    - Function
  - Important outcomes:
    - SUD (including OUD) and related events
    - Other AEs
    - QoL
    - Treatment adherence
- Key Question 6
  - Critical outcomes:
    - SUD (including OUD) and related events
    - Serious AEs
  - Important outcomes:
    - Other AEs
    - QoL
    - Function
    - Treatment adherence
    - Resource utilization and cost
- Key Question 7
  - Critical outcomes:
    - SUD (including OUD) and related events
    - Serious AEs
  - Important outcomes:
    - Other AEs
    - Pain (pain severity, pain interference, chronification of pain)
    - QoL
    - Function
    - Treatment adherence

- Key Question 8
  - Critical outcomes:
    - SUD (including OUD) and related events
    - Serious AEs
  - Important outcomes:
    - Other AEs
    - Pain (pain severity, pain interference, chronification of pain)
    - QoL
    - Function
    - Treatment adherence
- Key Question 9
  - Critical outcomes:
    - SUD (including OUD) and related events
    - Serious AEs
  - Important outcomes:
    - Other AEs
    - Pain (pain severity, pain interference, chronification of pain)
    - Function
    - Treatment adherence
    - Engagement in multimodal care (including non-opioid therapy for pain) and retention
- Key Question 10
  - Critical outcomes:
    - Serious AEs
    - Pain (pain severity, pain interference, chronification of pain)
    - QoL
    - Function
  - Important outcomes:
    - SUD (including OUD) and related events
    - Other AEs
    - Treatment adherence

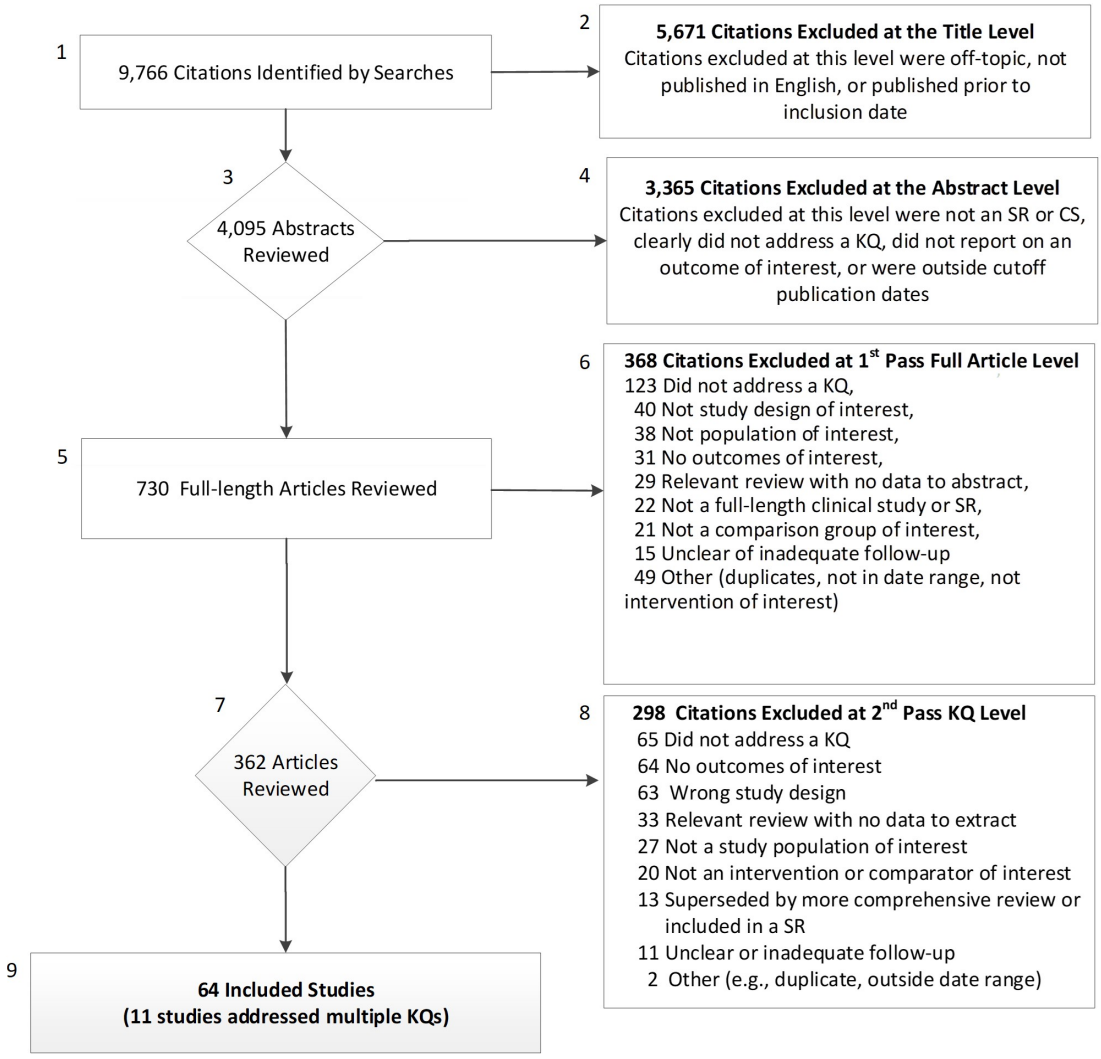
- Key Question 11
  - Critical outcomes:
    - Serious AEs
  - Important outcomes:
    - Cognitive and motor performance measures
    - Other AEs
    - SUD (including OUD) and related events
- Key Question 12
  - Critical outcomes:
    - Pain (pain severity, pain interference, chronification of pain)
    - Function
    - QoL
  - Important outcomes:
    - Opioid-induced hyperalgesia

B. Conducting the Systematic Review

Based on the Work Group's decisions regarding the CPG's scope, KQs, and PICOTS statements, the Lewin Team produced a systematic evidence review protocol before conducting the review. The protocol detailed the KQs, PICOTS criteria, methodology to be used during the systematic evidence review, and the inclusion and exclusion criteria to be applied to each potential study, including study type and sample size. The Work Group reviewed and approved the protocol.

Figure A-1 below outlines the systematic evidence review's screening process (see also the General Criteria for Inclusion in Systematic Review and Key Question Specific Criteria). In addition, Table A-2 indicates the number of studies that addressed each of the questions.

Figure A-1. Study Flow Diagram



Abbreviations: CS: clinical study; KQ: key question; SR: systematic review

Alternative Text Description of Study Flow Diagram

Figure A-1. Study Flow Diagram is a flow chart with nine labeled boxes linked by arrows that describe the literature review inclusion/exclusion process. Arrows point down to boxes that describe the next literature review step and arrows point right to boxes that describe the excluded citations at each step (including the reasons for exclusion and the numbers of excluded citations).

1. Box 1: 9,766 citations identified by searches
    a. Right to Box 2: 5,671 citations excluded at the title level
        i. Citations excluded at this level were off-topic, not published in English, OR published prior to inclusion date
    b. Down to Box 3

2. Box 3: 4,095 abstracts reviewed
    a. Right to Box 4: 3,365 citations excluded at the abstract level
        i. Citations excluded at this level were not an SR or CS, clearly did not address a KQ, did not report on an outcome of interest, or were outside cutoff publication dates
    b. Down to Box 5: 730 full-length articles reviewed
3. Box 5: 730 full-length articles reviewed
    a. Right to Box 6: 368 citations excluded at 1st pass full article level
        i. 123 did not address a KQ
        ii. 40 not study design of interest
        iii. 38 not population of interest
        iv. 31 no outcomes of interest
        v. 29 relevant review with no data to abstract
        vi. 22 not a full-length clinical study or SR
        vii. 21 not a comparison group of interest
        viii. 15 unclear of inadequate follow-up
        ix. 49 other (duplicates, not in date range, not intervention of interest)
    b. Down to Box 7
4. Box 7: 362 articles reviewed
    a. Right to Box 8: 298 citations excluded at 2nd pass KQ level
        i. 65 did not address a KQ
        ii. 64 no outcomes of interest
        iii. 63 wrong study design
        iv. 33 relevant reviews with no data to extract
        v. 27 not a study population of interest
        vi. 20 not an intervention or comparator of interest
        vii. 13 superseded by more comprehensive review or included in an SR
        viii. 11 unclear or inadequate follow-up
        ix. 2 other (e.g., duplicate, outside data range)
    b. Down to Box 9
5. Box 9: 64 Included Studies (11 studies addressed multiple KQs)

Table A-2. Evidence Base for KQs

KQ Number	KQ	Number and Study Type
1	What is the evidence that medical or mental health conditions are absolute or relative contraindications of prescribing opioids for chronic pain?	1 SR and 12 cohort studies
2	What demographic and opioid-related factors increase the risk of developing opioid misuse, OUD, or overdose when considering opioid prescribing for chronic pain?	1 SR and 10 cohort studies
3	What is the comparative effectiveness and safety of the addition of opioids to non-opioid therapies versus non-opioid therapies alone?	5 SRs
4	What is the comparative effectiveness and safety of various opioid formulations: a) Immediate-release/short-acting opioids compared to extended-release/long-acting opioids; b) Route of administration/delivery alternatives such as transdermal, buccal, sublingual, intrathecal pumps; c) Abuse deterrent formulations compared to non-abuse deterrent formulations; d) Tramadol and other dual-mechanism opioids; e) Buprenorphine; f) Methadone; g) Different prescribing regimens?	2 SRs and 5 RCTs
5	For patients with chronic pain, what is the effectiveness and safety of medications with central nervous system effects used in combination with opioids?	3 RCTs
6	What is the effectiveness of different risk mitigation strategies for patients either on prescribed opioids or being considered for opioid prescribing for chronic pain?	1 SR and 5 RCTs
7	What is the safety and comparative effectiveness of opioid tapering and tapering strategies for a) opioids and b) polypharmacy (including opioids)? Does the patient's starting morphine equivalent dose change the safety and efficacy?	1 SR and 1 RCT
8	For patients who are prescribed opioids for acute pain, what factors are associated with transition to chronic opioid use or other negative outcomes?	1 SR and 7 cohort studies
9	What is the effectiveness of risk mitigation strategies for patients prescribed opioids for acute pain?	5 RCTs
10	What is the impact of prescribed opioids on the underlying pain condition (e.g., worsening of pain/opioid-induced hyperalgesia), and what factors (dosage, regimen type, formulation, timing/length of use) affect the prognosis?	6 SRs
11	How does use of screening tools and predictive analytics allow management decisions that predict adverse outcomes in patients on prescribed opioids for chronic pain?	1 SR, 1 RCT, and 6 cohort studies
12	What is the comparative effectiveness of methadone, buprenorphine, and naltrexone as an adjunct for the treatment of chronic pain in patients with OUD?	1 RCT
	Total Evidence Base	**64 studies (11 studies addressed multiple KQs)**

Abbreviations: KQ: key question; RCT: randomized controlled trial; SR: systematic review

a. General Criteria for Inclusion in Systematic Evidence Review

- RCTs or systematic reviews published on or after December 1, 2015 to April 9, 2021. If multiple systematic reviews addressed a key question, we selected the most recent and/or comprehensive review. Systematic reviews were supplemented with RCTs published subsequent to the systematic review.
- Studies had to be published in English.
- Publication must have been a full clinical study or systematic review; abstracts alone were not included. Similarly, letters, editorials, and other publications that were not full-length clinical studies were not accepted as evidence.
- Systematic reviews must have searched MEDLINE or EMBASE for eligible publications, performed a risk of bias assessment of included studies, and assessed the quality of evidence using a recognizable rating system, such as GRADE or something compatible (e.g., the Strength of Evidence grading used by the Evidence-based Practice Centers of the Agency for Healthcare Research and Quality). If an existing review did not assess the overall quality of the evidence, evidence from the review must have been reported in a manner that allowed us to judge the overall risk of bias, consistency, directness, and precision of evidence. We did not use an existing review as evidence if we were unable to assess the overall quality of the evidence in the review.
- Study must have enrolled at least 20 patients (10 per study group) for treatment studies, 50 total patients for prognostic studies; Small sample size is associated with increased risk of bias and we downgrade small studies in the GRADE domain of precision: one downgrade for imprecision of a single study with <200 patients per study arm and 2 downgrades for imprecision for <50 total patients.
    - Newer Cochrane reviews already take into account small sample-size in their estimation of risk of bias. In these cases, where sample size has already contributed to the assessment of the evidence, we will not downgrade those data a second time.
- Study must have enrolled at least 85% of patients who meet the study population criteria: adults aged 18 years or older with chronic pain on prescribed opioids (or other populations noted in Table 1). For studies examining mixed patient populations, studies must have enrolled at least 85% of patients with the relevant condition.
- Study must have reported on at least one outcome of interest.

b. Key Question Specific Criteria for Inclusion in Systematic Evidence Review

- For all KQs, except KQ 1, 2, and 8, studies included in the systematic reviews or as independent papers must have been prospective RCTs with an independent control group.
    - KQ 1, 2, and 8 also included prognostic observational studies (cohort studies and case-control studies) that statistically compared outcomes for patients who have relevant prognostic factors and patients who lack these factors. Retrospective prognostic studies had to include at least 200 patients in a multivariate analysis.
    - KQ 6 and 9 also included prospective non-randomized cohort studies if insufficient evidence was available from systematic reviews and RCTs.

c. Literature Search Strategy

Information regarding the bibliographic databases, date limits, and platform/provider can be found in Table A-3. See Appendix I for additional information on the search strategies, including topic-specific search terms and search strategies.

Table A-3. Bibliographic Database Information

Name		Date Limits	Platform/Provider
Bibliographic Databases	EMBAS E (Excerpta Medica) and MEDLINE	December 1, 2015 through April 2, 2021	Elsevier
	PsycINFO (for selected KQs)	December 1, 2015 through April 8, 2021	Ovid
	PubMed (In-process and Publisher records)	December 1, 2015 through April 2, 2021	NLM
Grey Literature	Agency for Healthcare Research and Quality (AHRQ)	March 2015 through April 9, 2021	AHRQ
	U.S. Department of Veterans Affairs (VA) Evidence Synthesis Program	2015 through April 9, 2021	VA

d. Rating the Quality of Individual Studies and the Body of Evidence

The Lewin Team assessed the methodological risk of bias of individual diagnostic, observational, and interventional studies using the USPSTF method. Each study is assigned a rating of *Good*, *Fair*, or *Poor* based on a set of criteria that vary depending on study design. Detailed lists of criteria and definitions appear in Appendix VI of the USPSTF procedure manual.(217)

Following this, the Lewin Team assessed the overall quality of the body of evidence for each critical and important outcome using the GRADE approach. This approach considers the following factors: overall study quality (or overall risk of bias or study limitations), consistency of evidence, directness of evidence, and precision of evidence. The overall quality of the body of evidence is rated as *High*, *Moderate*, *Low*, and *Very low*.

C. Developing Evidence-based Recommendations

In consultation with the VA Office of Quality and Patient Safety and the Clinical Quality Improvement Program, DHA, the Lewin Team convened a four-day virtual recommendation development meeting on July 20, 2021 to develop this CPG's evidence-based recommendations. Two weeks before the meeting, the Lewin Team finalized the systematic evidence review and distributed the report to the Work Group; findings were also presented during the recommendation development meeting.

Led by the Champions, the Work Group interpreted the systematic evidence review's findings and developed this CPG's recommendations. Where appropriate, the Work Group carried forward and modified recommendations from the 2017 VA/DoD Opioids CPG as necessary (see Reconciliation of 2017 Clinical Practice Guideline Recommendations). The Work Group also developed new recommendations not included in the 2017 VA/DoD Opioids CPG based on the 2022 CPG evidence review.

The strength and direction of each recommendation were determined by assessing the quality of the overall evidence base, the associated benefits and harms, patient values and preferences, and other implications (see Determining Recommendation Strength and Direction).

a. Determining Recommendation Strength and Direction

Per GRADE, each recommendation's strength and direction is determined by the following four domains:(102)

1. Confidence in the Quality of the Evidence

Confidence in the quality of the evidence reflects the quality of the body of evidence supporting a recommendation (see Rating the Quality of Individual Studies and the Body of Evidence). The options for this domain include: *High*, *Moderate*, *Low*, or *Very low*. This is a direct reflection of the GRADE ratings for each relevant critical outcome in the evidence review (see Outcomes). Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(104, 105)

The recommendation strength generally aligns with the confidence in the quality of evidence. For example, *Strong* recommendations are typically supported by *High* or *Moderate* quality evidence. However, GRADE permits *Low* or *Very low* quality evidence to support a *Strong* recommendation in certain instances (e.g., life-threatening situation).(102)

2. Balance of Desirable and Undesirable Outcomes

The balance of desirable and undesirable outcomes (i.e., benefits and harms) refers to the relative magnitudes or tradeoffs of anticipated benefits (e.g., increased longevity, reduced morbidity, improved QoL, decreased resource use) and harms (e.g., decreased longevity, increased complications, impaired QoL). The options for this domain include: *benefits outweigh harms/burden*, *benefits slightly outweigh harms/burden*, *benefits and harms/burdens are balanced*, *harms/burdens slightly outweigh benefits*, and *harms/burdens outweigh benefits*. This domain assumes most clinicians will offer patients an intervention if its advantages exceed the harms. The Work Group's understanding of the benefits and harms associated with the recommendation influenced the recommendation's strength and direction.

3. Patient Values and Preferences

Patient values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life as they may apply to the intervention's potential benefits, harms, costs, limitations, and inconvenience. The options for this domain include: *similar values*, *some variation*, or *large variation*. For instance, there may be *some variation* in patient values and preferences for a recommendation on the use of acupuncture, as some patients may dislike needles. When patient values seem homogeneous, this domain may increase the recommendation's strength. Alternatively, when patient values seem heterogeneous, this domain may decrease a recommendation's strength. As part of this domain, the Work Group considered the findings from the patient focus group carried out as part of this CPG update (see Appendix E).

4. Other Implications

Other implications encompass the potential consequences or other impacts that might affect the strength or direction of the recommendation. The options for this domain include, e.g.: resource use, equity, acceptability, feasibility, and subgroup considerations. The following are example implications related to equity and subgroup considerations, respectively: some of the indicated population may be geographically remote from an intervention (e.g., complex radiological equipment); a drug may be contraindicated in a subgroup of patients.

Table A-4. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgment
Confidence in the quality of the evidence	Among the designated critical outcomes, what is the lowest quality of relevant evidence? How likely is further research to change the confidence in the estimate of effect?	High Moderate Low Very low
Balance of desirable and undesirable outcomes	What is the magnitude of the anticipated desirable outcomes? What is the magnitude of the anticipated undesirable outcomes? Given the best estimate of typical values and preferences, are you confident that benefits outweigh harms/burdens or vice versa?	Benefits outweigh harms/burdens Benefits slightly outweigh harm/burden Benefits and harms/burdens are balanced Harms/burdens slightly outweigh benefits Harms/burdens outweigh benefits
Patient values and preferences	What are the patients' values and preferences? Are values and preferences similar across the target population? Are you confident about typical values and preferences?	Similar values Some variation Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	What are the costs per resource unit? Is this intervention generally available? What is the variability in resource requirements across the target population and settings? Are the resources worth the expected net benefit from the recommendation? Is this intervention and its effects worth withdrawing or not allocating resources from other interventions?	Various considerations

b. Recommendation Categorization

A summary of the recommendation categories and definitions is available in Table 2.

1. Categorizing Recommendations with an Updated Review of the Evidence

Reviewed refers to recommendations on topics included in this CPG's systematic evidence review. *Reviewed*, *New-added* recommendations are original, new recommendations (i.e., not included in the previous CPG). These recommendations are based entirely on evidence included in the current CPG's systematic evidence review.

Reviewed, *New-replaced* recommendations were in the previous CPG but revised based on the updated evidence review. These recommendations may have clinically relevant edits. *Reviewed*, *Not changed*

recommendations were carried forward from the previous CPG unchanged. *Reviewed*, *Amended* recommendations were carried forward from the previous CPG with a nominal change. This allowed for the recommendation language to reflect GRADE approach and any other not clinically meaningful edits deemed necessary. These recommendations can be based on a combination of evidence included in the current CPG's systematic evidence review and the evidence base that supported the recommendation in the previous CPG.

Reviewed, *Deleted* refers to recommendations from the previous CPG that were deleted after a review of the evidence. This may occur if the evidence supporting the recommendation is outdated (e.g., there is no longer a basis to recommend use of an intervention and/or new evidence suggests a shift in care), rendering the recommendation obsolete.

2. Categorizing Recommendations without an Updated Review of the Evidence

There were also cases in which it was necessary to carry forward recommendations from the previous CPG without an updated review of the evidence. Given time and resource constraints, the systematic evidence review carried out for this CPG update could not cover all available evidence on opioids for chronic pain; therefore, its KQs focused on new or updated research or areas not covered in the previous CPG.

For areas in which the relevant evidence was not changed and for which recommendations made in the previous CPG were still relevant, recommendations could have been carried forward to the updated CPG without an updated review of the evidence. The evidence supporting these recommendations was thus also carried forward from the previous CPG. These recommendations were categorized as *Not reviewed*. If evidence had not been reviewed, recommendations could have been categorized as *Not changed*, *Amended*, or *Deleted*. *Not reviewed*, *Not changed* recommendations were carried forward from the previous CPG unchanged. *Not reviewed*, *Amended* recommendations were carried forward from the previous CPG with a nominal change. *Not reviewed*, *Deleted* recommendations were determined by the Work Group to not be relevant. A recommendation may not be relevant if it, for example, pertained to a topic (e.g., population, care setting, treatment) outside of the updated CPG's scope or if it was determined to be common practice.

The recommendation categories for the current CPG are noted in the Recommendations. The recommendation categories from the 2017 VA/DoD Opioids CPG are noted in Appendix G.

D. Drafting and Finalizing the Guideline

The Work Group wrote, reviewed, and edited three drafts of the CPG using an iterative review process to solicit feedback on and make revisions to the CPG. The first and second drafts were posted online for 20 and 14 business days, respectively, for the Work Group to provide feedback. Draft 3 was made available for a 14-day peer review and comment (see External Peer Review). The Work Group reviewed all feedback submitted during each review period and made appropriate revisions to the CPG. Following the Draft 3 review and comment period, the Work Group reviewed external feedback and created a final draft of the CPG. The Champions then presented the CPG to the VA/DoD EBPWG for approval. The Work Group considered the VA/DoD EBPWG's feedback and revised the CPG as appropriate to create the final version. To accompany the CPG, the Work Group produced toolkit products, including a provider summary, pocket card, and patient summary. The VA/DoD EBPWG approved the final CPG and toolkit products in May 2022.

Appendix B: Urine Drug Testing

A. Benefits of Urine Drug Testing

Substance misuse in patients on long-term opioids has been documented at over 30% in some studies.(218) The inaccuracies inherent to patient self-reporting coupled with the evident mortality and morbidity to the treated patients, their families, and others require additional methods to ascertain patient and public safety. Urine drug testing is an additional method of examining for patient substance misuse and adherence to the prescribed regimen. It can also help in the development of trust within the provider-family-patient relationship. It is critical that the UDT and confirmatory testing be done in a timely, confidential, accurate, and easily available manner to assure the prescribers, patients, and public that safety, fairness, and trust are being addressed.

Within the VA, verbal informed consent is required before UDT.(219) Patients can decline to consent to a UDT. However, providers should factor that declination into their consideration about whether it is safe to continue opioids. Urine drug testing is required if long-term opioids are to be initiated or continued. For more information, see the VA National Center for Ethics in Health Care website (http://www.ethics.va.gov/).

B. Types of Urine Drug Testing

There are three main types of UDT currently being utilized in clinical settings: immunoassay, gas chromatography-mass spectrometry (GCMS) confirmatory testing, and liquid chromatography-mass spectrometry (LCMS) confirmatory testing.(220, 221) Immunoassay screening is inexpensive, fast, and widely available. However, there are a number of drawbacks to using this test alone. There is a higher potential for false positives and negatives as well as a lack of specificity of the actual opiate or benzodiazepine being tested. GCMS is highly sensitive and specific; however, it is expensive and time-consuming. LCMS is less expensive than GCMS but more expensive than immunoassay. It can confirm a large number of medications, substances, and drugs at one time and may be helpful in many patients at initiation of opioids, periodically during treatment with opioids, and following cessation of opioids if SUD is a possibility. See Table B-1 through Table B-4 and Figure B-1 for more information.

Table B-1. Urine Toxicology Specimen Validity and Normal Characteristics of a Urine Sample (220, 222-225)

Urine Toxicology Specimen Validity	Normal Characteristics of a Urine Sample
• Urine samples that are adulterated, substituted, or diluted may avoid detection of drug use • Urine collected in the early morning is most concentrated and most reliable • Excessive water intake and diuretic use can lead to diluted urine samples (creatinine <20 mg/dL) • THC assays are sensitive to adulterants (e.g., eye drops)	Temperature within four minutes of voiding: 90-100° F
	pH: 4.5-8.0
	Creatinine: >20 mg/dL
	Specific gravity: >1.003
	Nitrates: <500 mcg/dL
	Volume: ≥30 mL

Abbreviations: ° F: degrees Fahrenheit; dL: deciliter(s); mcg: microgram(s); mg: milligram(s); mL: milliliter(s); THC: tetrahydrocannabinol

Table B-2. Urine Toxicology Screening Federal Work Place Cut Off Values (222-229)

Agent			Initial drug test level (immunoassay) (ng/mL)	Confirmatory drug test level (GCMS) (ng/mL)	Confirmatory test analyte	Detection period after last dose (days)[a]
Extended UTS	*Regular UTS*	Marijuana metabolites	50	15	THCA	2-8 single use 20-30 chronic use[b]
		Cocaine metabolites	300	150	Benzyolyecgonine	1-3
		Opioid metabolites	2000[c]	2000[c]	Codeine Morphine 6-MAM	2-3 days opiates 3-5 minutes heroin 12-24 hr 6-MAM
		Oxycodone				2-4
		Amphetamines	500	250	Amphetamine Methamphetamine MDMA MDA MDEA	1-3
		Methamphetamine	Incomplete data	500		3-4
		Benzodiazepines	300	200		3 short-acting 30 long-acting
		Barbiturates	300	200		1 short-acting 21 long-acting
		Methadone	300	200	EDDP	3-6
		Alcohol			EtG, EtS	12 hours

[a] Detection time for most drugs in urine is 1 – 3 days

[b] Long-term use of lipid-soluble drugs (THC, diazepam, ketamine) can be detected for a longer period of time

[c] Testing levels for opiates were raised from 300 ng/mL to 2000 ng/mL to reduce detection from foods containing poppy seeds

Abbreviations: 6-MAM: 6-monoacetylmorpine; EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; EtG: ethyl glucuronide; EtS: ethyl sulfate; GCMS: gas chromatography-mass spectrometry; hr: hour(s); MDA: 3,4- methylenedioxy-amphetamine; MDEA: 3,4-methylenedioxy-N-ethyl-amphetamine; MDMA: 3,4-methylenedioxy- methamphetamine; mL: milliliter(s); ng: nanogram(s); THC: tetrahydrocannabinol; THCA: delta-9- tetrahydrocannabinol-9-carboxylic acid; UTS: urine toxicology screening

Table B-3. Summary of Agents Potentially Contributing to False Positives (222-224, 226-228, 230)

Agent	Summary of Agents Potentially Contributing to False Positives	
Marijuana metabolites	• dronabinol • efavirenz • proton pump inhibitors	• NSAIDs[a] • hemp foods: tea, oil[b]
Cocaine metabolites	• coca leaf teas	• topical anesthetics containing cocaine
Opioid metabolites (229, 231-233)	• dextromethorphan • fluoroquinolones • verapamil • nalmefene • naloxone • diphenhydramine	• verapamil • papaverine • quinine • poppy seeds • poppy oil • rifampin
Amphetamines/ Methamphetamine (high rate of false positives)	• amantadine • benzphetamine • brompheniramine • bupropion • chlorpromazine • desipramine • dextroamphetamine • doxepin • ephedrine • trimipramine • diphenhydramine • papaverine • phentermine • phenylephrine • fluoxetine • verapamil	• isometheptene • isoxsuprine • labetalol • l-methamphetamine (OTC nasal inhaler) • methylphenidate • MDMA • nalmedfene • naloxone • propanolamine • promethazine • pseudoephedrine • ranitidine • selegiline • thioridazine • trazodone • trimethobenzamine
Benzodiazepines	• oxaprozin	• sertraline
Barbiturates	• ibuprofen • phenytoin	• naproxen • primidone
Methadone	• chlorpromazine • clomipramine • diphenhydramine • quetiapine	• doxylamine • ibuprofen • thioridazine • verapamil
Alcohol	• mouthwash • use of hand sanitizers • nonalcoholic beer or wine • communion wine	• food cooked with alcohol • short-chain alcohols • OTC cough products (isopropyl alcohol)
Buprenorphine/Naloxone metabolites	• naloxone-3-glucuronide • noroxymorphone	• naloxol

[a] Detection time for most drugs in urine is 1 – 3 days

[b] Long-term use of lipid-soluble drugs (THC, diazepam, ketamine) can be detected for a longer period

Abbreviations: NSAIDs: non-steroidal anti-inflammatory drugs; MDMA: 3,4-methylenedioxy-methamphetamine; OTC: over the counter; THC: tetrahydrocannabinol

Table B-4. Interpreting Urine Toxicology Screening (224, 234, 235)[a]

Drug or Class		Expected Results	Considerations
Non-opioids	Alcohol	Alcohol	• Testing for ethanol metabolites, ethyl glucuronide, or ethyl sulfate can identify alcohol up to 80 hr after consumption
	Amphetamines	**Immunoassay**–Amphetamines, methamphetamines, or MDMA **Confirmatory** – Amphetamines, methamphetamines, or MDMA	• Immunoassay tests are highly cross-reactive; therefore, confirmatory testing is required and can identify which amphetamine is present
	Benzodiazepines	**Immunoassay** – Unconjugated oxazepam or its metabolites **Confirmatory** – Alprazolam, diazepam, clonazepam, lorazepam, etc.	• Immunoassays for benzodiazepines have a 28% overall false negative rate • Confirmatory testing is needed when use is expected or suspected (alprazolam, clonazepam, and lorazepam often not detected by immunoassay)
	Barbiturates	**Immunoassay** – Barbiturates	• N/A
	Cocaine metabolites	**Immunoassay** – Cocaine or benzoylecgonine	• Cocaine's primary metabolite, benzoylecgonine, has low cross-reactivity with other substances and is highly predictive of cocaine use • A positive result should be interpreted as recent exposure to cocaine
Opioids or "Opiates" – Natural (From Opium)	Codeine (Tylenol #2,3/4)	**Opiates Immunoassay** – Positive **Confirmatory** – Codeine, possibly morphine and hydrocodone	• Immunoassays for "opiates" are responsive to morphine and codeine but do not distinguish which • Codeine is metabolized to morphine and small quantities of hydrocodone
	Morphine (Avinza, Embeda, MS Contin, Kadian)	**Opiates Immunoassay** – Positive **Confirmatory** – Morphine, possibly hydromorphone	• Immunoassays for "opiates" are responsive to morphine and codeine but do not distinguish which • Morphine (<10%) may be metabolized to hydromorphone
	Heroin	**Opiates Immunoassay** – Positive **Confirmatory** – Heroin (6-MAM), morphine, possibly codeine	• 6-MAM is pathognomonic for heroin use, detection 12 – 24 hr • Heroin is metabolized to morphine

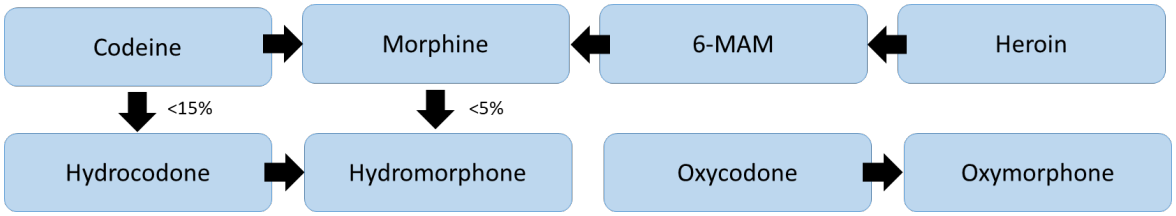
Drug or Class		Expected Results	Considerations
Opioids – Semisynthetic (Derived from Opium)	Hydrocodone (Lorcet, Lortab, Norco, Vicodin)	**Opiates Immunoassay** – Positive **Confirmatory** – Hydrocodone, possibly hydromorphone, norhydrocodone, or dihydrocodeine (236-240)	• "Opiates" immunoassay may detect semisynthetic opioids • Hydrocodone >hydromorphone >oxycodone • Negative result does not exclude use and confirmatory testing (GCMS) is required • Hydrocodone is metabolized in small amounts to hydromorphone, both may be found in urine • Oxycodone is metabolized to oxymorphone, both may be found in urine • Hydromorphone and oxymorphone use does not result in positive screens for hydrocodone and oxycodone, respectively
	Hydromorphone (Dilaudid, Exalgo)	**Opiates Immunoassay** – May be positive **Confirmatory** – Hydromorphone	
	Oxycodone (Roxicet, OxyContin)	**Opiates Immunoassay** – May be positive **Oxycodone Immunoassay** – Positive **Confirmatory** – Oxycodone possibly oxymorphone, noroxycodone (236-240)	
	Oxymorphone (Opana)	**Oxycodone Immunoassay** – Positive **Confirmatory** – Oxymorphone, noroxymorphone (236-240)	
Opioids – Synthetic (Man-made)	Buprenorphine	**Immunoassay** – Buprenorphine **LCMS, GCMS** – Buprenorphine, norbuprenorphine	• Current "opiates" immunoassays do not detect synthetic opioids • Confirmatory testing (GCMS or LCMS) is needed
	Fentanyl	**GCMS** – Fentanyl, norfentanyl, carfentanyl, sufentanyl	
	Meperidine (Demerol)	**GCMS** – Normeperidine, possibly meperidine	
	Methadone (Methadose)	**Methadone Immunoassay** – Positive **GCMS** – Methadone, EDDP	
	Tramadol	**LCMS, GCMS** – tramadol, O-desmethyl tramadol[b]	
	Novel synthetic opioids	**MT45** **U-47700**	

[a] Each facility may have its own order sets and lab policies and procedures; contact your lab for additional details

[b] For more information on tramadol, access Lexicomp Online

Abbreviations: 6-MAM: 6-monoacetylmorpine; EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; GCMS: gas chromatography-mass spectrometry; LCMS: liquid chromatography-mass spectrometry; MDMA: 3,4- methylenedioxy-methamphetamine

Figure B-1. Opioid Metabolic Pathways (223, 224, 226, 227)



Abbreviations: 6-MAM: 6-monoacetylmorpine

Appendix C: Diagnostic and Statistical Manual of Mental Disorders for Opioid Use Disorders

DSM-5 diagnostic criteria for OUD: A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the symptoms in Table C-1, occurring within a 12-month period.(241)

Table C-1: DSM-5 Diagnostic Criteria for OUD (241)

To confirm a diagnosis of OUD, at least two of the following should be observed within a 12-month period:
1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Exhibits tolerance (discussed below).
11. Exhibits withdrawal (discussed below).

A. Tolerance and Withdrawal Diagnostic Criteria (241)

The last two diagnostic criteria, related to tolerance and withdrawal, are not considered to be met for individuals taking opioids solely under appropriate medical supervision.

a. Tolerance

Tolerance is defined as either:

A. A need for markedly increased amounts of opioids to achieve intoxication or desired effect, or

B. A markedly diminished effect with continued use of the same amount of an opioid.

b. Withdrawal

You can refer specifically to DSM-5 Criteria A and B for opioid withdrawal syndrome:

A. Either of the following: 1) Cessation of (or reduction in) opioid use that has been heavy and prolonged (several weeks or longer), or 2) administration of an opioid antagonist after a period of opioid use

B. Three (or more) of the following, developing within minutes to several days after Criterion A: dysphoric mood; nausea or vomiting; muscle aches; lacrimation or rhinorrhea; pupillary dilation, piloerection, or sweating; diarrhea; yawning; fever; or insomnia

Table C-2: DSM-5 Diagnostic Criteria for Severity of OUD (242)

Severity of OUD	Number of Symptoms
Mild	Presence of 2-3 symptoms
Moderate	Presence of 4-5 symptoms
Severe	Presence of 6 or more symptoms

Appendix D: Drug Tables

A. Short-acting, Orally Administered Opioids

Table D-1: Use of Short-acting, Orally Administered Opioids in Adults (243)

Short-acting Opioids[a]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Timing	Dosing In Special Populations	Other Considerations
Codeine (alone or in combination with APAP or ASA) • Codeine available as 15, 30, and 60 mg tablets • Combination products vary in codeine content from 15 to 60 mg/dose unit • Oral solution codeine/APAP 12/120 mg per 5 ml	• 15 to 30 mg • every 4 to 6 hr • Initial dose • based upon codeine component, maximum dose based upon non-opioid component	• Maximum APAP dose: 4000 mg/d (2000 mg/d in chronic alcoholics or in hepatic impairment) • Codeine alone is a weak analgesic; more effective alternatives are available (including codeine in combination with APAP or ASA)	• **Analgesic Onset (min):** 15 to 30 • **Peak (min):** 30 to 60 • **Duration (hr):** 4 to 6 • **t½ (hr):** ~3	• *Elderly or debilitated*: Use with caution • *Hepatic dysfunction:* Conversion to active metabolite (morphine) may be reduced in patients with cirrhosis; avoid use in patients with liver disease • *Renal dysfunction:* Use lower dosage or an alternative analgesic	• Codeine may be less effective in patients with decreased CYP- 2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs[b]) because of decreased conversion to the active metabolite, morphine • CYP-2D6 ultra-rapid metabolizers[c] can have extensive conversion to morphine with increase in opioid-mediated effects
Hydrocodone (in combination with APAP, ASA, or IBU) • Hydrocodone/APAP available as oral elixir, solution, and tablets; hydrocodone/IBU available as tablets; combination products vary in hydrocodone content (2.5 to 10 mg per dosage unit)	• 5 to 10 mg • every 6 hr (hydrocodone component) • Initial dose • based upon hydrocodone component • Maximum dose based upon non-opioid component	• Maximum dose: • 60 mg/d (4000 ♦ mg/d APAP; 2000 mg/d APAP in chronic alcoholics or hepatic impairment) for hydrocodone + APAP combination OR ♦ 25 to 50 mg/d (1000 mg/d IBU) for hydrocodone + IBU combination	• **Analgesic Onset (min):** 10 to 20 • **Peak (min):** 60 to 100 • **Duration (hr):** 4 to 8 • **t½ (hr):** ~4	• *Elderly or debilitated*: Use with caution; start with reduced dose (2.5-5 mg) of hydrocodone component • *Hepatic dysfunction:* Use with caution	• Conversion to the active metabolite, hydromorphone, may be decreased in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs[b]) • CYP-2D6 ultra-rapid metabolizers[c] can have extensive conversion to hydromorphone with potential increase in opioid-mediated effects

Short-acting Opioids[a]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Timing	Dosing In Special Populations	Other Considerations
Hydromorphone • Available as oral liquid 1 mg/ml; 2, 4, and 8 mg tablets; 0.2, 1, and 2 mg/ml solution for injection; and 3 mg rectal suppository	• 2 mg every 4 to 6 hr • May give an initial dose of 4 to 8 mg for severe pain	• There is no optimal or maximum dose of hydromorphone; patients on LOT are likely to become tolerant[d] and require doses higher than the usual dosage range to maintain the desired effect	• **Analgesic Onset (min):** 15 to 30 • **Peak (min):** 30 to 60 • **Duration (hr):** 3 to 4 • **t½ (hr):** 2 to 3	• *Elderly or debilitated*: Use with caution, start at 25% to 50% of usual dose at low end of dosing range • *Hepatic / Renal dysfunction*: Reduce initial dose by 25% to 50% of usual dose depending on degree of impairment	• Women appear to have a 25% higher Cmax than men • Hepatic metabolism via glucuronidation to inactive metabolites, mainly to hydro-morphone 3-glucuronide, a potentially neuroexcitatory metabolite which can accumulate in renal impairment
Morphine • Available as oral solution (10 or 20 mg/5 ml, or 100 mg/5 ml for opioid- tolerant patients only) or as 15 or 30 mg tablets; also available as a 5, 10, 20, and 30 mg rectal suppository and as a solution for injection in various concentrations	• 10 to 30 mg every 4 hr	• There is no optimal or maximum dose of morphine; patients on LOT are likely to become tolerant[d] and require doses higher than the usual dosage range to maintain the desired effect	• **Analgesic Onset (min):** 30 • **Peak (min):** 60 • **Duration (hr):** 3 to 5 • **t½ (hr):** 2 to 4 in adults	• *Elderly or debilitated*: Give with extreme caution; use lower dose • *Hepatic dysfunction*: Use carefully in patients with cirrhosis and consider reducing dose or extending dosing interval by 1.5 to 2 times; half-life may be doubled (3 to 4 hr) and bioavailability is increased • *Renal dysfunction*: Reduce dose or, if severe renal impairment exists, avoid use (see *Other Considerations*)	• M6G, an active metabolite, may accumulate in renal impairment • M3G, a metabolite without analgesic activity, may accumulate in renal impairment; this metabolite has been implicated in morphine-induced neurotoxicity, hyperalgesia, and allodynia

Short-acting Opioids[a]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Timing	Dosing In Special Populations	Other Considerations
Oxycodone (alone or in combination with APAP or ASA) • Single-agent oxycodone available as oral solution 5 mg/5 ml, 20 mg/1 ml, and oral tablet 5, 10, 15, 20, and 30 mg • Combination products vary in oxycodone content, 2.5 to 10 mg per dose unit	• 5 to 15 mg every 4 to 6 hr • Initial dose based upon oxycodone component • Maximum dose based upon non-opioid component	• For combination products, maximum dose is limited by APAP or ASA content (4000 mg/d for both; 2000 mg/d APAP in chronic alcoholics or patients with hepatic impairment) • There is no optimal or maximum dose of oxycodone; patients on LOT are likely to become tolerant d and require doses higher than the usual dosage range to maintain the desired effect	• **Analgesic Onset (min):** 10 to 15 • **Peak (min):** 30 to 60 • **Duration (hr):** 3 to 6 • **t½ (hr):** 3.2 to ~4	• *Elderly or debilitated*: Reduce dosage • *Hepatic / Renal*: Use with caution; consider reducing dose and increasing frequency of dosing	• Conversion to the active metabolite, oxymorphone (< 15% plasma concentration), may be decreased in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs[b]) • Higher peak plasma oxycodone (50%) and noroxycodone (20%), higher AUC for oxycodone (60%), noroxycodone (50%), and oxymorphone (40%) in patients with CrCl < 60 ml/min • Higher oxycodone peak plasma concentration (50%) and AUC values (95%) in mild to moderate hepatic impairment; oxymorphone peak plasma concentration and AUC values are lower by 30% and 40%, respectively
Oxymorphone • Available as 5 or 10 mg tablets and 1mg/ml solution for injection	• 5 to 10 mg every 4 to 6 hr	• There is no optimal or maximum dose of oxymorphone; patients on LOT are likely to become tolerant and require doses higher than the usual dosage range to maintain the desired effect	• **Analgesic Onset (min):** 30 to 45 • **Peak (min):** N/A • **Duration (hr):** 4 • **t½ (hr):** 7 to 0	• *Elderly or debilitated*: Use with caution and start at low end of dosing range; levels are increased 40% in patients ≥65 years	• Food: When taken orally with a high-fat meal, food has been shown to increase peak levels of oxymorphone immediate-release are 38 to 50% greater; must be taken on an empty stomach at least 1 hr before or 2 hr after a meal

Short-acting Opioids[a]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Timing	Dosing In Special Populations	Other Considerations
Oxymorphone (cont.)				• *Hepatic dysfunction* ♦ *Mild hepatic impairment:* Use cautiously, start at low end of dosing range ♦ *Moderate and severe hepatic impairment:* Contraindicated • *Renal dysfunction*: Bioavailability is increased 57 – 65% in moderate and severe impairment; start at lower doses and adjust slowly	• Must NOT be taken concomitantly with alcohol; alcohol (240 ml of 4% to 40% ethanol) can cause highly variable effects on peak drug levels, ranging from a decrease of 50% to an increase of 270% (demonstrated with ER oxymorphone)
Tapentadol • Available as 50, 75, or 100 mg tablets	• 50 mg every 4 to 6 hr • For diabetic peripheral neuropathy (DPN): 50 mg every 12 hrs	• Subsequent dose is 50, 75, or 100 mg every 4 to 6 hr, adjusted to analgesia and tolerability • Second dose may be given 1 hr after the first dose if necessary • Max recommended dose: 700 mg on first day, 600 mg on subsequent days • Use tapentadol only under careful medical supervision at lowest effective dose • Patients on LOT are likely to become tolerant [d] and require doses higher than the usual dosage range to maintain the desired effect	• **Analgesic Onset (min):** N/A (rapid) • **Peak (min):** 60 • **Duration (hr):** 4 to 6 • **t½ (hr):** ~4	• *Elderly*: Consider starting at the lowest recommended dose • *Hepatic dysfunction:* ♦ *Mild hepatic impairment:* No dosage adjustment ♦ *Moderate hepatic impairment:* Start at 50 mg and give subsequent doses at least 8 hr apart (max. 3 doses in 24 hr) • *Severe hepatic impairment:* Use is not recommended • *Renal dysfunction:* No dosage adjustment for mild or moderate renal impairment; not recommended in severe renal impairment (CrCl < 30 ml/min)	• Must NOT be taken concomitantly with alcohol which can increase serum tapentadol concentration • Food: When administered after a high fat/calorie meal, the AUC and Cmax increased by 25% and 16% respectively; management: may administer without regards to meals • If used in combination with other CNS depressants, consider dose reduction of one or both agents • Use with or within 14 days of MAOIs is contraindicated • Monitor for signs and symptoms of serotonin syndrome when used in combination with serotonergic agents

Short-acting Opioids[a]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Timing	Dosing In Special Populations	Other Considerations
Tapentadol (cont.)		• For DPN: Titrate in increments of 50 mg no more-frequently than twice daily every 3 days to effective dose (therapeutic range: 100 to 250 mg every 12 hrs)		• *Respiratory dysfunction:* Use with caution because of respiratory depressant effects; consider non–mu opioid agonist analgesics	
Tramadol (alone or in combination with APAP) • Tramadol available as 50 mg and 100 mg tablets, a 5 mg/ml oral solution, and as a tablet in combination with APAP (325 mg APAP, 37.5 mg tramadol)	• 25 mg every morning	• May increase by 25 mg per day every 3 days to 100 mg tramadol/d (25 mg every 6 hr) • Subsequent increments of 50 mg/d may then be made every 3 days to 200 mg/d (50 mg every 6 hr) • After titration, may give 50 to 100 mg every 4 to 6 hr • Maximum daily dose of tramadol: 400 mg/d • Combination product: maximum 4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics or in hepatic impairment	• **Analgesic Onset (min):** <60 • **Peak (min):** ~120 to 180 • **Duration (hr):** 6 • **t½ (hr):** 6.3 ± 1.4	• *Elderly or debilitated:* In elderly patients >75 years: give <300 mg/d in divided dose; use with caution in debilitated patients • *Hepatic dysfunction:* Decrease dosage to 50 mg once every 12 hr in patients with cirrhosis • *Renal dysfunction*: ♦ *CrCl >30 ml/min:* No *change in dose or frequency required* ♦ *CrCl <30 ml/min: Increase* dosing interval to 12 hr and decrease maximum daily dose to 200 mg • *Dialysis patients*: Can receive their regular dose on the day of dialysis (<7% of a dose is removed by hemodialysis)	• Slower initiation and titration improves tolerability • Inhibits reuptake of serotonin and norepinephrine; concomitant use with MAOIs or SSRIs may increase risk of seizures, serotonin syndrome • Dose carefully or use another agent in patients on serotonergic agents • Seizures reported within the recommended dosage range; increased risk above recommended dosage range and in patient with seizure disorder, history of seizures, in conditions with increased risk of seizures, or with other drugs that increase seizure risk; observe maximum dose limits

Short-acting Opioids[a]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Timing	Dosing In Special Populations	Other Considerations
Tramadol (alone or in combination with APAP) (cont.)					• Serious anaphylactoid reactions reported, often following first dose; patients with a history of anaphylactoid reaction to codeine and other opioids may be at increased risk

[a] Check local formulary for available formulations

[b] CYP-2D6 Inhibiting Drugs: Antiarrhythmics (amiodarone, propafenone, quinidine [strong inhibitor]); analgesics (methadone [weak inhibitor], propoxyphene); antihistamines (diphenhydramine, chlorpheniramine [in vitro], brompheniramine [in vitro], triprolidine [in vitro]); histamine2 receptor antagonists (cimetidine); neuroleptics (chlorpromazine, haloperidol, methotrimeprazine, perphenazine, thioridazine); protease inhibitors (ritonavir), quinine compounds (hydroxychloroquine, quinacrine, quinine); selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine, sertraline), miscellaneous compounds (clomipramine, ketoconazole, ticlopidine)

[c] CYP-2D6 ultra-rapid metabolizers include 1% of Asian and Hispanic, 1-10% of Caucasians, 3% of African-Americans, and 16-28% of N. African and Arabic populations

[d] Opioid tolerance is assumed in patients already taking fentanyl 25 mcg/hr OR daily doses of the following oral agents for ≥ 1 week: ≥ 60 mg oral morphine, 30 mg oxycodone, 8 mg hydromorphone, 25 mg of oxymorphone, or an equianalgesic dose of another opioid

Abbreviations: APAP: acetaminophen; ASA: acetylsalicylic acid; CNS: central nervous system; CrCl: creatinine clearance; d: day(s); ER: extended-release; hr: hour(s); IBU: ibuprofen; LOT: long-term opioid therapy; M3G: morphine-3-glucuronide; M6G: morphine-6-glucuronide; MAOIs: monoamine oxidase inhibitors; mg: milligram(s); min: minute(s); mL: milliliter(s); SSRIs: selective serotonin reuptake inhibitors

B. Long-acting/Extended-release Opioids

Table D-2. Use of Long-acting/Extended-release Opioids in Adults (243)

- Long-acting/ER opioids expose patients and other users to the risks of opioid misuse and OUD, which can lead to overdose and death, even when used at recommended dosages. Long-acting/ER opioids should be reserved for patients for whom alternative analgesic treatment options (e.g., non-opioid analgesics or immediate-release opioid analgesics) are ineffective, not tolerated, or provide inadequate control of pain. Assess each patient's risk prior to prescribing long-acting/ER opioids and institute risk mitigation strategies.
- The FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) program (see http://www.er-la-opioidrems.com/IwgUI/rems/home.action) is necessary for all opioid analgesics intended for outpatient use to manage known or potential serious risks associated with their use.(244)
- Most abuse deterrent technologies have been designed to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding. Despite these efforts, no opioid formulation prevents consumption of a large number of intact capsules or tablets, which continues to be the most common method of abuse.

- Long-acting/ER opioids should not be used for management of acute pain (with exception of oxycodone/acetaminophen ER tablets), as an as-needed medication, or on initiation of long-term opioids (see Recommendation 11)

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Buprenorphine buccal film • Available in strengths of 75, 150, 300, 450, 600, 750 and 900 mcg/film for twice daily administration	• 75 mcg once or twice daily for at least 4 days, then increase dose to 150 mcg every 12 hr • There is potential for buprenorphine buccal film to precipitate withdrawal in patients already on opioids; to reduce risk, the dose of other opioids should be tapered to ≤30 mg MEDD before initiating buprenorphine buccal film • See Section E. Additional Buprenorphine Guidance for alternate dosing instructions	• After initial dosing, dosing changes as necessary can proceed in increments of 150 mcg every 12 hr, no more frequently than every 4 days • Patients on prior dose of opioid 30 to 89 mg MEDD may initiate buprenorphine film at 150 mcg every 12 hr, 90 to 160 mg MEDD may initiate at 300 mcg every 12 hr; if prior opioid is >160 mg MEDD – consider an alternative analgesic • Time to steady state ~3 days with every 12 hr dosing	• *Elderly:* Initiation at the low end of the dosing range is recommended • *Renal dysfunction:* No dose adjustment recommended • *Hepatic dysfunction:* Patients with severe hepatic impairment should have starting and titration doses reduced by half that of patients with normal liver function	• QTc prolongation reported with recommended doses of buprenorphine; maximum dose of 900 mcg every 12 hr established due to the potential for this adverse effect; avoid in patients with long QT syndrome, family history of long QT syndrome, or those taking Class IA or Class III antiarrhythmic drugs • Buprenorphine buccal film is a potential treatment option for patients with significant renal impairment and those with gastrointestinal structural or functional abnormality that interferes with swallowing or absorption of orally administered medications
Buprenorphine TDS • Available in every 7 day patch formulation that delivers transdermal buprenorphine at the following rates: 5 mcg/hr, 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, and 20 mcg/hr	• In opioid-naïve or in patients on <30 mg MEDD of alternate agent: Initiate treatment with 5 mcg/hr patch • There is potential for buprenorphine to precipitate withdrawal in patients already on opioids; to reduce risk, the dose of other opioid should be tapered to ≤30 mg MEDD before initiating buprenorphine; the 10 mcg/hr patch may then be initiated at the next dosing interval	• Initial buprenorphine TDS dose based on previous oral morphine equivalent: 5mcg/hr for <30mg MEDD, 10 mcg/hr for 30-80mg MEDD • The maximum dose of buprenorphine TDS 20 mcg/hr may not provide adequate analgesia for patients requiring greater than 80 mg MEDD; an alternate analgesic should be considered	• Dosage does not need to be adjusted in patients with mild or moderate hepatic impairment, renal impairment, or in the elderly	• Dose of one 20 mcg/hr patch per week should not be exceeded due to risk of QTc prolongation • Avoid use in patients with long QT syndrome, family history of long QT syndrome, or those taking Class IA or Class III antiarrhythmic medications • Advise patients that application of external heat (e.g., hot baths, sunbathing, saunas, heating pads) increases maximum plasma concentration of buprenorphine and risk of fatal overdose

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Buprenorphine TDS (cont.)		• Because steady-state plasma concentrations are achieved within 72 hours, buprenorphine TDS dosage may be adjusted every 3 days		• Potential treatment option for patients with significant renal impairment or those with gastrointestinal structural or functional abnormality that interferes with swallowing or absorption of oral medications
Buprenorphine and Buprenorphine/ Naloxone • Buprenorphine is available in 2 mg and 8 mg SL tabs • Buprenorphine/ naloxone is available in 2-0.5 and 8-2 mg/ SL tablets and 2-0.5, 4-1, 8-2, and 12-3 mg film	• **Used off-label for pain management:** FDA approved for the treatment of opioid dependence or OUD • 2 to 4 mg of buprenorphine or 2**/**0.5 mg to 4/1 mg of buprenorphine/ naloxone in divided doses should be adequate for most patients	• For patients who are on buprenorphine or buprenorphine naloxone for OUD, the current 24-hour dose could be split and divided for BID or TID dosing for pain management • To avoid precipitating withdrawal in patients that are being converted from other opioids, initiation with buprenorphine/naloxone SL tablet should be undertaken when objective and clear signs of mild withdrawal are evident; 2 to 4 mg of buprenorphine or 2**/**0.5 mg to 4/1 mg of buprenorphine/ naloxone in divided doses should be adequate for most patients	• *Elderly:* Use cautiously and monitor closely • Dosage does not need to be adjusted in patients with mild or moderate hepatic impairment or renal impairment; avoid in patients with severe hepatic impairment	• BUP sublingual tablet contains no naloxone and may be preferred during pregnancy • Buprenorphine/naloxone may be the preferred opioid in patients with comorbid pain and OUD

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Buprenorphine and Buprenorphine/ Naloxone (cont.)		• A buprenorphine dosing strategy designed to avoid precipitated withdrawal during the conversion is the low dose buprenorphine initiation (LDBI) strategy. This method introduces small incremental doses of buprenorphine while: simultaneously slowly reducing the dose of the full opioid agonist over time; or maintaining the current full agonist opioid dose and subsequently, stopping the full agonist once buprenorphine dose is sufficient to mitigate withdrawal symptoms. • Given that currently there is no consensus regarding a particular LDI approach or clinical trials comparing the proposed LDBI schedules or comparing traditional vs LDBI protocols, we cannot recommend and specific LDPI protocol at this time. • May titrate dose to 16 to 24 mg/day in divided doses if needed		

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Fentanyl TDS • Available in every 3 day patch formulation that delivers transdermal fentanyl at the following rates: 12 mcg/hr, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr	• The initial dose of fentanyl TDS in opioid- tolerant patients[2] is 25 mcg/hr, applied every 72 hr; the 12 mcg/hr dose has not been evaluated as an initial dose • Fentanyl TDS is contraindicated in non-opioid-tolerant patients • Fentanyl TDS is contraindicated in the management of mild or post-operative pain, and as an "as-needed" analgesic	• Fentanyl TDS must be used only on intact skin • Dose change increments should be based on supplemental opioid doses, using a ratio of fentanyl TDS 12 mcg/hr for every 45 mg/ 24 hr of supplemental oral MEDD • Dosing changes, as necessary, should occur at least 3 days after the initial dose; thereafter, not more often than every 6 days	• *Elderly:* Twice as sensitive to fentanyl as younger patients; avoid initiation at doses >25 mcg/hr unless patient is already taking >135 mg oral morphine or equivalent • *Hepatic impairment:* Reduce dose by 50% in mild- moderate impairment and avoid use if impairment is severe • *Renal Impairment:* ♦ CrCl >50 ml/minute: no dosage adjustment necessary ♦ CrCl 10 to 50 ml/ minute: 75% of normal dose ♦ CrCl < 10 ml/minute: 50% of normal dose	• Consider fentanyl TDS in patients with persistent, moderate-to- severe pain who cannot take oral ER morphine or oral ER oxycodone • Avoid application of external heat sources (e.g., heating pads, electric blankets, heat lamps, saunas, hot tubs, hot baths, sunbathing, heated water beds) to the application site while the patch is worn as heat may increase release and speed absorption of fentanyl • *Patients with fever*: Increased body temperature may increase release of fentanyl from the TDS; monitor patients for opioid adverse effects and modify dosage as necessary • Using damaged or cut fentanyl TDS patches can lead to rapid release of the contents of the patch and fatal overdose • Use of fentanyl TDS with CYP3A4 inhibitors[3] can result in increased fentanyl plasma concentrations, increased or prolonged opioid effects, including fatal respiratory depression; use extreme caution and frequent monitoring in patients receiving these combinations • CYP 3A4 inducers may increase fentanyl clearance

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Hydrocodone ER • **ER tablets** contain 20, 30, 40, 60, 80, 100 or 120 mg hydrocodone for once daily administration • **ER capsules** contain 10, 15, 20, 30, 40 or 50 mg hydrocodone for every 12 hr administration	• *Opioid-naïve patients:* 20 mg ER tablet once daily • *Opioid-naïve patients:* 10 mg ER capsule every 12 hr • *Opioid tolerant[b] patients:* Convert current opioid to equianalgesic daily dose of hydromorphone ER; reduce the calculated amount by 33-50% for initial start dose (see Table D-3)	• *For opioid-experienced, both ER tablets and capsules:* Convert current opioid to equianalgesic hydrocodone dose then reduce that dose by 33-50%; initiate at nearest whole-tablet or capsule strength, rounding down as necessary • *For both tablets and capsules:* Dose change increments of 20 mg per day may be made every 3 to 5 days • Steady state achieved in ~3 days of dosing	• *Elderly:* No significant pharmacokinetic differences • *Patients with renal impairment:* Hydrocodone plasma concentrations are increased in moderate or severe impairment; use low initial dose and monitor closely for AEs such as excessive sedation and respiratory depression • *Patients with hepatic impairment:* No dosage adjustment is required in mild or moderate hepatic impairment; start with the lowest dose, 10 mg, in patients with severe hepatic impairment, and monitor closely	• CYP3A4 inhibitors[c] may decrease clearance of hydrocodone, increase plasma concentrations, and increase risk of overdose; CYP3A4 inducers[d] may increase clearance and reduce opioid effect • Both ER tablets and ER capsules are formulated with polyethylene oxide which imparts ER properties • Hydrocodone ER tablets or capsules must be swallowed intact and should not be cut, broken, chewed, crushed or dissolved due to risk of fatal overdose • ER tablet has abuse deterrent labeling related to resistance to crushing and high viscosity when dissolved in aqueous solution • ER capsule has abuse deterrent properties but is not FDA-labeled as an abuse deterrent formulation

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Hydromorphone ER Tablets • Available as 8, 12, 16, and 32 mg tablets for once daily administration	• Not indicated in opioid – naïve patients due to the risk of respiratory depression • *Opioid tolerant[b] patients:* Convert current MEDD to equianalgesic daily dose of hydromorphone ER; reduce the calculated amount by 33-50% for initial start dose (see Table D-3)	• Dosage adjustments may be made in increments of 4 to 8 mg every 3 to 4 days as needed to achieve adequate analgesia • Steady state reached after 3 to 4 days of once-daily dosing	• *Elderly:* Initiate at low dose and titrate slowly; monitor closely • *Patients with renal impairment:* Start patients with moderate impairment at 50% of usual dose, and patients with severe impairment at 25% of usual dose • *Patients with hepatic impairment:* Start patients with moderate impairment at 25% of usual dose in non-impaired patients	• Hydromorphone ER tablets must be swallowed intact and should not be cut, broken, chewed, crushed or dissolved due to risk of fatal overdose • Hydromorphone ER contains sulfites • Hydromorphone ER has abuse deterrent properties but is not FDA-labeled as an abuse deterrent formulation
Methadone • Available as 5 and 10 mg tablets and oral solution, 5 or 10 mg/ 5 ml, for every 8 to 12 hr administration	• Start low and go slow • Should not be used for as-needed supplemental OT • *Initial dose:* 2.5 to 5 mg orally every 8 to 12 hr; more frequent administration (every 6 hr) may be necessary during initiation to maintain analgesia • See Section D. Methadone Dosing Guidance for detailed dosing information including dosing recommendations in patients previously exposed to opioids • Monitor patients carefully during initiation, conversions to and from other opioids, and dose titration	Dose change increments of 2.5 mg every 8 hr may be made every 5 to 7 days • Delayed analgesia or toxicity may occur because of drug accumulation after repeated doses, e.g., on days 2 to 5; if patient has excessive sedation during this timeframe, consider temporarily holding dose(s), lowering the dose, and/or slowing the titration rate • Once a stable analgesic dose is reached, the dosing interval may be extended to every 8 to 12 hr or longer	• *Elderly or debilitated*: Consider reduced dosing in elderly or debilitated patients who may be more sensitive to opioid adverse effects • *Hepatic dysfunction*: No dosage adjustments required in patients with stable chronic liver disease or mild-to-moderate hepatic dysfunction; avoid in severe liver disease • *Renal dysfunction*: Methadone and its metabolites do not accumulate in patients with renal failure; however, dosage reduction by up to 50- 75% is recommended in patients with CrCl <10 mL/ min	• Prescribers of methadone should be thoroughly familiar with its complex pharmacokinetic and pharmacodynamic properties or consult a clinician with experience in dosing methadone • Plasma half-life (22 to 128 hr short- term; 24 to 48 hr at steady-state) may be longer than the analgesic duration • Methadone has little cross-tolerance with other opioids; therefore, even patients with a high degree of opioid tolerance may be at risk for overdose when switched to methadone • Methadone is the only long-acting opioid available as an oral solution

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Methadone (cont.)				• Methadone may be subject to drug interactions with agents that can influence CYP2B6 (e.g., ticlopidine) • May prolong QTc intervals on ECG; risk of torsade de pointes; see Appendix D for detailed QTc monitoring information
Morphine CR or SR • Available in 15, 30, 60, 100, and 200 mg strengths for every 8 to 12 hr administration • Morphine ER capsules available in 10, 20, 30, 40, 50, 60, 75, 80, 90, 100, 120, and 200 mg capsule strengths for once daily administration **Morphine and Naltrexone ER Capsule** • Available as 20/0.8, 30/1.2, 50/2, 60/2.4, 80/3.2, and 100/4 capsule strengths (mg morphine/mg naltrexone) for once or twice-daily administration	• *Opioid-naïve patients:* Morphine CR or SR 15 mg every 8 to 12 hr • Total daily increments of <30 to 40 mg/d may be made every 2 days • *Opioid-naïve patients:* Morphine ER capsules are not indicated in opioid-naïve patients • *Patients who are not opioid tolerant:* Start morphine ER at 30 mg daily, may adjust every 1 to 2 days • *Opioid-naïve patients:* Initiate at the lowest dose, 20 mg/ 0.8 mg once daily • *Opioid tolerant[b] patients:* Convert current opioid to equianalgesic daily dose of morphine; reduce the calculated amount by 33-50% for initial start dose (see Table D-3) • Dose may be up titrated no more frequent than every 1 to 2 days	• Morphine CR or SR tablets should be swallowed whole, not broken, chewed, or crushed • For patients who have difficulty swallowing, SR and ER capsules may be opened and the pellets may be sprinkled onto a small amount of soft food (for administration without chewing) or administered via 16F gastrostomy tube • Steady state achieved with morphine ER within 24 to 36 hr • Morphine/naltrexone must be swallowed whole or the contents of the capsules sprinkled on apple sauce; crushing, dissolving, or chewing pellets may cause a fatal overdose (particularly in the opioid-naïve patient) and the absorption of naltrexone could increase the risk of precipitating withdrawal in opioid tolerant patients	*Information applies to all formulations of morphine listed* • *Elderly:* Use with caution and at lower dose • *Patients with renal dysfunction:* Bioavailability is increased and clearance is decreased; metabolites M3G and M6G accumulate significantly • Reduce dose for CrCl of 30 to ≤ 60 ml/min by 50 to 75%, For CrCl of 15% to 30% reduce dose by 25% to 50% or avoid use. *Patients with hepatic dysfunction:* Clearance decreases and half-life increases; M3G and M6G to morphine ratios are reduced; use carefully in patients with cirrhosis and consider reducing dose or extending dosing interval by 1.5 to 2 times	• Morphine SR is preferred first-line long-acting agent because of similar efficacy to other long-acting opioids, comparable safety profile, provider familiarity with use, and lower cost • M6G, an active metabolite, may accumulate in renal impairment and contribute to excessive opioid effects • M3G, a metabolite without analgesic activity, may accumulate in renal impairment; this metabolite has been implicated in morphine-induced neurotoxicity, hyperalgesia, and allodynia • Morphine/naltrexone ER capsule has abuse deterrent labeling related to potential to precipitate withdrawal if drug is taken by other than oral route

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Morphine CR or SR and Morphine and Naltrexone ER Capsule (cont.)		• Morphine/naltrexone: If once daily administration results in inadequate analgesia, may switch to twice daily dosing		
Oxycodone ER • **Tablets** available in 10, 15, 20, 30, 40, 60, and 80 mg strengths for every 12 hr administration • **Capsules** available in 9, 13.5, 18, 27 and 36 mg strengths for every 12 hr administration	• *Opioid-naïve patients:* 10 mg (tablets) or 9 mg (capsules) orally every 12 hr • *Opioid tolerant*[b] *patients:* Convert current opioid to equianalgesic daily dose of oxycodone ER; reduce the calculated amount by 33-50% for initial start dose (see Table D-3)	• *Dose change increments:* May increase to 20 mg (tablets) or 18 mg (capsules) every 12 hr after 1 or 2 days; thereafter, the total daily dose may be increased by 25-50% of the current dose every 1 or 2 days • ER tablets are not bioequivalent to ER capsules; 10 mg oxycodone HCl (ER tablet) = 9 mg oxycodone base (ER capsule) • Steady state achieved with tablets or capsules in 24 to 36 hr with repeat dosing	• *Elderly*: Plasma concentrations of oxycodone are increased ~15% in the elderly; however, usual dosing and dosing intervals may be appropriate • *Patients with renal dysfunction*: Plasma concentrations of oxycodone are increased ~50% in patients with CrCl <60 ml/min; dose conservatively and adjust according to clinical situation • *Patients with hepatic dysfunction*: Reduce initial dose to 1/3 to 1/2 of the usual dose and monitor closely	• Recommended for patients who experience intolerable, unmanageable adverse effects to long- acting morphine • Both ER tablets and ER capsules have abuse deterrent labeling related to resistance to abuse by intranasal and intravenous means • ER tablets should be swallowed whole, not broken, chewed, or crushed • ER capsules may be opened and sprinkled on soft food or administered via feeding tube

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Oxycodone/APAP ER • Available as tablets containing oxycodone 7.5 mg and APAP 325 mg for every 12 hr administration	• *Opioid-naïve patients:* May initiate therapy with the standard dose of 2 tablets every 12 hr • A standard, single dose consists of 2 tablets totaling 15 mg oxycodone/650 mg APAP • This is the only long-acting/ER opioid to have an acute pain indication	• The polyethylene oxide content causes the tablet to swell and become sticky when wet. This has the potential to cause obstruction of the airway or GI obstruction • Steady state concentration of both components are reached within 24 hr of product initiation	• *Elderly:* Take precautions when determining the dosing amount and frequency in geriatric patients since a greater sensitivity to oxycodone may be observed in this patient population when compared to younger patients • *Patients with renal or hepatic dysfunction:* Patients with renal dysfunction (CrCl <60 ml/min) or hepatic dysfunction should initiate therapy with 1 tablet every 12 hr and adjust as needed	• This long-acting/ER opioid is an exception to the REMS requirements due to the relatively low amount of oxycodone contained in each tablet • Oxycodone/APAP ER tablets are formulated with PEO which is responsible for its ER in addition to labeled abuse deterrent properties • Patients should be instructed not to pre-soak, lick, or otherwise wet tablets prior to swallowing and to take one tablet at a time with adequate water to insure complete and immediate swallowing • Breaking, chewing, crushing, cutting, dissolving, or splitting the tablets will result in uncontrolled release of oxycodone and can lead to overdose or death
Oxymorphone ER Tablets • Available as 5, 7.5, 10, 15, 20, 30 and 40 mg tablets for every 12 hr administration	• *Opioid-naïve patients:* Initiate at 5 mg every 12 hr • *Opioid tolerant[b] patients:* Convert current opioid to equianalgesic daily dose of oxycodone; reduce the calculated amount by 33-50% for initial daily start dose (see Table D-3)	• *Dose change increments:* May increase by 5 to 10 mg every 12 hr every 3 to 7 days • Oxymorphone ER tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth • Steady-state plasma levels are achieved after 3 days of multiple dose administration	• *Elderly:* Plasma drug levels are about 40% higher in elderly versus younger subjects; use caution, starting at the low end of dosing range and titrating slowly	• Must be taken on an empty stomach at least 1 hr before or 2 hr after a meal; food has been shown to increase peak levels of oxymorphone ER by 50% • Must NOT be taken concomitantly with alcohol, which can cause highly variable effects on peak drug levels, ranging from a decrease of 50% to an increase of 270%

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Oxymorphone ER Tablets (cont.)			• *Patients with renal dysfunction:* Bioavailability is increased by 57% in moderate impairment and by 65% in severe impairment; in patients with CrCl <50 mL/min, oxymorphone should be started with the lowest dose and titrated slowly • *Patients with hepatic dysfunction:* Use with caution in patients with mild hepatic impairment, starting with lowest dose and titrating slowly • Contraindicated in patients with moderate or severe hepatic impairment	
Tapentadol ER • Available as tablets containing 50, 100, 150, 200, or 250 mg tapentadol fortwice daily dosing	• *In opioid-naïve and non-tolerant patients:* Initiate therapy with 50 mg twice daily; use of higher starting doses in patients who • are not opioid tolerant may cause fatal respiratory depression • There are no established conversion ratios for conversion from other opioid to tapentadol ER; convert current opioid to an estimated equianalgesic daily dose of tapentadol; reduce the calculated amount by 33-50% for initial daily start dose (see Table D-3)	• *Dose change increments:* May increase dose by no more than 50 mg twice daily every 3 days • *Maximum daily dose*: 500 mg daily • Tapentadol ER tablets must be taken whole; crushing, chewing, or dissolving tablets will result in uncontrolled delivery of tapentadol and can lead to overdose or death • Steady state is attained after the third dose (24 hr after the first twice daily multiple dose administration)	• *Elderly:* No dosing adjustment needed, consider starting at lowest recommended dosage • *Patients with renal dysfunction:* No dosage adjustment for mild or moderate renal impairment; not recommended in severe renal impairment • *Patients with hepatic dysfunction:* Use not recommended in severe hepatic impairment	• Must NOT be taken concomitantly with alcohol which can increase serum tapentadol concentration and cause fatal overdose • Use with or within 14 days of MAOIs is contraindicated

Long-Acting/ER Opioids[a]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Tramadol ER • Available as 100, 200 and 300 mg tablets and capsules for once daily administration	• Patients not currently on tramadol: 100 mg once daily • Converting from tramadol IR: Start at 24 hr dosage equivalent rounded down to closest 100 mg increment	• Dose change increments: May increase by 100 mg every 5 days based on analgesia and tolerability • Maximum dose: 300 mg/day	• Elderly: Start at low end of dosing range; use particular caution, especially in patients >75 years • Renal dysfunction: Avoid use if CrCl <30 ml/min • Hepatic dysfunction: Avoid use in severe hepatic impairment (Child-Pugh Class C)	• Must be swallowed whole and must not be chewed, crushed, or split • See warnings and precautions under Other Considerations for tramadol IR (Table D-1)

[a] Check local formulary for available formulations

[b] Opioid tolerance is assumed in patients already taking fentanyl 25 mcg/hr OR daily doses of the following oral agents for ≥ 1 week: ≥ 60 mg oral morphine, 30 mg oxycodone, 8 mg hydromorphone, 25 mg of oxymorphone or equianalgesic dose of another opioid

[c] CYP3A4 inhibiting agents include: ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil

[d] CYP3A4 inducing agents include: carbamazepine, phenobarbital, phenytoin, primidone, rifampin

Abbreviations: APAP: acetaminophen; CR: morphine controlled; CrCl: creatinine clearance; CYP2B6: cytochrome P450 2B6; CYP3A4: cytochrome P450 3A4; ECG: electrocardiogram; ER: extended-release; GI: gastrointestinal; HCl: hydrochloride; hr: hour(s); IR: immediate release; M3G: morphine-3-glucuronide; M6G: morphine-6-glucuronide; MAOIs: monoamine oxidase inhibitors; mcg: microgram(s); MEDD: morphine equivalent daily dose; mg: milligram(s); min: minute(s); mL: milliliter(s); OT: opioid therapy; PEO: polyethylene oxide; TDS: transdermal system; QTc: the heart rate's corrected time interval from the start of the Q wave to the end of the T wave; REMS: Risk Evaluation and Mitigation Strategy; SR: sustained release

C. Morphine Milligram Equivalent Doses

Table D-3: Morphine Milligram Equivalent Doses for Commonly Prescribed Full Opioid Receptor Agonist (17)

- All doses in mg/d except for fentanyl.
- Multiply the daily dosage for each opioid by the conversion factor to determine the equianalgesic dose in MME. Equianalgesic dose conversions are only estimates and cannot account for individual variability in genetics and pharmacokinetics.
- Do not use the calculated dose in MME to determine the doses to use when converting one opioid to another. When converting opioids, the new opioid is typically dosed at substantially lower than the calculated MME dose (33-50% less) to avoid accidental overdose due to incomplete cross-tolerance and individual variability in opioid pharmacokinetics.
- Use particular caution with fentanyl because it is dosed in mcg/hr instead of mg/d, and absorption is affected by heat and other factors.
- See Table D-2 for conversion guidance for buprenorphine-containing agents.

Morphine Milligrams Equivalent Doses (MME)[a]	
Opioid Agent	**Conversion Factor**
Codeine[b]	0.15
Tapentadol[c]	0.4
Morphine	1
Hydrocodone	1
Oxycodone	1.5
Oxymorphone	3
Hydromorphone	4

[a] The U.S. Department of Health and Human Services (HHS) *Opioid Oral Morphine Equivalent (MME) Conversion Factors Table for Prescription Drug Coverage* does not have an associated MME conversion factor for buprenorphine products. As a partial opioid agonist, buprenorphine is not expected to be associated with overdose risk in the same dose-dependent manner as doses for full agonist opioids. Given the wide variability in the recommended dose equivalencies between buprenorphine and morphine, the Work Group is unable to make any recommendations for equianalgesic dosing.

[b] When converting from weak opioid analgesics to more potent opioids, use the recommended initial doses of the new opioid for opioid-naïve patients

[c] The conversion factor estimate for tapentadol is based upon μ-receptor agonist activity in animal models where tapentadol has been shown to be 2-3 times less potent than morphine

Abbreviations: d: day(s); hr: hour(s); mcg: microgram(s); mg: milligrams; MME: morphine milligram equivalent dose

D. Methadone Dosing Guidance

a. Summary

- Methadone is not a first-line agent for the treatment of chronic pain.(17) It is an alternative long-acting opioid analgesic that may be useful in managing pain severe enough to require continuous daily treatment for which alternative treatment options are inadequate.
- In general, as with other opioids, methadone should be used as one aspect of a comprehensive pain management plan, as agreed upon by the practitioner and the patient.

- Methadone should be initiated and adjusted by, or in consultation with, a practitioner who has the relevant knowledge and expertise;(17) if a provider with clinical experience is not available, then another long-acting opioid may be used until such consultation is obtained.
- The general principles utilized in the dosing of methadone are different than those of other opioids; these differences are due to methadone's unique pharmacokinetic and pharmacodynamic properties and include, but are not limited to:
    - Dose titration should occur after at least 5-7 days on a designated dose (in the large majority of cases)
    - Careful consideration must be given to potential drug interactions and to the potential for QT prolongation
- Methadone is considered to be safe in patients with renal and/or hepatic impairment but should be used with caution in end-stage disease cases of these conditions.
- There are a number of methods available that use conversion ratios to initiate or titrate methadone; no single method is considered superior to others. Titration should be based on patient response and not solely based on equianalgesic dosing tables.
- Monitoring ECG for QTc interval prolongation is recommended based upon certain clinical scenarios.

b. Overview

Methadone is indicated for persistent, moderate-to-severe chronic pain in patients requiring continuous, around-the-clock opioid administration over an extended time. Methadone's pharmacokinetic properties are complex and incompletely documented.(245, 246) It has a long elimination half-life that has wide inter-patient variability (mean or median half-life, depending on subject type, ranges from 3-128 hr) (247-259) and does not reflect duration of analgesia.(256, 260) Initially, methadone duration of analgesia ranges from 4-6 hr; however, with repeated dosing, duration of analgesia can extend to 8-12 hr. Accordingly, while initial dosing may require more frequent administration (three times per day [TID]) to achieve adequate analgesia,(261, 262) once steady-state levels are established, reducing dosing frequency to two times per day (BID) can be considered. In elderly and frail patients, consideration may be given to starting with BID dosing. Also, as a result of the dissociation between half-life and analgesic duration, tissue accumulation of methadone can occur. It may take ten days for plasma levels to stabilize; thus, as a general rule, dose titration should not be more frequent than every 5-7 days.(263) Patients should be reassessed more frequently (e.g., every few days) when methadone is initiated and when the dose is increased.(17) Once stable dosing is established, follow-up can be as clinically warranted.

While methadone is an alternative to ER morphine or oxycodone for treatment of moderate-to-severe pain, a number of authors have cautioned about the complexities of dosing and suggested the drug be prescribed by practitioners with relevant experience, in an adequately monitored setting.(17, 245, 261, 262, 264-269) Significant toxicity has occurred particularly when doses were increased too frequently, conversion doses were too high, or dosing intervals too close.(266, 270-272)

In 2014, a methadone safety guideline was developed by the American Pain Society and College of Problems of Drug Dependence, in collaboration with the Heart Rhythm Society, which made

recommendations for safer prescribing of methadone.(273) Table D-4 outlines baseline and monitoring recommendations based on categorization of patients for risk of QTc prolongation. Palliative care patients with the goal of comfort care may require less vigilance with ECG monitoring.

Table D-4: Baseline and Monitoring Recommendations Based on Categorization of Patients for Risk of QTc Prolongation (273)

Category	Baseline ECG	Follow Up ECGs[a]	Action
Patients with risk factors for QTc prolongation, any prior QTc >450, or history of syncope	Obtain baseline • ECG within last 3 months is sufficient • Strong recommendation • Low quality • evidence	• 2-4 weeks after initiation • With significant dose increases • When methadone dose reaches 30-40[b] mg/d • When methadone dose reaches 100 mg/d[b] • When new risk factors arise or signs or symptoms of suggestive arrhythmia	• Avoid use if QTc >500 ms[c] • Consider alternative to methadone for QTc 450-500[3] • Evaluate and correct reversible causes of QTc prolongation
Patients not known to be at higher risk of QTc prolongation	Consider baseline • ECG within the last 12 months is sufficient • Weak recommendation • Low quality • evidence	• When methadone dose reaches 30-40[b] mg/d • When dose reaches 100 mg/d[b] • When new risk factors arise or signs or symptoms of suggestive arrhythmia	• Avoid use if QTc >500 ms[c] • Consider alternative to methadone for QTc 450-500[3] • Evaluate and correct reversible causes of QTc prolongation

[a] Consider obtaining yearly ECGs once a stable dose is reached

[b] Doses this high are not recommended for chronic pain and are typically observed only for patients receiving methadone as MOUD

[c] For patients on stable doses of methadone in whom a prolonged QTc has been noted (QTc >450 ms), consider tapering the dose of methadone and repeating the ECG. Other QT prolonging medications should be evaluated, and cardiology specialty care should be consulted for expert opinion.

Abbreviations: d: day(s); ECG: electrocardiogram; MAT: medication assisted treatment; ms: millisecond(s); mg: milligram(s); OUD: opioid use disorder; QTc: QTc interval (the heart rate's corrected time interval from the start of the Q wave to the end of the T wave)

Special caution is recommended with concurrent benzodiazepines and drugs that prolong the QT interval. (274)

Methadone is primarily metabolized by CYP450 2B6to inactive/nontoxic metabolites.(275-280) CYP2B6 is a highly polymorphic gene (281) and may help to explain why the pharmacokinetics of methadone can be extremely variable from individual to individual. Currently, it is unclear whether cytochrome P450 3A has any influence on methadone metabolism and caution is encouraged when using drugs that interact with both enzymes.

c. Dosing Strategies

The dosing recommendations listed below (in Table D-5) are provided to offer guidance on using methadone in the treatment of patients with chronic pain, particularly when converting from another opioid to methadone. The use of methadone for pain should be done in the context of a pain clinic or with assistance of local pain management experts, including healthcare providers or pharmacists, who have

experience with methadone's use. If such resources are not readily available, other long-acting opioids should be considered (e.g., morphine sustained action [SA], or oxycodone SA).

Various methadone dosing strategies have been employed (268, 282, 283) and methods are still evolving. Older, prospective studies found no evidence to support the superiority of one dosing strategy over another.(284-286) The lack of prospective and comparative studies concerning methadone dosing strategies highlights the need to carefully individualize the dosing regimen of methadone.

For opioid tolerant patients, a number of different equianalgesic dose ratio tables can be used to determine the dose of methadone.(267, 286-290) This VA/DoD OT CPG includes one of the more conservative equianalgesic dose ratio tables as a reference for providers to discuss and/or consider (Table D-3).(289) Local subject matter experts may prefer, or be more familiar with, other accepted (evidence-based) equianalgesic dose ratio tables. No equianalgesic dose ratio table is considered superior and all have similar limitations. When converting to methadone, lower MEDDs have lower conversion ratios than higher MEDDs. As compared to lower MEDDs, higher MEDDs may convert to smaller methadone doses than one might expect. For example, 60 mg MEDD would be ~15 mg of methadone/day (a ratio of ~4:1); whereas 180 mg MEDD would be ~22.5 mg/day (a ratio of ~8:1). Methadone dose conversion is not a linear process. Furthermore, while the equianalgesic dose ratio tables account for cross-tolerance, (263) some subject matter experts feel the calculated methadone dose should be further decreased for incomplete cross-tolerance, especially for patients on higher MEDDs.(273, 291)

Table D-5: Dosing Recommendations for Patients Receiving Codeine Preparations or No Previous Opioids (292, 293)

Dosing Strategy	Initial Methadone Dose	Increments	Comments
Gradual titration (For CNCP and situations necessitating less frequent monitoring)	2.5 mg every 12 hr or 8 hr	2.5 mg every 12 hr or 8 hr, no more often than every 5 to 7 d	As a general rule, *start low and go slow*
Faster titration (For cancer pain and situations where frequent monitoring is possible)	2.5-5 mg every 8 hr	2.5 to 5 mg every 8 hr as often as every third day	

Note: All doses refer to oral administration

Abbreviations: CNCP: chronic non-cancer pain; d: day(s); hr: hour(s); mg: milligram(s)

Table D-6: Equianalgesic Dose Ratios (289, 291)

Morphine Dose (mg/d)	<30	31-99	100-299	300-499	500-999	1000-1200	>1200
Morphine: Methadone	2:1	4:1	8:1	12:1	15:1	20:1	Consult

Note: The conversion ratio increases as the morphine equivalent dose increases (17, 265, 266, 286, 294)

Abbreviations: d: day(s); mg: milligram(s)

The equianalgesic dose ratio is only one component of the process for appropriate dosing of methadone and other opioids. Once the dose is determined, there are two different methods to make the switch: a

rapid conversion method and a stepwise/phased conversion. Again, no one conversion method has been determined to be superior to the others.

- For rapid conversion, the previous opioid is discontinued and the calculated methadone dose is started on day one.
- For the stepwise/phased conversion, the dose of the previous opioid is decreased by 1/3 and replaced with 1/3 of the calculated methadone dose (given in three divided doses). Then the previous opioid dose is decreased by an additional 1/3 and the methadone dose is increased by 1/3. Finally, the remaining 1/3 of the previous opioid dose is discontinued and the methadone dose is increased to the initial calculated dose. This can be done over several days or weeks.(263, 295)

For breakthrough pain, a short-acting opioid preparation (e.g., acetaminophen with hydrocodone, oxycodone with or without acetaminophen, or immediate-release morphine) may be used until steady state is achieved (i.e., 5-7 days). As-needed methadone has also been used in a palliative care setting;(268, 282, 284) however, it is generally discouraged to avoid drug accumulation. It is important to note that use of breakthrough pain medications in patients with CNCP is controversial. If opioid medications for breakthrough pain are indicated, following titration to a stable methadone dose in CNCP patients, they should be used sparingly.(285)

d. Converting from Methadone to Oral Morphine

Switching from methadone to another opioid is not simply the reverse process; the equianalgesic dose ratio tables previously mentioned are not bi-directional and cannot be used in reverse (i.e., the morphine to methadone conversion ratio may not be the same as the methadone to morphine ratio).(296) There is no widely accepted conversion strategy for switching from methadone to another opioid. A proposed safe and conservative approach is a 1:3 methadone to morphine ratio (10 mg methadone/day = 30 mg oral morphine/day).(263) However, literature suggests patients may end up on as high as 1:4.7 methadone to morphine ratio (10 mg methadone = 47 mg morphine).(297)

e. Special Patient Populations

Patients 65 years and older may have decreased clearance of methadone.(258) Dosage adjustments do not appear necessary in patients with stable chronic liver disease; in addition, methadone and its metabolites do not accumulate in patients with renal failure.(298) However, two prospective studies on methadone dosing strategies excluded patients with liver or renal disease,(284, 286) thus caution should be observed when dosing methadone in these populations. Dosage adjustments may be necessary in patients with end-stage liver or renal disease.

f. Patient Education

Discuss the following information with patients prior to and during treatment with methadone:(288)

- Methadone must be taken only as directed. Patients should never take extra doses without getting approval from the prescriber.
- Taking methadone as frequently as other opioids may produce a fatal overdose.

- Patients should use other CNS depressants (especially benzodiazepines) with caution and only as directed by a healthcare provider.
- Patients should only use methadone in combination with other opioids as prescribed by a healthcare provider.
- The use of illicit drugs and/or alcohol with methadone may be fatal.
- Pain relief builds gradually and usually takes 5-7 days to see the full effects of a particular dose.
- Patients should tell all medical providers that they are taking methadone. Adding medications or changing dosing of other medications can affect methadone and should be coordinated with the methadone prescriber.
- Patients should avoid activities requiring mental alertness or coordination (such as driving or using machinery) until the effects of methadone are realized, typically a week orlonger.
- Patients should rise slowly from a sitting/supine position, as methadone may causedizziness.
- Methadone, like other opioids, can cause significant constipation. Patients should take a prescribed laxative as directed.
- Patients should report any of the following symptoms immediately and/or seek urgent/emergent care: dizziness or lightheadedness, irregular heartbeat (palpitations), falls or near falls, chest pain/pressure, and shortness of breath.
- Patients should avoid abrupt discontinuation of methadone without first consulting a healthcare provider.

E. Additional Buprenorphine Guidance

Providers may consider an alternative initiation approach for patients with concern for/history of intolerable opioid withdrawal during buprenorphine initiation or otherwise unable to taper to 30 mg MEDD. It is recommended to either convert directly to an equivalent dose or cross-titrate for a short period of time. Provide a medication disposal bag for any remaining full agonist opioids.

Alternative initiation approach for a patient converting from full opioid agonist to buprenorphine buccal film:(299)

- For patients taking ≥80 mg MEDD, convert directly to an equivalent dose of buprenorphine buccal film:
    - **80 – 160 mg MEDD**: initiate 300 mcg 8 – 12 hours after last dose of full agonist opioids, q12 hr
    - **161 – 220 mg MEDD**: initiate 450 mcg 8 – 12 hours after last dose of full agonist opioids, q12 hr
- Alternatively, continue current full agonist opioids for 4 – 8 days while gradually up-titrating buprenorphine buccal film to the lowest effective dose. Once the buprenorphine dose is roughly an equianalgesic full agonist dose, stop the full agonist opioid (usually around day 4-8). For patients who stabilize (no withdrawal, tolerable pain) before reaching the proposed end dose, it is not necessary to proceed with further buprenorphine dose escalations.(300-305)

- For patients taking ≤80 mg MEDD, consider converting to buprenorphine transdermal delivery system (BTDS). When switching patients from oral MEDDs of 30 to 80 mg to BTDS, a patch strength of 10 mcg/h is recommended as a conservative initial conversion dose. The highest available BTDS strength of 20 mcg/h may be equianalgesic to an oral MEDD of 36 to 55 mg, whereas the product information states that the 20 mcg/h patch may not provide adequate analgesia for patients requiring greater than an oral MEDD of 80 mg.[a]

[a] For more information on BTDS, refer to the following guidance from VA PBM Services: https://www.pbm.va.gov/PBM/clinicalguidance/drugmonographs/Buprenorphine_Transdermal_System_BUTRANS_Monograph.pdf

Appendix E: Patient Focus Group Methods and Findings

A. Methods

VA and DoD Leadership recruited five participants for the focus group, with support from the Champions and other Work Group members as needed. While participant recruitment focused on eliciting a range of perspectives likely to be relevant and informative in the CPG development process, patient focus group participants were not intended to be a representative sample of VA and DoD patients. Participants were not incentivized for their participation or reimbursed for travel expenses.

The Work Group, with support from the Lewin Team, identified topics on which patient input was important to consider in developing the CPG. The Lewin Team developed and the Work Group approved the patient focus group guide covering these topics. The focus group facilitator led the discussion using the guide to elicit the patients' perspectives about their treatment and overall care. Given the limited time and the range of interests of the focus group participants, not all questions were addressed.

B. Patient Focus Group Findings

a. Participants noted that chronic pain has a significant impact on multiple aspects of their lives, including daily functioning, employment, QoL, and relationships.

- Participants indicated that they experience challenges with daily functioning resulting from their chronic pain, which in turn negatively impact their QoL and relationships.
- Participants noted their chronic pain and associated treatments impact their ability to maintain and/or secure employment in their desired field.

b. Participants expressed a perception that some providers lacked: respect and care in interactions and communication; understanding regarding severity of pain symptoms, the impact of pain, and their military experience; preparation prior to the visit and attentiveness to the participants' concerns during the visit; and knowledge and communication of the range of available treatment options.

- Participants felt there was a lack of care and attentiveness on the part of PCPs during appointments. They stated that providers were unable to understand and accept the severity of their pain and did not recognize its broader effect on their physical and mental health.
- Participants valued providers who actively listened to their symptoms and daily problems and who were able to discuss a full range of options during treatment planning, focused not only on their pain symptoms but also on improving their overall function and QoL.

c. Participants described the importance of continuity of care and coordination of care between their providers within and across treatment settings. They suggested a need for care navigators (e.g., case managers, care managers) to assist them.

- Participants recognized the importance of continuity of care and coordination of care between providers within and across treatment settings. They noted that lack of continuity and smooth transitions impacts the effectiveness of healthcare, especially in treating chronic conditions.
- Participants reported difficulty in using the virtual appointment system to communicate with providers during the pandemic and challenges regarding the length of visits.
- Participants suggested that they need care navigators (e.g., case managers, care managers, care coordinators, patient advocates) to assist them in monitoring treatment progress, ensure continuity and coordination of care related to their treatment plan, and to support them in getting access to various treatment options.

d. Participants stated they have behavioral health comorbidities (e.g., depression, PTSD, anxiety) that are impacted by their pain symptoms and indicated that these comorbidities need to be addressed as part of their chronic pain treatment plan.

- Participants stated that they experience a variety of behavioral health comorbidities including depression, PTSD, and anxiety, some of which are exacerbated by their chronic pain.
- Participants expressed concern, including anger, about providers failing to address the full range of their healthcare needs and the impact this had on their mental health.
- Every participant shared that they had experienced suicidal thoughts because of their pain.

e. None of the participants reported current use of opioids to manage their chronic pain. Participants indicated that non-opioid pharmacologic treatments used to reduce pain (e.g., gabapentin, duloxetine, NSAIDs) did not eliminate their pain and were associated with side effects.

- None of the participants reported that they were currently using opioids for treatment of their pain. They reported using other non-opioid pharmacological treatments to reduce pain (e.g. gabapentin, duloxetine, and NSAIDs) but they noted that these pharmacotherapies did not eliminate their pain and had associated side effects.
- Participants shared that opioid therapy is critical to pain management in the immediate postsurgical period, but continued treatment with opioids is not preferred.
- Participants recommended that attention be devoted to identifying “middle-ground medications” that can fill the gap between strong medications such as opioids and over-the-counter medications such as NSAIDs. Some participants identified this as their greatest need.

f. Participants valued a whole/holistic health approach to their care that focuses not only on pain symptoms but improving overall function and QoL. Participants described success in coping with their pain through treatment in their local VA's Empower Veterans Program (EVP).[a]

- Participants recognized the importance of whole/holistic health approaches, in which the provider offers a range of treatment options considering the patient's chronic pain, function, and QoL.
- Participants emphasized the effectiveness of the EVP in offering health and wellness techniques to manage their chronic pain.

[a] According to the EVP webpage, "Empower Veterans Program coaches Veterans with chronic pain to live a fuller life, a life based on each Veteran's life mission, and what matters most to them." In the EVP, a range of providers and coaches work with the Veterans to maximize their Whole Health. The EVP is comprised of the following three group classes: Acceptance and Commitment Therapy, Whole Health, and Mindful Movement. The classes meet weekly for three hours for 10 consecutive weeks. For more information, see: https://www.atlanta.va.gov/services/Empower_Veterans_Program.asp.

Appendix F: Evidence Table

Table F-1. Evidence Table[a,b,c,d]

Recommendation	2017 Strength of Recommendation	Evidence	2022 Strength of Recommendation	Recommendation Category
1. We recommend against the initiation of opioid therapy for the management of chronic non-cancer pain (for non-opioid treatments for chronic pain, see the VA/DoD CPGs for Low Back Pain, Headache, and Hip and Knee Osteoarthritis*).	Strong against	(117, 118, 120-133, 135)	Strong against	Reviewed, New-replaced
2. We recommend against long-term opioid therapy, particularly for younger age groups, as age is inversely associated with the risk of opioid use disorder and overdose.	Strong against	(117, 118, 120, 129-133, 137-145) **Additional references:** (136, 146-150)	Strong against	Reviewed, New-replaced
3. We recommend against long-term opioid therapy, particularly for patients with chronic pain who have a substance use disorder (refer to the VA/DoD CPG for the Management of Substance Use Disorders†).	Strong against	(116, 118, 120, 130, 132, 137, 138, 140, 145, 151-154) **Additional references:** (136)	Strong against	Reviewed, New-replaced

[a] 2017 Strength of Recommendation column: The 2017 VA/DoD Opioids CPG was developed using the GRADE approach to determine the strength of each recommendation. Inclusion of more than one 2017 strength of recommendation indicates that more than one 2017 VA/DoD Opioids CPG recommendation is covered by the 2022 recommendation. "Not applicable" indicates that the 2022 VA/DoD Opioids CPG recommendation was a new recommendation, and therefore does not have an associated 2017 strength of recommendation.

[b] Evidence column: The first set of references listed in each row in the evidence column constitutes the evidence base for the recommendation. To be included in the evidence base for a recommendation, a reference needed to be identified through a systematic evidence review carried out as part of the initial development or update of this CPG. The second set of references in the evidence column (called "Additional References") includes references that provide additional information related to the recommendation, but which were not identified through a systematic evidence review. These references were, therefore, not included in the evidence base for the recommendation and did not influence the strength and direction of the recommendation.

[c] 2022 Strength of Recommendation column: The 2022 VA/DoD Opioids CPG was developed using the GRADE approach to determine the strength of each recommendation. Refer to the Determining Recommendation Strength and Direction section for more information.

[d] Recommendation Category column: Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.

Recommendation	2017 Strength of Recommendation	Evidence	2022 Strength of Recommendation	Recommendation Category
4. For patients receiving medication for opioid use disorder, there is insufficient evidence to recommend for or against the selection of any one of the following medications over the other for the management of their co-occurring chronic pain: methadone, buprenorphine, or extended-release naltrexone injection. Treat the opioid use disorder according to the VA/DoD CPG for the Management of Substance Use Disorders.†	Strong for	(156-158) **Additional references:** (155, 159)	Neither for nor against	Reviewed, New-replaced
5. For patients receiving daily opioids for the treatment of chronic pain, we suggest the use of buprenorphine instead of full agonist opioids due to lower risk of overdose and misuse.	Not applicable	(121, 124, 127, 160, 161) **Additional references:** **(159, 162-172)**	Weak for	Reviewed, New-added
6. We recommend against the concurrent use of benzodiazepines and opioids for chronic pain (refer to Recommendation 10 in the VA/DoD CPG for the Management of Substance Use Disorders† for further guidance related to tapering one or both agents).	Strong against	(116, 130) **Additional references:** (136, 173)	Strong against	Reviewed, Amended
7. If prescribing opioids, we recommend using the lowest dose of opioids as indicated by patient-specific risks and benefits.	Strong for	(116-120, 129, 130, 132-134, 140, 174) **Additional references:** (136)	Strong for	Reviewed, Amended
8. If considering an increase in opioid dosage, we recommend reevaluation of patient-specific risks and benefits and monitoring for adverse events including opioid use disorder and risk of overdose with increasing dosage.	Strong for	(116-120, 129, 130, 132-134, 140, 174) **Additional references:** (136)	Strong for	Reviewed, New-replaced
9. When prescribing opioids, we recommend the shortest duration as indicated.	Strong for	(129, 132, 137, 140, 142) **Additional references:** (17, 136)	Strong for	Reviewed, New-replaced
10. After initiating opioid therapy, we recommend reevaluation at 30 days or fewer and frequent follow-up visits, if opioids are to be continued.	Strong for	(129, 132, 137, 140, 142) **Additional references:** (17, 136)	Strong for	Reviewed, New-replaced

Recommendation	2017 Strength of Recommendation	Evidence	2022 Strength of Recommendation	Recommendation Category
11. We recommend against prescribing long-acting opioids: • For acute pain • As an as-needed medication • When initiating long-term opioid therapy	Strong against	(129, 132, 138, 160, 161, 177-183) **Additional references:** (136, 176)	Strong against	Reviewed, Amended
12. We suggest a collaborative, patient-centered approach to opioid tapering.	Strong for	(184, 185)	Weak for	Reviewed, New-replaced
13. There is insufficient evidence to recommend for or against any specific tapering strategies.	Strong for	(184, 185)	Neither for nor against	Reviewed, New-replaced
14. We recommend assessing risk of suicide and self-directed violence when initiating, continuing, changing, or discontinuing long-term opioid therapy (refer to the VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide‡ for guidance on intervention timing and strategies).	Strong for	(120, 134, 175) **Additional references:** (94, 136, 186-193)	Strong for	Reviewed, New-replaced
15. For patients with chronic pain, we recommend assessing for behavioral health conditions, history of traumatic brain injury, and psychological factors (e.g., negative affect, pain catastrophizing) when considering long-term opioid therapy, as these conditions are associated with a higher risk of harm.	Not applicable	(120, 130-132, 138, 145, 152, 194, 196) **Additional references:** (136)	Strong for	Reviewed, New-added
16. For patients with acute pain when opioids are being considered, we suggest screening for pain catastrophizing and co-occurring behavioral health conditions to identify those at higher risk for negative outcomes.	Not applicable	(145, 197-201)	Weak for	Reviewed, New-added
17. For patients on opioids, we suggest ongoing reevaluation of the benefits and harms of continued opioid prescribing based on individual patient risk characteristics.	Strong for	(120, 129-134, 138, 144, 145, 202)	Weak for	Reviewed, New-replaced
18. We suggest urine drug testing for patients on long-term opioids.	Strong for	(203-207)	Weak for	Reviewed, New-replaced

Recommendation	2017 Strength of Recommendation	Evidence	2022 Strength of Recommendation	Recommendation Category
19. We suggest interdisciplinary care that addresses pain and/or behavioral health problems, including substance use disorders, for patients presenting with high risk and/or aberrant behavior.	Strong for	(208, 209)	Weak for	Not reviewed, Amended
20. We suggest providing patients with pre-operative opioid and pain management education to decrease the risk of prolonged opioid use for post-surgical pain.	Not applicable	(210-215)	Weak for	Reviewed, New-added

* Other VA/DoD CPGs are available at: https://www.healthquality.va/gov/

† See the VA/DoD CPG for the Management of Substance Use Disorders, available at: https://www.healthquality.va.gov/

‡ See the VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide, available at: https://www.healthquality.va.gov/

Appendix G: 2017 Recommendation Categorization Table

Table G-1. 2017 Opioids CPG Recommendation Categorization Table[a,b,c,d,e,f]

2017 CPG Recommendation #	2017 CPG Recommendation Text	2017 CPG Strength of Recommendation	2017 CPG Recommendation Category	2022 CPG Recommendation Category	2022 CPG Recommendation #
1	a) We recommend against initiation of long-term opioid therapy for chronic pain. b) We recommend alternatives to opioid therapy such as self-management strategies and other non-pharmacological treatments. c) When pharmacologic therapies are used, we recommend non-opioids over opioids.	a) Strong against b) Strong for c) Strong for	Reviewed, New-replaced	a) Reviewed, New-replaced b) Reviewed, Deleted c) Reviewed, Deleted	a) 1 b) N/A c) N/A
2	If prescribing opioid therapy for patients with chronic pain, we recommend a short duration. Note: Consideration of opioid therapy beyond 90 days requires reevaluation and discussion with patient of risks and benefits.	Strong for	Reviewed, New-added	Reviewed, New-replaced	9, 10
3	For patients currently on long-term opioid therapy, we recommend ongoing risk mitigation strategies (see Recommendations 7-9), assessment for opioid use disorder, and consideration for tapering when risks exceed benefits (see Recommendation 14).	Strong for	Reviewed, New-replaced	Reviewed, New-replaced	18

[a] 2017 CPG Recommendation # column: This indicates the recommendation number of the recommendation in the 2017 VA/DoD Opioids CPG.
[b] 2017 CPG Recommendation Text column: This contains the wording of each recommendation from the 2017 VA/DoD Opioids CPG.
[c] 2017 CPG Strength of Recommendation column: The 2017 VA/DoD Opioids CPG used the GRADE approach to determine the strength of each recommendation. The strength of recommendations in the 2017 VA/DoD Opioids CPG were: Strong for, Weak for, N/A, Weak against, or Strong against.
[d] 2017 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2017 VA/DoD Opioids CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[e] 2022 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2022 VA/DoD Opioids CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[f] 2022 CPG Recommendation # column: For recommendations that were carried forward to the 2017 VA/DoD Opioids CPG, this column indicates the new recommendation(s) to which they correspond.

2017 CPG Recommendation #	2017 CPG Recommendation Text	2017 CPG Strength of Recommendation	2017 CPG Recommendation Category	2022 CPG Recommendation Category	2022 CPG Recommendation #
4	a) We recommend against long-term opioid therapy for pain in patients with untreated substance use disorder. b) For patients currently on long-term opioid therapy with evidence of untreated substance use disorder, we recommend close monitoring, including engagement in substance use disorder treatment, and discontinuation of opioid therapy for pain with appropriate tapering (see Recommendation 14 and Recommendation 17).	a) Strong against b) Strong for	Reviewed, Amended	a) Reviewed, New-replaced b) Reviewed, Deleted	a) 3 b) N/A
5	We recommend against the concurrent use of benzodiazepines and opioids. Note: For patients currently on long-term opioid therapy and benzodiazepines, consider tapering one or both when risks exceed benefits and obtaining specialty consultation as appropriate (see Recommendation 14 and the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders).	Strong against	Reviewed, New-added	Reviewed, Amended	6
6	a) We recommend against long-term opioid therapy for patients less than 30 years of age secondary to higher risk of opioid use disorder and overdose. b) For patients less than 30 years of age currently on long-term opioid therapy, we recommend close monitoring and consideration for tapering when risks exceed benefits (see Recommendation 14 and Recommendation 17)	a) Strong against b) Strong for	Reviewed, New-replaced	a) Reviewed, New-replaced b) Reviewed, Deleted	a) 2 b) N/A

2017 CPG Recommendation #	2017 CPG Recommendation Text	2017 CPG Strength of Recommendation	2017 CPG Recommendation Category	2022 CPG Recommendation Category	2022 CPG Recommendation #
7	We recommend implementing risk mitigation strategies upon initiation of long-term opioid therapy, starting with an informed consent conversation covering the risks and benefits of opioid therapy as well as alternative therapies. The strategies and their frequency should be commensurate with risk factors and include: • Ongoing, random urine drug testing (including appropriate confirmatory testing) • Checking state prescription drug monitoring programs • Monitoring for overdose potential and suicidality • Providing overdose education • Prescribing of naloxone rescue and accompanying education	Strong for	Reviewed, New-replaced	Reviewed, New-replaced	18
8	We recommend assessing suicide risk when considering initiating or continuing long-term opioid therapy and intervening when necessary.	Strong for	Reviewed, Amended	Reviewed, New-replaced	14
9	We recommend evaluating benefits of continued opioid therapy and risk for opioid-related adverse events at least every three months.	Strong for	Reviewed, New-replaced	Reviewed, New-replaced	17
10	If prescribing opioids, we recommend prescribing the lowest dose of opioids as indicated by patient-specific risks and benefits. Note: There is no absolutely safe dose of opioids.	Strong for	Reviewed, New-replaced	Reviewed, Amended	7
11	As opioid dosage and risk increase, we recommend more frequent monitoring for adverse events including opioid use disorder and overdose. Note: • Risks for opioid use disorder start at any dose and increase in a dose dependent manner. • Risks for overdose and death significantly increase at a range of 20-50 mg morphine equivalent daily dose.	Strong for	Reviewed, New-replaced	Reviewed, New-replaced	8

2017 CPG Recommendation #	2017 CPG Recommendation Text	2017 CPG Strength of Recommendation	2017 CPG Recommendation Category	2022 CPG Recommendation Category	2022 CPG Recommendation #
12	We recommend against opioid doses over 90 mg morphine equivalent daily dose for treating chronic pain. Note: For patients who are currently prescribed doses over 90 mg morphine equivalent daily dose, evaluate for tapering to reduced dose or to discontinuation (see Recommendations 14 and 15).	Strong against	Reviewed, New-replaced	Reviewed, Deleted	N/A
13	We recommend against prescribing long-acting opioids for acute pain, as an as-needed medication, or on initiation of long-term opioid therapy.	Strong against	Reviewed, New-replaced	Reviewed, Amended	11
14	We recommend tapering to reduced dose or to discontinuation of long term opioid therapy when risks of long-term opioid therapy outweigh benefits. Note: Abrupt discontinuation should be avoided unless required for immediate safety concerns.	Strong for	Reviewed, New-added	Not reviewed, Deleted	N/A
15	We recommend individualizing opioid tapering based on risk assessment and patient needs and characteristics. Note: There is insufficient evidence to recommend for or against specific tapering strategies and schedules.	Strong for	Reviewed, New-added	Reviewed, New-replaced	12, 13
16	We recommend interdisciplinary care that addresses pain, substance use disorders, and/or mental health problems for patients presenting with high risk and/or aberrant behavior.	Strong for	Reviewed, New-replaced	Not reviewed, Amended	19
17	We recommend offering medication assisted treatment for opioid use disorder to patients with chronic pain and opioid use disorder. Note: See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders.	Strong for	Reviewed, New-replaced	Reviewed, New-replaced	4

2017 CPG Recommendation #	2017 CPG Recommendation Text	2017 CPG Strength of Recommendation	2017 CPG Recommendation Category	2022 CPG Recommendation Category	2022 CPG Recommendation #
18	a) We recommend alternatives to opioids for mild-to-moderate acute pain. b) We suggest use of multimodal pain care including non-opioid medications as indicated when opioids are used for acute pain. c) If take-home opioids are prescribed, we recommend that immediate-release opioids are used at the lowest effective dose with opioid therapy reassessment no later than 3-5 days to determine if adjustments or continuing opioid therapy is indicated. Note: Patient education about opioid risks and alternatives to opioid therapy should be offered.	a) Strong for b) Weak for c) Strong for	Reviewed, New-added	a) Not reviewed, Deleted b) Not reviewed, Deleted c) Not reviewed, Deleted	a) N/A b) N/A c) N/A

Appendix H: Participant List

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Appendix I: Literature Review Search Terms and Strategy

A. EMBASE and Medline in EMBASE.com syntax (all KQs)

KQ	Set #	Concept	Strategy
Population and Prescribed Opioids	#1	Population – Adults with chronic pain	(‘chronic disease’/exp AND pain:ti,ab,kw) OR 'chronic pain'/exp OR 'chronic pain' OR 'chronic inflammatory pain'/de or ‘persistent pain’
	#2		(chronic NEXT/3 pain*) OR ('long term' NEXT/3 pain*) OR 'chronic regional pain syndrome' OR (('pain'/exp/mj OR pain*:ti,ab) AND (chronic*:ti,ab OR longterm:ti,ab OR 'long term':ti,ab OR persistent:ti,ab OR prolonged:ti,ab OR weeks:ti,ab OR months:ti,ab OR year*:ti,ab OR '30 days' OR '60 days' OR '90 days'))
	#3		(‘arthropathy’/exp OR ‘central sensitatization’/de OR arthritis OR low-back OR ‘low back’ OR lbp OR neck OR ‘cervical spine’ OR spine OR spinal OR disabilit* OR fibromyalgia OR headache* OR injury OR joint* OR lupus OR musculoskelet* OR ‘multiple sclerosis’ OR myofascial OR ((neurogenic OR neuropathic OR nociplastic) NEXT/5 pain*) OR osteoarthriti* OR osteo-arthritis OR ‘degenerative joint’ OR skeletal OR hip OR hips OR knee*) AND ('pain'/exp/mj OR pain*:ti,ab) AND (chronic*:ti,ab OR intractable:ti,ab OR refractory:ti,ab OR longterm:ti,ab OR 'long term':ti,ab OR persistent:ti,ab OR prolonged:ti,ab weeks:ti,ab OR months:ti,ab OR year*:ti,ab OR '30 days' OR '60 days' OR '90 days')
	#4		#1 OR #2 OR #3
	#5	Prescribed opioids	‘codeine’/de OR ‘fentanyl’/de OR ‘morphine’/de OR ‘narcotics’/exp OR 'narcotic agent'/exp OR 'narcotic analgesic agent'/exp OR 'opiate'/de OR 'opiate'/de/dd_ad,dd_cb,dd_cm,dd_cr,dd_do,dd_it,dd_to
	#6		benzhydrocone OR butorphanol OR codeine OR fentanyl OR hydrocodone OR hydromorphine OR hydromorphone OR methadone OR morphine OR nalbuphine OR narcotic* OR oliceridine OR opiate* OR opioid* OR opon OR oposal OR oxycodone OR oxymorphone OR propoxyphene OR remifentanil OR sufentanil OR tapentadol OR tramadol OR algopan OR biopon OR cofapon OR laudanon OR laudanum OR laudopan OR nepenthe OR omnopon OR opia* NEXT/1 alkaloid* OR opiu* NEXT/1 (alkaloid* OR derivative OR poppy OR tincture) OR pantopon OR pantopone OR papaveretum OR pavon OR tetrapon

KQ	Set #	Concept	Strategy
Population and Prescribed Opioids (cont.)	#7	Prescribed opioids (cont.)	'alfentanil'/de OR alfentanil OR 'alphaprodine'/de OR alphaprodine OR 'beta casomorphin'/de OR 'beta casomorphin' OR 'buprenorphine'/de OR buprenorphine OR 'carfentanil'/de OR carfentanil OR 'codeine'/de OR codeine OR 'deltorphin'/de OR deltorphin OR 'dextromethorphan'/de OR dextromethorphan OR 'dezocine'/de OR dezocine OR 'dihydrocodeine'/de OR dihydrocodeine OR 'dihydromorphine'/de OR dihydromorphine OR 'enkephalin'/de OR enkephalin OR 'ethylketocyclazocine'/de OR ethylketocyclazocine OR 'ethylmorphine'/de OR ethylmorphine OR 'etorphine'/de OR etorphine OR 'fentanyl'/de OR fentanyl OR 'heroin'/de OR heroin OR 'hydrocodone'/de OR hydrocodone OR 'hydromorphone'/de OR hydromorphone OR 'ketobemidone'/de OR ketobemidone OR 'levorphanol'/de OR levorphanol OR 'lofentanil'/de OR lofentanil OR 'meperidine'/de OR meperidine OR 'meptazinol'/de OR meptazinol OR 'methadone'/de OR methadone OR methadyl AND ('acetate'/de OR acetate) OR 'morphine'/de OR morphine OR 'nalbuphine'/de OR nalbuphine OR 'opium'/de OR opium OR 'oxycodone'/de OR oxycodone OR 'oxymorphone'/de OR oxymorphone OR 'pentazocine'/de OR pentazocine OR 'phenazocine'/de OR phenazocine OR 'phenoperidine'/de OR phenoperidine OR 'pirinitramide'/de OR pirinitramide OR 'promedol'/de OR promedol OR 'propoxyphene'/de OR propoxyphene OR 'remifentanil'/de OR remifentanil OR 'sufentanil'/de OR sufentanil OR 'tilidine'/de OR tilidine OR 'tapentadol'/de OR tapentadol OR 'tramadol'/de
	#8		('pain'/exp/mj OR pain*:ti) AND ('drug therapy'/lnk OR (drug* AND therap*):ti,ab) AND ('opiate'/de OR opi*:ti,ab,kw)
	#9		#5 OR #6 OR #7 OR #8
KQ 1	#10	Population and Prescribed opioids	#4 AND #9
	#11	Interventions: Co-occurring broad	'comorbidity'/de OR 'contraindication'/exp OR comorbid* OR co-morbid*OR contraindication* OR co-occurring OR multimorbidit*
	#12	Physical comorbidities	'arthritis'/exp OR 'chronic disease'/exp OR 'disability'/exp/mj OR 'functional abdominal pain' OR 'gastrointestinal motility disorder'/de OR 'inflammation'/exp OR 'injury'/exp OR 'kidney disease'/exp OR 'low back pain'/exp OR 'musculoskeletal pain'/exp OR 'neurogenic pain'/de OR 'osteoarthritis'/exp OR 'osteoporosi'/exp OR 'posttraumatic stress disorder' OR 'renal disease'/exp OR 'traumatic brain injury'/de
	#13		(arthritis OR abdominal OR 'back pain' OR COPD OR 'chronic obstructive pulmonary dis*' OR 'centralized pain' OR disabilit* OR gastro* OR fibromyalgia OR headache* OR 'immune status' OR 'immune system' OR injur* OR joint* OR kidney* OR liver* OR musculoskelet* OR 'multiple sclerosis' OR neuralgia OR neurogenic OR neuropathic OR osteoarthriti* OR osteoporosis OR 'pain catastrophizing' OR 'posttraumatic stress dis*' OR 'post-traumatic stress dis*' OR ptsd OR 'qt prolongation' OR renal OR rheumatoid* OR skeletal OR trauma OR 'traumatic brain injur*'):ti,ab
	#14	Behavioral/Mental health, substance abuse comorbidities	'pursuit of compensation' OR 'workman compensation'/de OR 'anxiety'/exp OR 'fear avoidance'/de OR 'kinesiophobia'/de OR 'mental disease'/exp OR 'psychiatric comorbidity'/de OR 'cognitive defect'/exp OR 'social behavior'/exp OR 'sleep disorder'/exp OR (anxiety OR avoidance OR bipolar OR dementia OR depress* OR 'fear avoid*' OR 'impulse control' OR incarcerat* OR jail* OR kinesiophob* OR prison* OR stress* OR suicid*):ti,ab
	#15		((cognitive OR mental OR neuro* OR personality OR psych* OR sleep) NEXT/3 (comorbidit* OR defect* OR disorder* OR disease* OR dysfunction* OR illness* OR impair*)):ti,ab

KQ	Set #	Concept	Strategy
KQ 1 (cont.)	#16	Behavioral/Mental health, substance abuse comorbidities (cont.)	Aberrant:ti,ab OR 'addiction'/exp OR 'drug abuse'/exp OR 'substance use disorder'/exp OR 'opioid use disorder'/de OR 'medical cannabis'/de OR 'medical marijuana':ti,ab OR kratom:ti,ab OR ((substance OR drug* OR alcohol* OR behavior* OR behaviour* OR cannabin* OR opi*) NEXT/5 (disorder* OR abuse OR addict* OR use)):ti,ab
	#17	Combine physical comorbidities	#12 OR #13
	#18	Combine behavior/ psych comorbidities	#14 OR #15 OR #16
	#19	Adults with chronic pain on Prescribed opioids AND comorbidities general concept (tight)	#10 AND #11
	#20	Adults with chronic pain on Prescribed opioids AND physical conditions	#10 AND #17
	#21	Adults with chronic pain on Prescribed opioids AND mental, behav/ pscyh comorbidities	#10 AND #18
	#22	Combine final intervention sets	#19 OR #20 OR #21
KQ 2	#23	Standard population, Adults with chronic pain considered for Prescribed opioids	#4 AND #9
	#24	Opioid misuse or opioid use disorder	'opioid use disorder'/de OR 'drug misuse'/exp OR (oud OR 'opioid use disorder' OR (opi* NEXT/2 misuse) OR (opi* NEXT/2 disorder*) OR (opi* NEXT/2 abuse) OR overdose* OR adverse OR safe*):ti,ab
	#25	Interventions: Opioid related factors	'opiate'/exp/dd_ad,dd_cb,dd_cm,dd_cr,dd_do,dd_it,dd_to OR 'drug dose'/exp OR 'drug formulation'/exp OR ((drug* OR opi*) AND (dose OR dosage OR formulation OR regimen OR duration OR intensification OR schedule* OR megadose OR microdose OR underdose OR overdose OR 'multiple cycle')):ti,ab OR ((drug* OR opi*) AND (dose OR dosage OR regimen) AND (regular OR 'as needed' OR as-needed OR contin* OR scheduled OR duration)):ti,ab
	#26	Demographic-related, sociodemographic factors	'aged'/exp OR 'demographics'/de OR 'ethnic or racial aspects'/exp OR 'gender'/exp OR 'marriage'/exp OR 'sociodemographic factor'/de OR 'socioeconomics'/exp OR (age* OR demographic* OR divorce* OR ethnic* OR gender OR 'marital status' OR married OR race OR racial OR socioeconomic* OR sociodemographic* OR poverty OR homeless* OR rural*):ti,ab OR (insecur* AND (food* OR housing OR shelter)):ti,ab
	#27	Healthcare utilization	'emergency ward'/de OR 'health care utilization'/exp OR 'mental health care'/exp OR 'preventive care'/de OR (('health care' OR healthcare OR 'health service*') NEXT/2 (use OR utilization)):ti,ab

KQ	Set #	Concept	Strategy
KQ 2 (cont.)	#28	Diversion considerations Anxiety Catastrophizing Comorbidities (PTSD) Co-prescriptions Depression Marijuana use	('anxiety disorder'/exp OR 'catastrophizing'/de OR 'cannabis use'/exp OR 'depression'/exp) AND 'drug abuse'/exp) OR ('complication'/exp AND 'prescription'/exp) OR 'polypharmacy'/exp OR 'posttraumatic stress disorder'/de OR 'comorbidity'/de OR ((comorbid* OR co-morbid* OR 'co occurring' OR multimorbidit*):ti,ab OR (pain NEXT/2 catastrophiz*):ti,ab OR anxiety:ti,ab OR depression:ti,ab OR cannabis:ti,ab OR marijuana:ti,ab OR polypharmacy:ti,ab OR 'post traumatic stress disorder':ti,ab OR ptsd:ti,ab
	#29	Combine interventions	#24 AND (#25 OR #26 OR #27 OR #28)
	#30	Combine population and interventions	#23 AND #29
KQ 3	#31	Population: Adults with chronic pain	#1 OR #2 OR #3
	#32	Non-opioid therapy or other pain management strategies: Non-opioid sedating pain medications	(Pharmacologic*:ti,ab OR pharmacotherap*:ti OR analgesic*:ti OR 'analgesic agent'/exp/mj OR 'paracetamol'/de OR 'valproic acid'/de) NOT opi*
	#33		(amitriptyline or carbamazepine or clomipramine or desipramine or doxepin or duloxetine or gabapentin or imipramine or levetiracetam or maprotiline or milnacipran or mirtazapine or nortriptyline or oxcarbazepine or pregabalin or protriptyline or tiagabine or topiramate or trimipramine or 'valproic acid' or venlafaxine or zonisamide):ti,ab,tn
	#34	Muscle relaxants	'muscle relaxant agent'/exp/mj OR 'muscle relax*':ti OR 'muscular relax*':ti
	#35		((Aspirin AND Carisoprodol) OR baclofen OR 'Chlorphenesin Carbamate' OR chlorzoxazone OR (Acetaminophen AND Chlorzoxazone) OR carisoprodol OR Metaxalone OR (Aspirin AND Caffeine AND Orphenadrine) OR (Aspirin AND Methocarbamol) OR Dantrolene OR 'Orphenadrine Citrate' OR 'Orphenadrine Hydrochloride' OR tizanidine):ti,ab,tn
	#36	NSAIDS, Pain relievers	'nonsteroid antiinflammatory agent'/exp OR (('non steroid*' OR nonsteroid*) NEXT/1 (anti-inflammator* OR antiinflammator*')):ti,ab OR (nsaid* OR n-said* OR advil OR aleve OR aspirin OR benaxaprofen OR advil OR Celecoxib OR 'Choline Magnesium Trisalicylate' OR Diclofenac OR (Diclofenac AND Misoprostol) OR 'Diclofenac Epolamine' OR 'Diclofenac Nano' OR Diflunisal OR Etodolac OR Fenoprofen OR Flurbiprofen OR Ibuprofen OR (Ibuprofen AND Famotidine) OR Indomethacin OR 'Indomethacin Nano' OR Ketoprofen OR Ketorolac OR Meclofenamate OR 'Mefenamic Acid' OR Meloxicam OR Motrin OR Nabumetone OR Naproxen OR (Naproxen AND Esomeprazole) OR 'Naproxen Nano' OR Oxaprozin OR Piroxicam OR Rofecoxib OR 'Salicylic Acid' OR salicylate* OR Salsalate OR Sulindac OR Suprofen OR Tolmetin OR Valdecoxib):ti,ab,tn
	#37		'paracetamol'/de OR (acetaminophen OR 'acetaminophen tramadol'):ti,ab,tn
	#38	Prescribed opioids	#5 OR #6 OR #7 OR #8
	#39	Comp and integrative approach	'nonpharmaceutical intervention'/de OR (nonpharma* OR non-pharma*):ti,ab OR 'alternative medicine'/exp OR 'integrative medicine'/de OR 'complement* integrat* health':ti,ab,kw OR 'complementary and alternative medicine' OR ((complement* OR alternat*) NEXT/5 (therap* OR care OR intervent*)):ti,ab OR 'functional medicine':ti,ab
	#40	Acupuncture	'acupuncture'/exp OR (electroacupuncture OR 'electro acupuncture' OR acupuncture OR acupressure):ti,ab OR 'massage'/exp OR massage*:ti,ab OR 'dry needling'/de OR 'dry needl*':ti,ab

KQ	Set #	Concept	Strategy
KQ 3 (cont.)	#41	Biofeedback	'biofeedback'/de OR 'biofeedback therapy'/de OR 'biofeedback training'/exp OR 'neurofeedback'/de OR 'neurofeedback training'/de OR 'neurofeedback therapy'/de OR ('bio feed back*' OR 'bio feedback*' OR 'biofeed back*' OR biofeedback* OR feedback* OR myobiofeedback* OR myofeedback* OR neurobiofeedback* OR neurofeedback*):ti,ab
	#42	Behavioral/mental health Cognitive behave therapy mindfulness Meditation Guided imagery Clinical hypnosis Relaxation breathing	'behavioral health'/de OR 'behavioral health care'/de OR (behavi* NEXT/3 (health OR therap*)):ti,ab OR 'cognitive behavioral therapy'/exp OR 'cognitive therapy'/exp OR 'behavior therapy'/exp OR 'cognitive behavior* therap*':ti,ab OR 'group therapy'/exp OR 'guided imagery'/de OR 'guide* imagery':ti,ab OR 'hypnosis'/de OR hypnosis:ti,ab OR 'mindfulness'/exp OR 'meditation'/exp OR 'muscle relaxation'/exp OR mediat*:ti,ab OR mindful*:ti,ab OR mindfulness:ti,ab OR 'mindfulness based stress reduc*':ti,ab OR (mbct OR mbsr OR mbt OR micbt):ti,ab,kw OR 'mind body':ti,ab OR relaxation:ti,ab OR ((deep:ti,ab OR diaphragm*:ti,ab) AND breath*:ti,ab) OR visualization:ti,ab
	#43	Tai chi/Yoga	'tai chi'/de OR 'qigong'/de OR ('chi kung' OR 'ch i kung' OR chigung OR 'qi gong' OR 'tai chi' OR 't ai chi' OR taichi OR 'tai ji' OR taiji*):ti,ab OR 'yoga'/exp OR yoga*:ti,ab
	#44	Physical therapy Ultrasound Stimulation	'physiotherapy'/de OR 'home physiotherapy'/de OR 'joint mobilization'/de OR 'physical therap*':ti,ab OR ((exercise OR mobilization OR movement):ti,ab AND ('at home' OR 'in home' OR assist OR assisted OR therapist):ti,ab) OR 'physiotherapy ultrasound system'/de OR (physiotherapy NEXT/2 ultrasound) OR 'sonophoresis' OR (ultrasound* NEXT/3 stimulat*):ti,ab OR 'ultrasound guide*':ti,ab
	#45	Exercise	'exercise'/exp OR exercise*:ti,ab OR 'physical activit*':ti,ab OR 'range of motion':ti,ab OR (daily NEAR/5 activit*):ti,ab
	#46	Chrio/Osteo manipulation	'chiropractic manipulation'/de OR chiropract*:ti,ab OR 'joint mobilization'/de OR 'osteopathic manipulation'/de OR 'spine manipulation'/de OR 'manipulative medicine'/exp OR ((osteopath* OR spinal OR joint*) NEXT/2 (manipulat* OR mobiliz*)):ti,ab OR 'range of motion':ti,ab OR 'manual therap*':ti,ab
	#47	Combine non-opioid pharma interventions	#32 OR #33 OR #34 OR #35 OR #36 OR #37
	#48	Combine non-pharma interventions	#39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46
	#49	Population and Prescribed opioids and non-opioid therapies	#31 AND #38 AND (#47 OR #48)
	#50	Population and non-opioid therapies	#31 AND (#47 OR #48)
	#51	Combine	#49 OR #50

KQ	Set #	Concept	Strategy
KQ 4	#52	Population: Adults with chronic pain on Prescribed opioids	#4 AND #9
	#53	Immediate-release/short-acting opioid drugs (need to specify) compared to extended release/long-acting opioid drugs or combination short and long-acting drugs (WG to prepare list of specific drug names)	'drug formulation'/exp OR 'controlled release formulation'/exp OR 'extended release formulation'/de OR 'immediate release formulation'/exp OR 'short acting analgesic agent'/de OR ((drug* OR medic* OR pharma*) AND (control* OR extend* OR formula* OR immediate* OR long* OR short* OR sustain* OR acting OR release*) AND (opi*:ti,ab,kw OR 'opiate'/exp))
	#54	Transdermal patches, buccal, sublingual, or intrathecal pumps	'buccal drug administration'/exp OR 'intrathecal drug administration'/de OR OR 'transdermal patch'/de OR ((buccal OR intrathecal OR patch OR sublingual OR transdermal):ti,ab AND (drug* OR pharma*):ti,ab AND (administ* OR deliver*):ti,ab) OR ('drug delivery device'/exp AND (buccal OR intrathecal OR patch OR sublingual OR transdermal):ti,ab)
	#55	Abuse deterrent formulations	'abuse deterrent formulation'/exp OR ((abuse- deterrant OR abuse NEXT/2 deterr*) AND formula*)
	#56	Tramadol and other dual-mechanism opioids	'tramadol'/de OR tramadol OR 'dual opi*' OR dual NEXT/3 opi*
	#57	Buprenorphine	'buprenorphine'/de OR buprenorphine
	#58	Methadone	'methadone'/de OR methadone
	#59	One prescribing regimen (e.g., prn use), method	('drug dose'/exp OR 'drug dosage form'/exp OR 'drug therapy'/exp OR (drug* NEXT/3 therap*):ti OR (drug* NEXT/3 dos*):ti OR (drug* AND regimen*):ti OR (drug* NEXT/5 deliver*):ti) AND ((schedule* OR regimen* OR sequence OR cycle* OR formula* OR route OR tablet* OR tab* OR cap* OR intravenous* OR lozenge* OR 'oral concentrate' OR 'oral solution' OR intramuscular OR subcutaneous OR 'by mouth' OR insufflation OR inhalation OR rectal OR spray OR epidural OR intrathecal):ti,ab)
	#60	Combine interventions	#53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59
	#61	Combine population and interventions	#52 AND #60
KQ 5	#62	Population: Adults with chronic pain on opioid therapy	#4 AND #9
	#63	Intervention: Medications with CNS effects (prescribed and OTC): Benzodiazepines	'antidepressant agent'/exp OR 'benzodiazepine' OR 'benzodiazepine derivative'/exp OR 'eszopiclone'/exp OR 'narcotic analgesic agent'/exp OR 'zaleplon'/exp OR 'zolpidem'/exp OR (benzo* OR Alprazolam OR Xanax* OR chlordiazpoxide OR Librium OR clobazam OR onfi OR clonazepam OR klonopin OR clorazepate OR Tranxene OR Gen-xene OR diazepam OR Valium OR estazolam OR Prosom OR flurazepam OR Dalmane OR lorazepam OR Ativan OR midazolam OR Versed OR Nayzilam OR oxazepam OR Serax OR temazepam OR restoril OR triazolam OR Halcion OR quazepam OR Doral OR 'zolpidem' OR 'zaleplon' OR 'eszopiclone' OR ambien OR lunesta OR sonata OR benzodiazepine* OR antidepressant* OR 'anti-depressant' OR 'anti depressant' OR stimulant* OR 'z drug' OR 'z drugs' OR hypnotic* OR psychoactive*):ti,ab,tn

KQ	Set #	Concept	Strategy
KQ 5 (cont.)	#64	CNS depressants and antidepressants (SNRIs and TCAs) Serotonin and norepinephrine reuptake inhibitors Tricyclic antidepressants	'antidepressant agent'/exp OR 'central depressant agent'/exp OR 'tricyclic antidepressant agent'/exp OR 'serotonin noradrenalin reuptake inhibitor'/exp OR 'duloxetine'/de OR ('noradrenalin serotonin reuptake inhibitor*' OR 'noradrenalin serotonin uptake inhibitor*' OR 'norepinephrine serotonin reuptake inhibitor*' OR 'norepinephrine serotonin uptake inhibitor*' OR 'serotonin and noradrenaline reuptake inhibitor*' OR 'serotonin and noradrenaline uptake inhibitor*' OR 'serotonin and norepinephrine reuptake inhibitor*' OR 'serotonin and norepinephrine uptake inhibitor*' OR 'serotonin noradrenalin uptake inhibitor*' OR 'serotonin norepinephrine reuptake inhibitor*' OR 'serotonin norepinephrine uptake inhibitor*' OR desvenlafaxine OR pristiq OR duloxetine OR cymbalta OR levomilnaciran OR fetzima OR milnacipran OR savella* OR venlafaxine OR Effexor*):ti,ab,tn OR (Antidepressant* OR 'anti depressant*' OR (antidepress* NEAR/2 (drug* OR agent*)) OR ((tricyclic* OR tca*) NEAR/2 (antidepress*))):ti,ab OR (amiptriptyline OR Elavil OR Amoxapine OR anafranil* OR clomipramine OR desipramine OR norpramin OR doxepin OR silenor OR imipramine OR tofranil OR maprotiline OR nortriptyline OR pamelor* OR protriptyline OR triminpramine* OR surmontil):ti,ab,tn
	#65	Antiepileptics	'anticonvulsive agent'/exp OR (anticonvulsive* OR antiepileptic*):ti,ab OR (Benzodiazepines OR clobazam OR clonazepam OR clorazepate OR diazepam OR lorazepam OR brivaracetam OR Briviact OR carbamazepine OR Carbatrol OR Epitol OR Equetro OR Tegretrol* OR eslicarbazepine OR Aptiom OR ethosuximide OR Zarontin OR felbamate OR felbatol OR gabapentin OR Gralise* OR Neurontin OR lacosamide OR Vimpat OR lamotrigine OR LaMICtal* OR Subvenite* OR levetiracetam OR Keppra* OR Roweepra* OR Spritam OR oxcarbazepine OR OXtellar* OR Trileptal OR perampanel OR Fycompa OR phenobarbital OR Luminal OR 'phenytoin and fosphenytoin' OR Dilantin OR Phenytek OR pregabalin OR Lyrica* OR primidone OR Mysoline OR rufinamide OR Banzel OR stiripentol OR Diacomit OR tiagabine OR Gabitril OR topiramate OR Topamax* OR Qudexy* OR Trokindi* OR valproate OR Depakote*OR vigabatrin OR Sabril OR Vigadrone OR zonisamide OR Zonegran):ti,ab,tn
	#66	Gabapentinoids	'pregabalin'/de OR pregabalin:ti,ab,kw,tn OR 'gabapentin'/de OR gabapentin:ti,ab,tn
	#67	Non-opioid analgesics (ketamine)	'neuroleptic agent'/exp OR (antipsychotic* OR abilify* OR alprazolam* OR aripiprazole* OR asenapine* OR buspirone* OR clozapine* OR clozaril* OR fanapt* OR fazaclo* OR geodon* OR iloperidone* OR invega* OR latuda* OR lurasidone* OR molindone* OR neuroleptic* OR nialamide* OR olanzapine* OR paliperidone* OR pregabalin* OR quetiapine* OR reserpine* OR risperdal* OR risperidone* OR saphris* OR seroquel* OR spiroperidol* OR sulpiride* OR tetrabenazine* OR tranquiliz* OR tranquilliz* OR triazolam* OR ziprasidone* OR zyprexa*):ti,ab,tn
	#68	Stimulants	'amphetamine'/de OR 'amphetamine plus dexamphetamine'/exp OR 'dexamphetamine'/de OR 'methylphenidate'/de OR 'central stimulant agent'/exp/mj OR (methylphenidate* OR Adhansia* OR Aptensio* OR Concerta* OR Cotempla* OR Dayrana* OR Jornay* OR Metadate* OR Methylin OR QuiliChew* OR Quilivant* OR Relexxii* OR Ritalin* OR Amphetamine* OR dextroamphetmine* OR Dexedrine OR ProCentra OR Zenedi OR 'dextroamphetamine amphetamine*' OR Adderall* OR Mydayis*):ti,ab,tn

KQ	Set #	Concept	Strategy
KQ 5 (cont.)	#69	Muscle relaxants	'muscle relaxant agent'/exp OR 'musc* relax*':ti OR (baclofen OR Gablofen* OR Lioresal* OR Ozobax* OR benzodiazepine* OR oxazepam OR Serax* OR diazepam OR Valium* OR carisoprodol OR Soma* OR chlorzoxazone OR Lorzone* OR cyclobenzaprine OR Amrix* OR Fexmid* OR FlexePax* OR 'FusePaq Tabradol' OR dantrolene OR Dantrium* OR metaxalone OR Skelaxin* OR Metaxall* OR 'Lorvatus PharmaPak' OR methocarbamol OR Robaxin* OR Robaxin-750 OR orphenadrine OR Norflex* OR tizanidine OR 'Comfort Pac with Tizanidine' OR Zanaflex*):ti,ab,tn
	#70	Anesthetics	'local anesthetic agent'/exp OR 'ketamine'/de OR ketamine:ti,ab,tn OR 'lidocaine'/de OR lidocaine:ti,ab,tn
	#71	Cannabinoids	'cannabinoid'/exp OR 'cannabis'/de OR 'medical cannabis'/de OR 'cannabinoids' OR cannabi*:ti,ab OR (medical NEXT/2 marijuana):ti,ab OR (medical NEXT/2 cannabi*):ti,ab
	#72	Z-drugs (hypnotics for sleep)	'hypnotic sedative agent'/exp OR 'z drug'/de OR 'z drug*':ti OR ((drug* NEAR/3 (hypnotic* OR psychoactive*)) OR eszopiclone OR Lunesta* OR zaleplon OR Sonata* OR zolpidem OR Ambien* OR Edluar* OR Zolpimist*):ti,ab,tn
	#73	Kratom OR Seroquel	'Mitragyna speciosa'/de OR kratom:ti,ab,tn OR 'quetiapine'/de OR Seroquel:ti,ab,tn
	#74	Antihistamines and Diphenhydramine	'antihistaminic agent'/exp OR 'diphenhydramine'/de OR antihistamin*:ti,ab OR 'anti histamin*':ti,ab OR diphenhydramin*:ti,ab
	#75	Combine interventions	#63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74
	#76	Combine population AND Prescribed opioids AND interventions	#62 AND #75
KQ 6	#77	Population: Adults with chronic pain on/ considering prescribed opioids	#4 AND #9
	#78	Risk mitigation – general concept	'risk'/exp/mj OR (risk* NEAR/10 mitigat*) OR 'safe prescribing':ti,ab OR (risk*:ti,ab AND (evaluat* OR assess* OR limit* OR minimis* OR minimiz* OR measure* OR mitigat* OR reduc* OR screen* OR stratif*)):ti,ab OR (opi*:ti AND mitigate*):ti,ab
	#79	Naloxone rescue	'naloxone'/de OR 'naloxone rescue':ti,ab OR (naloxone AND (dose* OR kit* OR rescue* OR prevent* OR revive* OR revers*):ti,ab
	#80	Informed consent, written consent (contracts)	'contracts'/exp OR 'informed consent'/de OR (consent OR contract OR contracts OR agreement)):ti,ab
	#81	Risk assessment instruments	'risk assessment'/exp OR (risk*:ti,ab AND (instrument* OR survey* OR questionnaire* OR tool OR tools OR "ORT" OR "SOAPP" OR "SISAP" OR "DIRE" OR "PDUQ-p" OR "COMM" OR "PMQ" OR "PADT" OR "ABC" OR "CAGE" OR 'Stratification Tool for Opioid Risk Mitigation' OR "STORM" OR "RIOSORD"):ti,ab AND (assess* OR evaluat* OR screen* OR measure* OR factor*):ti,ab)
	#82	Patient education	'education'/exp OR 'education program*':ti,ab OR 'health education':ti,ab OR 'opioid education':ti,ab OR ((train* OR educat*):ti AND (outpatient* OR patient*):ti AND opi*:ti)

KQ	Set #	Concept	Strategy
KQ 6 (cont.)	#83	Urine drug testing (UDT)	'urinalysis'/exp OR 'urine test strip'/exp OR (urin* NEXT/5 (screen* OR test* OR detect* OR analysis OR analyze OR monitor*)):ti,ab OR "UDT":ti,ab
	#84	Opioid management plans, case management, Compliance with other therapies	('opiate'/exp OR Opi*:ti) AND (('case management'/exp OR casework*:ti,ab OR 'case manag*':ti,ab OR manag*:ti,ab OR management:ti,ab OR plan:ti,ab OR plans:ti,ab OR planning:ti,ab OR strategy:ti,ab OR strategies:ti,ab OR 'medication assisted treatment':ti,ab OR 'follow up':ti,ab) OR (('medication compliance'/de OR comply:ti,ab OR compliance:ti,ab) AND ('polypharmacy'/de OR ((concurrent OR multiple OR adjuvant):ti AND (medication* OR drug* OR prescription* OR therap*)):ti)))
	#85	Monitoring: Prescription monitoring program, Pill counts. Limited amounts of pills per prescription (consider quantity of pills per prescription or refill), Monitoring frequency, monitoring instruments	'prescription drug monitoring program'/de OR 'prescription monitoring' OR 'prescription monitoring program'/de OR 'prescription monitoring program*' OR 'drug monitoring program*' OR "PDMP" OR "opioid refill*' OR (((dispense* OR prescri*) NEAR/3 (rate* OR refill*)):ti,ab) OR stewardship* OR (multiple AND provider*):ti,ab OR "doctor shopper*":ti,ab OR "opi* shop*":ti,ab
	#86		'electronic prescribing'/de OR 'electronic prescri*':ti,ab OR (day* NEXT/2 supply):ti,ab OR ((quantit* OR number) AND (tablet* OR pill* OR doses)):ti,ab OR 'pill count'/de OR 'pill count*':ti,ab OR (pill NEXT/3 count*)
	#87		((SOAPP OR STORM OR 'RIOSORD' OR PHQ-9 OR DAST-10 OR instrument* OR survey* OR question* OR frequen*):ti,ab AND (assess* OR monitor*)):ti,ab OR (('bi monthly' NEXT/2 visit*):ti,ab OR ((daily* OR weekly* OR periodic*) AND (monitor* OR communicat* OR telephone* OR phone OR call* OR check-in*)):ti OR 'interactive voice response'
	#88	Abuse deterrant formulations	'abuse deterrent formulation'/exp OR 'abuse deter*':ti,ab
	#89	Diversion prevention interventions (securing drug supply, medication take back, public health education)	'prescription drug diversion'/exp/mj OR ((drug* OR opi* OR prescription* OR medication*):ti,ab AND diversion:ti) OR 'medication take back' OR 'safe NEAR/2 dispos*' OR ((health:ti OR opi* OR drug*):ti AND ('education'/exp OR educat*:ti))
	#90	Pharmacogenetic testing	'pharmacogenetic testing'/de OR 'pharmacogenetics'/exp/mj OR 'pharmacogenetic test*':ti OR 'pharmacogenomic test*':ti OR 'cytochrome P450 2D6' OR 'CYP2D6' OR genotype* OR 'panel based test*' OR individual*:ti OR pharmacogenetic*:ti OR pharmacogenomic*:ti OR personaliz*:ti OR precision:ti
	#91	Random call-backs	callback* OR 'call back*'
	#92	Periodic check of state databases	('drug control'/exp OR (drug* OR opi*):ti,ab) AND (govern* OR legislat* OR regulat* OR insur* OR prescri*):ti,ab AND database*:ti,ab
	#93	Needle exchange programs	'needle exchange program'/de OR 'needle exchange*' OR 'syringe service*'
	#94	Monitoring for aberrant or high risk behaviors	(('drug abuse'/exp OR 'drug monitoring'/exp OR 'prescription drug misuse'/de) AND monitor*:ti) OR 'prescription drug monitoring program'/exp OR 'drug monitoring'/exp OR (((drug* OR prescription*):ti AND (addict* OR abuse OR dependen* OR misuse):ti AND monitor*:ti) OR diversion:ti OR ((risk* NEXT/5 (mitigate* OR reduc*)):ti) OR (('risk'/exp OR 'risk behavior' OR polysubstance) AND (assess* OR monitor*):ti) OR 'risk reduction'/exp OR 'risk evaluation and mitigation strategy'

KQ	Set #	Concept	Strategy
KQ 6 (cont.)	#95	Drug safety (opioids) general concept	('drug safety'/exp/mj OR 'adverse events':ti OR ((drug* NEXT/3 safe*) OR safe*:ti) AND ('opiate'/exp/mj OR opi:ti)
	#96	Combine interventions	#78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95
	#97	Combine interventions and population	#77 AND #97
KQ 7	#98	Population: Adults with chronic pain on prescribed opioids	#4 AND #9
	#99	Intervention: Tapering concepts: pharmacotherapy	'drug dose reduction'/de OR 'drug dose titration'/de OR 'drug dose escalation'/de OR ((drug OR drugs OR pharmacotherapy OR 'opiate'/de OR opi* OR medication*) AND (adjust* OR combin* OR decreas* OR escalat* OR chang* OR increas* OR lower* OR monotherap* OR multiple OR polypharm* OR reduc* OR regimen OR schedul* OR sequenc* OR single OR switch* OR taper* OR titrat* OR transition*):ti,ab)
	#100	Taper	(taper OR tapering OR tapered OR 'guided opioid taper*'):ti,ab
	#101	Non-pharma tapering assist – CIH, psychotherapies, behavioral health interventions	'drug dose reduction'/de OR 'detoxification'/exp OR taper*:ti,ab OR detox*:ti,ab OR 'medication assisted treatment' OR combin*:ti,ab OR wean*:ti,ab
	#102		('alternative medicine'/exp OR 'complementary integrat* health' OR ((alternat* OR complement* OR integrat*) NEXT/3 (approach* OR therap* OR interven* OR medic*)):ti,ab OR (complement* NEXT/3 integrat*):ti,ab
	#103		'psychotherapy'/exp OR 'behavior modification'/de OR 'behavior therapy'/exp OR 'patient education'/de OR (psychotherap* OR 'behav* health' OR 'health educat*' OR 'patient educat*' OR 'behav* modification' OR 'behav* therap*' OR 'behav* treatment*' OR (cognitive NEXT/2 (therap* OR treatment*))):ti,ab)
	#104		#101 AND (#102 OR #103)
	#105	Buprenorphine assisted taper	('buprenorphine'/exp/dd_ae,dd_ad,dd_cb,dd_do,dd_it OR buprenorphine:ti,ab) AND ('detoxification'/exp OR (detox* OR facilitate* OR 'medication assisted treatment' OR combin* OR taper* OR wean*):ti,ab) OR (buprenorphine NEAR/5 taper*)
	#106	Rapid detox (ketamine)	'detoxification'/exp OR (detox* OR 'medication assisted treatment' OR 'rapid detox' OR taper* OR wean*):ti,ab)
	#107		('ketamine'/de OR ketamine:ti,ab,tn) AND (detox* OR facilitate* OR 'rapid detox*' OR taper* OR wean*):ti,ab
	#108	Combine interventions	#99 OR #100 OR #104 OR #105 OR #106 OR #107
	#109	Combine population and interventions	#98 AND #108
KQ 8	#110	Population: Adults with acute pain and prescribed opioids	('pain'/exp OR pain*:ti OR (pain*:ti,ab AND (arthritis:ti,ab OR back:ti,ab OR bone:ti,ab OR disabilit*:ti,ab OR fibromyalgia:ti,ab OR injury:ti,ab OR joint*:ti,ab OR lupus:ti,ab OR musculoskelet*:ti,ab OR 'multiple sclerosis':ti,ab OR neurogenic:ti,ab OR neuropathic:ti,ab OR nociceptive:ti,ab OR osteoarthriti*:ti,ab OR radicular:ti,ab OR rheumatoid*:ti,ab OR skeletal:ti,ab OR surgical:ti,ab OR ((tissue NEXT/3 damage):ti,ab))) AND (acute OR emergen* OR exacerbat* OR injur* OR intermittent* OR short-term* OR 'short term' OR trauma*):ti,ab
	#111		#110 AND (#5 OR #6 OR #7 OR #8)

KQ	Set #	Concept	Strategy
KQ 8 (cont.)	#112	Chronic distress in daily life, societal issues, adverse childhood events, socio-environmental demographic factors Psychological factors, behavioral health conditions, emotional and personality factors Failed treatments Pain catastrophizing Pain severity Tissue damage Nociceptive vs. neuropathic vs. Central/Nociplastic High disability/ impairment rating Worker's compensation	'demographics'/de OR 'ethnic or racial aspects'/exp OR 'gender'/exp OR 'marriage'/exp OR 'sociodemographic factor'/de OR 'socioeconomics'/exp OR 'social problems'/exp OR (demographic* OR divorce* OR ethnic* OR gender OR homeless* OR 'marital status' OR unemploy* OR poverty OR stress* OR (childhood AND (advers* OR trauma* OR event*)) OR bullying OR displace* OR crisis OR crises OR socioenvironment* OR socio-environment* OR socioeconomic* OR sociodemographic* OR rural*):ti,ab OR (insecur* AND (food* OR housing OR shelter)):ti,ab
	#113		'anxiety disorder'/exp OR 'central sensitization'/de OR 'coping behavior'/exp OR 'depression'/exp OR 'fear avoidance'/de OR 'pain intensity'/de OR 'pain severity'/de OR 'posttraumatic stress disorder'/exp OR 'tissue injury'/de OR 'nociceptive pain'/de OR 'neuropathic pain'/de OR 'catastrophizing' OR ((social OR environment* OR emotional OR personality OR psych*) AND (condition* OR factor* OR comorbid*)):ti,ab OR (anxious OR anxiety OR depress* OR "PTSD" OR 'posttraumatic stress' OR 'combat stress' OR trauma*' OR 'fear avoid*' OR 'pain avoid*' OR cope OR coping OR distress OR stress OR stressor* OR 'failed treatment*' OR 'pain catastrophiz*' OR neuropath* OR nociceptive OR nociplastic OR (pain AND sever*)):ti,ab OR 'workman compensation'/de OR 'disability'/exp OR (disabilit* OR 'work* compensat*'):ti,ab
	#114	Drug abuse/addiction/ misuse	'opiate addiction'/de OR 'opioid use disorder'/de OR 'drug misuse'/de OR 'OUD' OR smoking OR smoker OR ((drug* OR opi* OR alcohol OR nicotine) AND (addict* OR abuse OR misuse OR disorder OR dependen*)):ti,ab OR (transition AND chronic* AND opi*):ti,ab
	#115	TBI	'traumatic brain injury'/de OR 'TBI' OR 'traumatic brain injur*':ti,ab
	#116	Combine Interventions	#112 OR #113 OR #114 OR #115
	#117	Combine Interventions AND Population	#111 AND #116
KQ 9	#118	Population: Adults with acute pain and opioids	('pain'/exp OR pain*:ti OR (pain*:ti,ab AND (arthritis:ti,ab OR back:ti,ab OR bone:ti,ab OR disabilit*:ti,ab OR fibromyalgia:ti,ab OR injury:ti,ab OR joint*:ti,ab OR lupus:ti,ab OR musculoskelet*:ti,ab OR 'multiple sclerosis':ti,ab OR neurogenic:ti,ab OR neuropathic:ti,ab OR nociceptive:ti,ab OR osteoarthriti*:ti,ab OR radicular:ti,ab OR rheumatoid*:ti,ab OR skeletal:ti,ab OR surgical:ti,ab OR ((tissue NEXT/3 damage):ti,ab))) AND (acute OR emergen* OR exacerbat* OR injur* OR intermittent* OR short-term* OR 'short term' OR trauma*):ti,ab
	#119		#118 AND (#5 OR #6 OR #7 OR #8)
	#120	Risk mitigation – general concept	'risk'/exp OR 'safe prescribing':ti,ab OR (risk* AND (evaluat* OR assess* OR limit* OR measur* OR minims* OR minimiz* OR mitigat* OR reduc* OR screen* OR stratif*)):ti,ab OR (opi*:ti AND mitigat*):ti,ab
	#121	Naloxone rescue	'naloxone'/de OR 'naloxone rescue':ti,ab OR (naloxone AND (dose* OR kit* OR rescue* OR prevent* OR reviv* OR revers*):ti,ab
	#122	Informed consent, written consent (contracts)	'contracts'/exp OR 'informed consent'/de OR (consent OR contract OR contracts OR agreement)):ti,ab
	#123	Risk assessment instruments	'risk assessment'/exp OR (risk*:ti,ab AND (instrument* OR survey* OR questionnaire* OR tool OR tools OR "ORT" OR "SOAPP" OR "SISAP" OR "DIRE" OR "PDUQ-p" OR "COMM" OR "PMQ" OR "PADT" OR "ABC" OR "CAGE" OR 'Stratification Tool for Opioid Risk Mitigation' OR "STORM" OR "RIOSORD") AND (assess* OR evaluat* OR screen* OR measur* OR factor*)):ti,ab

KQ	Set #	Concept	Strategy
KQ 9 (cont.)	#124	Patient education	'education'/exp OR 'education* program*':ti,ab OR 'health education':ti,ab OR 'opioid education':ti,ab OR ((train* OR educat*):ti AND (outpatient* OR patient*)):ti
	#125	Urine drug testing (UDT)	'urinalysis'/exp OR 'urine test strip'/exp OR (urin* NEXT/5 (screen* OR test* OR detect* OR analysis OR analyze OR monitor*)):ti,ab OR "UDT":ti,ab
	#126	Opioid management plans, case management, Compliance with other therapies	('opiate'/exp OR Opi*:ti) AND ('case management'/exp OR manag* OR casework OR 'case work' OR management OR plan OR plans OR strategy OR strategies OR 'medication assisted treatment' OR 'follow up' OR follow-up)
	#127		('opiate'/de OR opi*:ti) AND (('medication compliance'/de OR comply:ti,ab OR compliance:ti,ab) AND ('polypharmacy'/de OR (((concurrent OR multiple OR adjuvant) AND (medication* OR drug* OR prescription* OR therap*)):ti,ab)))
	#128	Monitoring Prescription Monitoring instruments	'prescription drug monitoring program'/de OR 'prescription monitoring' OR 'prescription monitoring program'/de OR 'prescription monitoring program*' OR 'drug monitoring program*' OR "PDMP" OR 'opioid refill*' OR ((dispens* OR prescrip*) NEAR/3 (rate* OR refill*)):ti,ab OR stewardship* OR (multiple AND provider*):ti,ab OR "doctor shopper*":ti,ab OR "opi* shop*":ti,ab
	#129		'electronic prescribing'/de OR 'electronic prescri*':ti,ab OR (day* NEXT/2 supply):ti,ab OR ((quantit* OR number) AND (tablet* OR pill* OR doses)):ti,ab OR 'pill count'/de OR 'pill count*':ti,ab OR pill NEXT/3 count*
	#130		((SOAPP OR STORM OR 'RIOSORD' OR PHQ-9 OR DAST-10 OR instrument* OR survey* OR question* OR frequen*):ti,ab AND (assess* OR monitor*)):ti,ab OR ('bi monthly' NEXT/2 visit*):ti,ab OR ((daily* OR weekly* OR periodic*) AND (monitor* OR communicat* OR telephone* OR phone OR call* OR check-in*)):ti,ab OR 'interactive voice response'
	#131	Abuse deterrant formulations	'abuse deterrent formulation'/exp OR 'abuse deter*':ti,ab
	#132	Diversion prevention interventions (securing drug supply, medication take back, public health education)	'prescription drug diversion'/exp OR ((drug* OR opi* OR prescription* OR medication*) AND diversion):ti,ab OR 'medication take back' OR 'safe NEAR/2 dispos*' OR 'education'/exp OR 'education program' OR 'health education' OR 'opioid education' OR educat*:ti,ab
	#133	Pharmacogenetic testing	'pharmacogenetic test*' OR 'pharmacogenetics' OR 'pharmacogenomic test*' OR 'cytochrome P450 2D6' OR 'CYP2D6' OR genotype* OR 'panel based test*' OR (individuali* OR pharmacogenetic* OR pharmacogenomic* OR personalis* OR personaliz* OR precision):ti
	#134	Random call-backs	call-back* OR callback*
	#135	Drug safety (opioids) general concept	('drug safety'/exp/mj OR 'adverse event*' OR (drug* NEXT/3 safe*) OR safe*:ti) AND ('opiate'/exp OR opi:ti,ab,kw)
	#136	Periodic check of state databases	('drug control'/exp OR (drug* OR opi*):ti,ab) AND (govern* OR legislat* OR regulat* OR insur* OR prescri*):ti,ab AND database*:ti,ab
	#137	Needle exchange programs	'needle exchange program'/de OR 'needle exchange*' OR 'syringe service*'
	#138	Monitoring for aberrant or high risk behaviors	'drug monitoring'/exp OR (monitor* AND (drug abuse'/exp OR 'prescription drug misuse'/de OR (drug* AND (addict* OR abuse OR depend* OR misuse OR diversion) OR (risk* NEXT/5 (mitigat* OR reduc*))) OR 'risk'/exp OR 'risk reduction'/exp OR 'risk evaluation and mitigation strategy' OR 'risk behavior' OR polysubstance

KQ	Set #	Concept	Strategy
KQ 9 (cont.)	#139	Combine interventions	#120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129 OR #130 OR #131 OR #132 OR #133 OR #134 OR #135 OR #136 OR #137 OR #138
	#140	Combine population (acute) and interventions	#119 AND #139
KQ 10	#141	Population: Adults with chronic pain on prescribed opioids	(#1 OR #2 OR #3) AND #9
	#142	Disease severity, Prognosis	'disease severity'/exp OR 'disease severity assessment'/exp OR 'disease course'/exp OR 'prognosis'/exp OR 'pain severity'/de OR 'pain intensity'/de OR 'opioid induced hyperalgesia'/de OR ((disease OR pain*):ti,ab AND (deteriorat* OR decreas* OR improve* OR outcome* OR prognos* OR sever* OR reduc*OR worse*):ti,ab)
	#143	Prescribed Opioids, dosage, regimen, formulation	'drug formulation'/exp OR 'controlled release formulation'/exp OR 'extended release formulation'/de OR 'immediate release formulation'/exp OR 'short acting analgesic agent'/de OR ((drug* OR medic* OR pharma*):ti,ab AND (control* OR extend* OR formula* OR immediate* OR long* OR short* OR sustain* OR acting OR release*):ti,ab AND (opi*:ti OR 'opiate'/exp)) OR 'drug dose'/exp OR 'drug dosage form'/exp OR 'drug therapy'/exp OR (((drug* NEXT/3 therap*) OR (drug* NEAR/3 dos*) OR (drug* NEAR/5 regimen*) OR (drug* NEAR/5 deliver*)) AND ((schedule* OR regimen* OR sequence OR cycle* OR formula* OR route OR tablet* OR tab* OR cap* OR intravenous* OR lozenge* OR 'oral concentrate' OR 'oral solution' OR intramuscular OR subcutaneous OR 'by mouth' OR insufflation OR inhalation OR rectal OR spray OR epidural OR intrathecal):ti,ab))
	#144	Combine	#141 AND (#142 OR #143)
KQ 11	#145	Population: Adults with chronic pain on prescribed opioids	#4 AND #9
	#146	Screening tools	'risk assessment'/exp OR 'screening tool of older person prescription*' OR 'screening tool to alert doctors to right treatment' OR 'Systematic Tool to Reduce Inappropriate Prescribing' OR (risk*:ti,ab AND (ORT OR SOAPP OR SISAP OR DIRE OR PDUQ-p OR COMM OR PMQ OR PADT OR ABC OR CAGE OR 'Stratification Tool for Opioid Risk Mitigation' OR STORM OR RIOSORD)) OR (assess* OR evaluat* OR instrument* OR screen* OR measure* OR factor* OR score*):ti,ab) OR 'beers criteria' OR 'screening test*' OR 'screening tool*' OR ((start OR stopp) NEXT/3 criteria) OR 'stopp NEXT/2 start' OR (stopp AND screening) OR (start AND 'screening tool' AND alert) OR 'stopp/start'
	#147	Predictive analytics	'clinical decision support system'/de OR 'clinical decision support' OR 'decision support' OR 'prediction of risk' OR 'predictive analytics' OR 'predictive model' OR (predict*:ti,ab AND (mortality OR risk*)) OR 'risk score*'
	#148	Disease management, Adverse outcomes	'inappropriate prescribing'/exp OR 'potentially inappropriate medication'/de OR 'appropriateness of medication prescribing' OR ((appropriate OR inappropriate) AND (drug OR drugs OR medic* OR pharma* OR polypharmacy OR prescribing OR prescription*)):ti,ab,kw OR misprescrib*:ti,ab OR overprescrib* OR underpresrib*:ti,ab OR 'prescribing omission*'

KQ	Set #	Concept	Strategy
KQ 11 (cont.)	#149	Screening for risk factors, comorbidity, polypharmacy	'comorbidity'/de OR 'mulitple chronic conditions'/exp OR 'polypharmacy'/exp OR 'social behavior'/exp OR 'anxiety disorder'/exp 'catastrophizing'/de OR 'depression'/exp OR ('risk factor*' OR comorbidit* OR co-morbidit* OR co-occuring OR multimorbidit* OR impuls* OR suicid* OR depression OR bipolar OR anxiety OR anxious* OR stress OR catastrophizing OR (social NEXT/5 (behavio* OR functioning)) OR ((drug* OR medic* OR pharma* OR prescrib* OR prescription* OR treatment) AND (criteria OR review)):ti,ab
	#150	Combine interventions	(#146 OR #147) AND (#148 OR #149)
	#151	Combine interventions and population	#145 AND #150
KQ 12	#152	Population: Adults with OUD and chronic pain on prescribed opioids	#4 AND #9 AND ('opiate addiction'/exp OR 'opioid use disorder'/exp OR 'analgesic agent abuse'/exp OR (('drug abuse'/exp OR 'drug dependence'/exp OR 'narcotic dependence'/exp OR 'addiction'/exp OR 'withdrawal syndrome'/exp OR 'treatment withdrawal'/exp/mj OR 'drug withdrawal'/exp/mj) AND ('narcotic analgesic agent'/exp/mj OR opi*:ti)) OR (((analgesic* OR codeine OR fentanyl OR heroin OR hydrocodone OR methadone OR morphine OR narcotic* OR opiate* OR opioid* OR opium OR oxycodone OR oxycontin OR percocet) NEAR/3 (abuse OR addict* OR dependen* OR disorder* OR withdraw* OR detoxif*)):ti,ab))
	#153	Methadone	'methadone'/de OR methadone
	#154	Buprenorphine	'buprenorphine'/de OR buprenorphine OR suboxone OR 'buprenorphine naloxone' OR subutex OR subsolv OR sublocade
	#155	Naltrexone	'naltrexone'/de OR naltrexone OR vivitrol
	#156	Combine interventions	#153 OR #154 OR #155
	#157	Combine interventions and population	#152 AND #156

KQ	Set #	Concept	Strategy
Apply hedges and limits	#158	Combine final sets	#22 OR #30 OR #51 OR #61 OR #76 OR #97 OR #109 OR #117 OR #140 OR #144 OR #151 OR #157
	#159	Apply limits, remove unwanted publications types, limit to randomized controlled trials or systematic reviews or meta-analyses	#158 AND ('meta analysis'/exp OR 'systematic review'/de OR [cochrane review]/lim OR systematic*:ti OR (cochrane OR metaanaly* OR "meta analy*" OR (search* AND (databases OR electronic OR methodolog* OR embase* OR ebsco* OR medline* OR ovid* OR sciencedirect* OR scopus* OR systematic OR web)) OR (systematic* NEAR/2 review*)):ti,ab)
	#160		#158 AND ('random sample'/de OR 'randomized controlled trial'/de OR randomization/de OR (random* OR RCT):ti,ab)
	#161		#159 OR #160
	#162		#161 NOT ('conference paper'/exp OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR ('case report' OR book OR editorial OR erratum OR letter OR note OR 'short survey')/de OR (book OR conference OR editorial OR erratum OR letter OR note OR 'short survey'):it OR ('a case' OR 'year old'):ti,ab OR (book OR 'conference proceeding'):pt OR ('case report' OR comment OR ((rationale OR study) NEAR/3 protocol)):ti)
	#163		#162 NOT (([animals]/lim NOT [humans]/lim) OR (animal* OR experimental OR (vitro NOT vivo) OR canine OR dog OR dogs OR mouse OR mice OR murine:ti OR pig OR pigs OR piglet* OR porcine OR rabbit* OR rat OR rats OR rodent* OR sheep OR swine):ti)
	#164		#163 NOT ((adolescen* OR baby OR babies OR boys OR child* OR girls OR infancy OR infant* OR juvenile* OR neonat* OR newborn* OR NICU OR nurser* OR paediatric* OR pediatric* OR preschool* OR school OR schools OR teen* OR toddler* OR youth*) NOT (adult* OR women OR woman OR pregnan*)):ti
	#165		#164 AND [English]/lim AND [2015-2021]/py
	#166		#165 AND [1-12-2015]/sd NOT [XX-03-2021]/sd [NOTE: final date entered range to be completed when full searches are run]

B. PsycINFO in Ovid Syntax (all KQs)

Set #	Concept	Strategy
#1	Prescribed opioids	Exp opiates/ OR opiate*.ti. OR opioid*.ti.
#2		exp analgesic drugs/ or exp analgesia/ or exp anesthetic drugs/ or exp anti inflammatory drugs/ or exp cns depressant drugs/ or exp hypnotic drugs/ or exp narcotic drugs/ or exp pain/ or exp sedatives/
#3		#1 OR #2
#4	Pain – chronic	Exp chronic pain/
#5	Pain – chronic or acute	(Exp pain/ OR pain*.ti.) AND (chronic or long-term or 'long term' or refractory or intractable or weeks or months or year* or '90 days' or '60 days' or '30 days' or acute or emergen* or injur* or trauma).ti,ab.
#6		#4 OR #5
#7	Combine opioids and pain	#3 AND #6
#8	Final set – pain; pain and opioids	#6 OR #7
#9		#8 NOT ((baby OR babies OR boys OR child* OR girls OR infancy OR infant* OR juvenile* OR neonat* OR newborn* OR NICU OR nurser* OR paediatric* OR pediatric* OR preschool* OR school OR schools OR toddler* OR youth*) NOT (adult* OR women OR woman OR pregnan* OR adolescen* OR teen*)).ti.
#10		#9 NOT ((chapter OR "column/opinion" OR "comment/reply" OR dissertation OR editorial OR letter OR review-book).dt. OR (book or encyclopedia OR "dissertation abstract").pt. OR ("case report" OR "a case" OR "year old").ti,ab. OR ((rationale OR study) ADJ3 protocol).ti.)
#11		#10 NOT (animal* OR experimental OR (vitro NOT vivo) OR canine OR dog OR dogs OR mouse OR mice OR murine OR pig OR pigs OR piglet* OR porcine OR rabbit* OR rat OR rats OR rodent* OR sheep OR swine).ti.
#12		#11 AND (meta analysis/ or ("meta analysis" or "meta analytic" or metaanaly* or pooled or pooling or RCTs or "research synthesis" or search* or (systematic adj3 review)).ti,ab. or ("critical review" or "evidence based" or systematic).ti. or cochrane.jw.)
#13		#11 AND (systematic review/ OR systematic.ti. OR (cochrane OR "meta analy*" OR metaanaly* OR (search* AND (databases OR electronic OR methodolog* OR embase* OR ebsco* OR medline* OR ovid* OR sciencedirect* OR scopus* OR systematic OR web)) OR (systematic ADJ3 review)).ti,ab.)
#14		#11 AND random sampling/ OR (random* OR rct).ti,ab.
#15		#11 AND (exp Cohort Analysis/ or exp longitudinal studies/ or exp prospective studies/ or exp clinical trials/ or exp treatment outcomes/ OR ('between groups' or 'case control*' or cohort* or comparison* OR comparative or 'control group*' or 'controlled study' or 'controlled trial' or 'cross over' or crossover or 'double blind' or 'double blinded' or longitudinal or 'matched controls' or (observational adj3 study) or placebo* or prospective or retrospective OR random* or sham).ti,ab. or (versus or vs).ti.)
#16	Combine	#12 OR #13 OR #14 OR #15
#17	Remove PubMed records	#16 NOT (1* or 2* or 3* or 4* or 5* or 6* or 7* or 8* or 9*).pm.
#18	Limit	Limit #17 to yr="2015-2021"
#19	Limit	Limit #18 to English language

Appendix J: Alternative Text Descriptions of Algorithm

The following outline narratively describes the Use of Opioids in the Management of Chronic Pain algorithm. An explanation of the purpose of the algorithm and description of the various shapes used within the algorithm can be found in the Algorithm section. The sidebars referenced within this outline can also be found in the Algorithm section.

A. Module A: Determination of Appropriateness for Opioids for Chronic Pain

1. **Module A** begins with Box 1, in the shape of a rounded rectangle: "Patient with chronic pain"
2. Box 1 connects to Box 2, in the shape of a rectangle: "Obtain pain and biopsychosocial assessment (see **Sidebar A**)"
3. Box 2 connects to Box 3, in the shape of a hexagon, and asks the question: "Is the patient currently on opioids for chronic pain?"
    a. If the answer is "Yes" to Box 3, then continue to Box 4, in the shape of an oval: "Go to **Module C**"
4. If the answer is "No" to Box 3, then continue to Box 5, in the shape of a rectangle: "Educate/re-educate on, implement, and optimize non-opioid treatments for chronic pain (see **Sidebar B**), including:
    - Self-management to promote health and wellness
    - Non-opioid pharmacologic management
    - Non-pharmacologic pain treatments:
        - Behavioral therapies (e.g., cognitive behavioral therapy)
        - Physical/movement-based therapies (e.g., physical therapy)
        - Manipulative therapies (e.g., chiropractic care)
        - Complementary and integrative health treatments (e.g., acupuncture)
    - Interventional pain care (e.g., joint injection, radiofrequency ablation)
    - Realistic expectations and limitations of medical treatment
    - Refer to the LBP, OA, and Headache CPGs as appropriate for further condition-specific guidance"; VA/DoD CPGs are available here: https://www.healthquality.va.gov/
5. Box 5 connects to Box 6, in the shape of a hexagon, and asks the question: "After regular follow-up and treatment optimization, has the treatment plan been effective in managing pain and optimizing function?"
    a. If the answer is "Yes" to Box 6, then continue to Box 17, in the shape of a rectangle: "Exit algorithm; manage with non-opioid modalities"
6. If the answer is "No" to Box 6, then continue to Box 7, in the shape of a rectangle: "Complete opioid risk assessment; refer for interdisciplinary pain and specialty consultations, as appropriate (see **Sidebar C**)"

7. Box 7 connects to Box 8, in the shape of a hexagon, and asks the question: "Do potential benefits outweigh risks? Consider strength and number of risk factors and patient preferences (see **Sidebar C**)"
    a. If the answer is "No" to Box 8, then continue to Box 17, in the shape of a rectangle: "Exit algorithm; manage with non-opioid modalities"
8. If the answer is "Yes" to Box 8, then continue to Box 9, in the shape of a rectangle: "Refer/consult for appropriate interdisciplinary treatments"
9. Box 9 connects to Box 10, in the shape of a hexagon, and asks the question: "Is the patient able and willing to engage in a comprehensive pain care plan?"
    a. If the answer is "No" to Box 10, then continue to Box 17, in the shape of a rectangle: "Exit algorithm; manage with non-opioid modalities"
10. If the answer is "Yes" to Box 10, then continue to Box 11, in the shape of a rectangle: "Educate patient and family about treatment options, including education on:
    - Known risks and unknown long-term benefits of opioids
    - Risks of SUD and overdose
    - Need for risk mitigation strategies
    - Naloxone rescue"
11. Box 11 connects to Box 12, in the shape of a hexagon, and asks the question: "Is adding opioids to comprehensive pain therapy indicated at this time? (see **Sidebar D**)"
    a. If the answer is "No" to Box 12, then continue to Box 17, in the shape of a rectangle: "Exit algorithm; manage with non-opioid modalities"
12. If the answer is "Yes" to Box 12, then Box 13, in the shape of a hexagon, asks the question: "Is patient prepared to accept responsibilities of and is provider prepared to implement risk mitigation strategies?"
    a. If the answer is "No" to Box 13, then continue to Box 17, in the shape of a rectangle: "Exit algorithm; manage with non-opioid modalities"
13. If the answer is "Yes" to Box 13, then continue to Box 14, in the shape of a rectangle: "Discuss and complete written informed consent with patient and family"
14. Box 14 connects to Box 15, in the shape of a rectangle: "Modify and document comprehensive pain management plan including opioids"
15. Box 15 connects to Box 16, in the shape of an oval: "Go to **Module B**"

B. Module B: Initiation of Treatment with Opioids

1. **Module B** begins with Box 18 in the shape of a rounded rectangle: "Candidate for opioids with consent (begin a trial in conjunction with comprehensive pain care plan"
2. Box 18 connects to Box 19, in the shape of a rectangle:
   "Initiate opioids using the following approach:
   - Use short duration (e.g., 1-week prescription)
   - Plan to reevaluate at 30 days or fewer
   - Use lowest effective dose, recognizing that no dose is completely safe
     - A strategy of escalating dose to achieve benefit increases risk (see **Sidebar L**) and has not been shown to improve function
   - Long-acting opioids should not be prescribed for opioid-naïve individuals (see **Recommendation 11** and **Appendix D**)
   - Consider alternatives to methadone and transdermal fentanyl (see **Appendix D**)
   - Assess improvement in pain and functional status and adverse effects
   - Complete risk mitigation strategies (see **Sidebar E**)
   - Provide medication and overdose education, offer naloxone prescription"
3. Box 19 connects to Box 20, in the shape of a rectangle:
   "Reevaluation as needed clinically and based on patient risk factors (e.g., 1-4 weeks after initiation of opioids, not later than 30 days)
   - Assess:
     - Function, pain, risks, and benefits of opioids
     - Adverse effects
     - Adherence to treatment plan
     - Complications or co-occurring conditions (e.g., medical, behavioral health, and/or SUD)
     - Patient preference
   - Complete risk mitigation strategies (see **Sidebar E**)
   - Review and optimize comprehensive pain care plan (e.g., non-opioid treatments, self-management strategies)"
4. Box 20 connects to Box 21, in the shape of a hexagon, and asks the question: "Does the patient want to continue opioid therapy?"
   a. If the answer is "No" to Box 21, then continue to Box 22, in the shape of a rectangle: "Taper to discontinuation (consult **Module C** if needed). Manage with non-opioid modalities."

5. If the answer is "Yes" to Box 21, then Box 23, in the shape of a hexagon, asks the question: "Is there clinically meaningful improvement in function and pain that outweighs risks?"
    a. If the answer is "No" to Box 23, then continue to Box 22.
6. If the answer is "Yes" to Box 23, then Box 24, in the shape of a hexagon, asks the question: "Is the patent sufficiently medically and behaviorally stable to continue opioid medication?"
    a. If the answer is "No" to Box 24, then continue to Box 25, in the shape of a rectangle: "Provide medical and/or behavioral health treatment to stabilize as indicated; consider tapering opioids to discontinuation (consult **Module C**)"
7. If the answer is "Yes" to Box 24, then Box 26, in the shape of a hexagon, asks the question: "Are there factors that increase risks of opioids (e.g., non-adherence, co-occurring conditions, indications of OUD)"
    a. If the answer is "No" to Box 26, then continue to Box 28, in the shape of a rectangle: "Reassess in 1-3 months or more frequently as determined by patient risk factors (see **Sidebar G**)". This connects back to Box 20.
8. If the answer is "Yes" to Box 26, then continue to Box 27, in the shape of a rectangle: "Consider one or more of the following:
    - Shortening prescribing interval
    - Intensifying risk mitigation strategies (see **Sidebar E**)
    - Referring to interdisciplinary care
    - Consulting with or referring to specialty care
    - Switching to partial agonist opioids
    - See VA/DoD SUD CPG if there are indications of OUD"; VA/DoD SUD CPG is available here: https://www.healthquality.va.gov/
9. Box 27 connects to Box 29, in the shape of a hexagon, and asks the question: "Are there indications to discontinue or taper? (see **Sidebar F**)"
    a. If the answer is "No" to Box 29, then continue to Box 28.
10. If the answer is "Yes" to Box 29, then continue to Box 30, in the shape of an oval: "Taper to reduced dose or taper to discontinuation; proceed to **Module C**"

C. Module C: Maintaining, Tapering, Discontinuing, or Switching from Full agonist Opioids

1. **Module C** begins with Box 31 in the shape of a rounded rectangle: "Indication to maintain, taper, discontinue, or switch from full agonist opioids (see **Sidebars H** and **I**)"
2. Box 31 connects to Box 32, in the shape of a rectangle: "Repeat comprehensive biopsychosocial assessment (see **Sidebars A** and **C**)"

3. Box 32 connects to Box 33, in the shape of a hexagon, and asks the question: "Does the patient demonstrate signs or symptoms of SUD? (VA/DoD SUD CPG is available here: https://www.healthquality.va.gov/)"
    a. If the answer is "Yes" to Box 33, then continue to Box 34, in the shape of a rectangle:
        - "Initiate or refer to SUD treatment with appropriate monitoring and follow-up (e.g., MOUD, treatment for comorbidities) (VA/DoD SUD CPG is available here: https://www.healthquality.va.gov/)"
        - Consider switch to partial agonist opioids or taper opioids to discontinuation (see **Sidebar J**)
        - Manage with non-opioid modalities (see **Sidebar B**)
        - Exit algorithm"
4. If the answer is "No" to Box 33, then Box 35, in the shape of a hexagon, asks the question: "Is there evidence of diversion (according to the CDC, drug diversion is when prescription medicines are obtained or used illegally)?"
    a. If the answer is "Yes" to Box 35, then continue to Box 36, in the shape of a rectangle:
        - "Address safety and misuse
        - Assess for elevated suicide risk
        - Assess for withdrawal symptoms and offer expedited taper, immediate discontinuation, or medically-assisted withdrawal as indicated
        - Continue to monitor for SUD and behavioral health comorbidities and offer treatment as indicated (VA/DoD SUD CPG is available here: https://www.healthquality.va.gov/ and Academic Detailing Tapering Document)
        - Consider switch to partial agonist opioids or taper opioids to discontinuation (see **Sidebar J**)
        - Manage with non-opioid modalities (see **Sidebar B**)
        - Exit algorithm"
5. If the answer is "No" to Box 35, then Box 37, in the shape of a hexagon, asks the question: "Is there high risk or dangerous behavior (e.g., intentional/self-harm overdose event, accidents, threatening provider)?"
    a. If the answer is "Yes" to Box 37, then continue to Box 36.
6. If the answer is "No" to Box 37, then continue to Box 38, in the shape of a rectangle: "Develop individualized treatment plan (including pace of tapering if applicable and setting of care) based on patient and treatment characteristics (see **Sidebar J** and **Recommendations 12** and **13**)"

7. Box 38 connects to Box 39, in the shape of a rectangle:
    - "Follow-up as clinically indicated after each change in dosage and after discontinuation, considering patient and treatment characteristics.
    - Consider the following at each interaction with patient:
        - Educate on self-management and risks of opioids (see **Sidebar K**)
        - Optimize whole person approach to pain care
        - Optimize treatment of co-occurring behavioral health conditions
        - Optimize non-opioid pain treatment modalities
        - Reassess for OUD and readiness for OUD treatment as indicated
    - If continuing treatment with opioids, use the following approach:
        - Shortest duration
        - Use lowest effective dose (recognizing that no dose is completely safe and overdose risk increases at doses >20 – 50 mg MEDD) (see **Sidebar L**)
        - Continual assessment of improvement in pain and functional status and adverse effects"
8. Box 39 connects to Box 40, in the shape of a hexagon, and asks the question:
   "Are one of the following present?
    - Patient resistance to taper
    - High risk or dangerous behaviors (including elevated risk of suicide)
    - Increase in patient distress"
9. If the answer is "No" to Box 40, then continue to Box 39.
10. If the answer is "Yes" to Box 40, then continue to Box 32.

Appendix K: Abbreviations

Abbreviation	Definition
ABC	addiction behavior checklist
ACP	attention control psychoeducation
ADSM	active duty Service Member
AE	adverse event
AUD	alcohol use disorder
BMI-MTM	Brief Motivational Intervention-Medication Therapy Management
CDC	The Centers for Disease Control and Prevention
CCMI	collaborative care motivational interviewing
CNCP	chronic non-cancer pain
CNS	central nervous system
COI	conflicts of interest
COMM	Current Opioid Misuse Measure
CPG	Clinical Practice Guideline
C-SSRS	Columbia-Suicide Severity Rating Scale
DoD	Department of Defense
EBPWG	Evidence-Based Practice Work Group
EVP	Empower Veterans Program
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HBRS	Health Related Behaviors Survey
IASP	International Association for the Study of Pain
KQ	key question
MEDD	morphine equivalent daily dose
MHS	Military Health System
MME	morphine milligrams equivalent
MOUD	medications for opioid use disorder
NAM	National Academy of Medicine
NICE	National Institute for Health and Care Excellence
NSAID	nonsteroidal anti-inflammatory drugs
OSI	Opioid Safety Initiative
OUD	opioid use disorder
PCP	primary care provider
PDMP	prescription drug monitoring program
PICOT	population, intervention, comparison, outcome, timing, and setting
PRN	as-needed
PTSD	posttraumatic stress disorder
QoL	quality of life
RCT	randomized controlled trial
SR	systematic review

Abbreviation	Definition
SUD	substance use disorder(s)
TDS	transdermal delivery system
UDT	urine drug testing
U.S.	United States
USPSTF	U.S. Preventive Services Task Force
VA	Department of Veterans Affairs
VHA	Veterans Health Administration

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