AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

Opioids

Effective December 12, 2023

1. SUMMARY OF RECOMMENDATIONS

The following summary table contains recommendations for the treatment of patients with opioids from the ACOEM Evidence-based Practice Opioids Panel. These recommendations are based on critically appraised higher-quality research evidence or, when such evidence was unavailable or inconsistent, on expert consensus as described in ACOEM's Methodology. The panel reached at least 80% agreement on these recommendations.

The reader is cautioned to use the more detailed indications, specific diagnoses, temporal sequencing, prior testing or treatment, and contraindications that are elaborated in more detail in the body of this guideline when using these recommendations in clinical practice or medical management. These recommendations are not simple "yes/no" criteria, and the evidence supporting them is in nearly all circumstances developed from typical patients, not unusual situations or exceptions.

Recommendations are made under the following categories:

- Strongly Recommended, "A" Level
- Moderately Recommended, "B" Level
- Recommended, "C" Level
- Insufficient – Recommended (Consensus-based), "I" Level
- Insufficient – No Recommendation (Consensus-based), "I" Level
- Insufficient – Not Recommended (Consensus-based), "I" Level
- Not Recommended, "C" Level
- Moderately Not Recommended, "B" Level
- Strongly Not Recommended, "A" Level

Category	Recommendation	Evidence
History and Physical Evaluation	Conducting Comprehensive History and Physical Evaluation Prior to Prescribing Opioids	Recommended, Insufficient Evidence (I)
Safety-Critical Jobs	Use of Opioids by Workers in Safety-Critical Jobs	Not Recommended, Evidence (C)
Acute Pain *(up to 4 weeks)*	Routine Use of Opioids for Treatment of Non-severe Acute Pain	Strongly Not Recommended, Evidence (A)
	Opioids for Treatment of Acute, Severe Pain	Recommended, Evidence (C)
	Initial Screening of Patients Prior to Initiation of Opioids	Recommended, Insufficient Evidence (I)

Category	Recommendation	Evidence
	Maximum Daily Oral Opioid Doses for Patients in Acute Pain	Recommended, Evidence (C)
Postoperative Pain *(up to 4 weeks; after 4 weeks, see subacute pain)*	Limited Use of Opioids for Postoperative Pain	Moderately Recommended, Evidence (B)
	Screening Among Surgical Patients Prior to Opioid Initiation	Recommended, Insufficient Evidence (I)
	Maximum Daily Oral Opioid Dose for Postoperative Pain	No Recommendation, Insufficient Evidence (I)
Subacute *(1-3 Months)* **and Chronic Pain** *(>3 Months)*	Opioid Prescriptions for Subacute and Chronic Nonmalignant Pain	Moderately Not Recommended, Evidence (B)
	Opioid Trial for Subacute or Chronic Severe Pain	Recommended, Insufficient Evidence (I)
	Screening Patients Prior to Initiation of Opioids	Recommended, Evidence (C)
	Maximum Daily Oral Opioid Dose for Patients with Subacute and Chronic Pain	Recommended, Evidence (C)
	Opioid Rotation	Recommended, Insufficient Evidence (I)
Diagnostics and Monitoring	Use of an Opioid Treatment Agreement (Opioid Contract, Doctor/Patient Agreement, Informed Consent)	Recommended, Insufficient Evidence (I)
	Urine Drug Testing for Patients Prescribed Opioids	Recommended, Evidence (C)
	Screening Tools to Identify Risk for Aberrant Drug-Related Behaviors	No Recommendation, Insufficient Evidence (I)
Discontinuation and Tapering	Discontinuation and Tapering of Opioids	Recommended, Evidence (C)
Treatment of Dependency and Opioid Use Disorder	Medications for Opioid Use Disorder	Moderately Recommended, Evidence (B)
	Buprenorphine for Opioid Tapering	Recommended, Insufficient Evidence (I)
	Methadone for Opioid Tapering	Recommended, Insufficient Evidence (I)
	Lofexidine for Opioid Withdrawal Symptoms	Moderately Recommended, Evidence (B)
	Clonidine for Opioid Withdrawal Symptoms	Recommended, Evidence (C)
	Naltrexone for Treatment of Opioid Use Disorder	Moderately Recommended, Evidence (B)
	Cognitive Behavioral Therapy for Aberrant Drug-Related Behavior	Recommended, Evidence (C)
Breakthrough Pain	Opioids for Breakthrough Nonmalignant Pain	Not Recommended, Insufficient Evidence (I)
Intrathecal Drugs *("pain pumps")*	Intrathecal Drug Delivery Systems for Chronic Nonmalignant Pain Conditions	Not Recommended, Insufficient Evidence (I)
Prevention of Overdose Fatalities	Naloxone (Narcan) for Opioid Overdose	Recommended, Insufficient Evidence (I)

Category	Recommendation	Evidence
Guideline Usage	Adherence to Opioid Guidelines	Recommended, Insufficient Evidence (I)
Antiemetics	Antiemetics for Opioid Use	See the ACOEM Antiemetics Guideline

2. WORKFLOW

Opioid Use for Chronic Pain

3. INTRODUCTION

The ACOEM Opioids Guideline is designed to provide healthcare providers (who are the primary target users of this guideline) with evidence-based guidance on the use of opioids for the treatment of working-age adults with acute, subacute, chronic, or post-operative nociceptive pain. While the primary patient population target is working adults, it is recognized that this guidance may apply more broadly. This guideline does not address pain associated with malignancy, although the U.S. Food and Drug Administration (25) has recognized that there does not appear to be evidence that cancer-related, non-terminal pain should be treated differently. This guideline also does not include detailed guidance on treatment of substance use disorders, and readers are referred to other sources for that information (26-29). Pain has been defined as an "unpleasant sensory and emotional experience" (30) and has been traditionally thought of as associated with tissue damage, although it may also occur due to central nervous system (CNS) and psychological causes.

Topics in this guideline include evaluations of the following: baseline patient evaluation, comparative effectiveness of opioids, indications for use, informed consent, opioid treatment agreements, benefits, harms and adverse effects, dose escalation, dose limits, mortality, risk factors, screening tools, drug screening and monitoring, intrathecal pumps, tapering and safety in working populations. This guideline does not address comprehensive pain management, including pharmacological and nonpharmacological methods for patients. Instead, those are addressed by disorder in other ACOEM Practice Guidelines. It is recognized that there are differences in workers' compensation systems (31). There also are regional differences in treatment approaches (32-35). The Evidence-based Practice Opioids Panel and the Research Team have complete editorial independence from the American College of Occupational and Environmental Medicine (ACOEM) and MDGuidelines, neither of which have influenced the guideline. The guideline is planned to be updated at least every five years or more frequently should evidence require it, as described in the ACOEM Methodology. The health questions for acute, subacute, chronic, and post-operative pain addressed by this guideline are:

- What evidence supports the need for a history and physical before prescribing opioids?
- Are opioids superior to other medications or other treatments for pain relief and functional improvement?
- What evidence supports use of these medications in safety-critical jobs?
- Is screening for risk factors effective for reducing adverse effects of treatment from opioids?
- What is the dose-response relationship between morphine-equivalent dose and fatalities, overdoses and other adverse effects?
- What evidence addresses the balance of risk and benefits of opioid use for acute, subacute, chronic and post-operative pain?

- What evidence supports the use of opioids for treatment of acute, subacute, chronic and post-operative non-malignant pain?
- Are opioid treatment agreements (opioid contract, doctor/patient agreement, or informed consent) effective?
- Should urine drug testing be performed for patients using opioids in the treatment of chronic pain?
- What evidence supports the use of intrathecal drug delivery systems for the treatment of chronic, non-malignant pain?
- What tapering regimens are effective for weaning off opioids?
- What methods are effective for long-term treatment of those with prior opioid use disorder?

A detailed methodology document used for guideline development including evidence selection, scoring, incorporation of cost considerations (36), and formulation of recommendations is available online as a full-length document (ACOEM Methodology) and also summarized (37-38). This guideline includes many large epidemiological studies for evidence of harms used for guidance. All evidence in the prior opioid guidelines (39-49) from 7 databases searched was included in this Guideline (Medline, EBM Online, Cochrane, TRIP, CINAHL, EMBASE, PEDro). There was no limit on year of publication. Search terms are listed with each table of evidence. A more detailed search strategy is available in ACOEM's Methodology.

Guidance is developed with sufficient detail to facilitate assessment of compliance per the Institute of Medicine (IOM) and auditing/monitoring per the Appraisal of Guidelines for Research and Evaluation (AGREE) (36, 50, 51). Alternative options to manage conditions are provided succinctly below when comparative trials are available, however, alternative management strategies are provided in greater detail in other ACOEM guidelines.

This guideline has undergone extensive external peer review. All AGREE (52), IOM (53), AMSTAR, and GRADE criteria were adhered to. In accordance with the IOM's Trustworthy Guidelines, detailed records are kept, including responses to external peer reviewers (50).

3.1. BASIC PRINCIPLES AND DEFINITIONS

Aberrant Drug Behaviors: Departure from strict adherence to the prescribed therapeutic plan of care. These behaviors range from self-escalation of dose, using medication for purposes other than prescribed, stockpiling, and overt diversion (52,54).

Aberrant Drug Use: Drug use including any of the behaviors listed above.

Acute pain: Acute pain is the normal, predicted, physiological response to an adverse chemical, thermal, or mechanical stimulus associated with surgery, trauma, and/or acute illness. For the purposes of this guideline, acute pain is considered to have a duration of less than 1 month.

Addiction: See *Opioid Use Disorder.*

Advocagenesis: Influences that are conscious or unwitting influences of lawyers and/or litigation processes on patients, including injured workers, that make the clinical presentation foment, worse, prolonged, or in some other manner, worse than would otherwise be (55). Examples of these influences include overt manufacture of symptoms, instructions from legal counsel to misstate facts, and instructions to not comply with treatment. Advocagenesis is parallel to iatrogenesis.

Chronic pain: Pain lasting more than 3 months is defined herein as "chronic." Chronic pain has also been sometimes defined as persisting beyond expected healing time and not clearly ascribable to a specific injury or area of tissue pathology.

Dependency: Drug dependence means that a person needs a drug to function normally. Abruptly stopping the drug leads to withdrawal symptoms (53).

Iatrogenesis: Inadvertent and preventable induction of disease or complications by the medical treatment or procedures of a physician, surgeon or other healthcare provider (56). Iatrogenesis usually refers to acts by which physicians and other health professionals cause or prolong undesirable events in patients. This includes failure to recognize chronic pain as an expression of emotional distress. The term "social iatrogenesis" was suggested in 1976 as a descriptor for illness caused or prolonged by wider sociopolitical inputs, which could also include marketing-induced demand (56,57).

Intractable pain: Pain in which the cause cannot be removed or otherwise treated and no relief or cure has been found after reasonable efforts.

Medicalization: A normal non-medical condition of life that is transformed in the mind of the patient into a disease or disorder. Also, known as pathologization, this includes expressions of emotional distress as chronic pain. For example, medicalization of low back pain may lead the sufferer to believe that an abnormality is present of sufficient gravity to require ongoing medical treatment such as the use of opioids" (58,59).

Opioids: Opioids are a class of compounds that activate the mu receptor and include natural synthetic and semi-synthetic compounds. Opiates are naturally occurring compounds that are derived from the opium poppy and are considered opioids. Opioids are potent analgesics that are widely used to manage moderate to severe acute pain and cancer pain (41). They reduce the intensity of pain signals reaching the brain and affect those brain areas controlling emotions. Effects include diminishing reactions to painful stimuli, elevating mood, sedation and reduction in anxiety (60).

Opioid dependence: Dependence typically includes both physical and psychological manifestations that become apparent on opioid withdrawal. Dependence includes symptoms and signs such as tachycardia. It is often accompanied by an unwarranted fear of pain or need for an opioid, either for its positive effects or to avoid negative effects associated with its abstinence. Dependence may be relieved in total or in part by re-administration of the opioid.

Opioid use disorder: A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring 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. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of an opioid. *Note:* This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic opioid withdrawal syndrome

b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms" (61)

Note: The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V) definition no longer makes a distinction between substance abuse and substance dependence. Both of these conditions are now included within *Substance Use Disorder,* which can be measured on a continuum from mild to severe (61,62).

Opioid withdrawal: Opioid withdrawal is a constellation of symptoms and signs that may occur with cessation of ongoing opioid use, whether in the setting of medical management of pain, during opioid agonist therapy for opioid use disorder, in the context of private recreational use, or following attempts to self-treat symptoms of mental disorders with opioids (61). Signs and symptoms may include:

- dysphoric mood,
- nausea and/or vomiting,
- muscle aches,
- lacrimation or rhinorrhea,
- pupillary dilation, piloerection and/or sweating,
- diarrhea,
- yawning,
- fever and
- insomnia.

Opioid withdrawal is distinct from opioid use disorder and does not necessarily occur in the presence of the drug-seeking behavior associated with opioid use disorder.

Physical dependence: A physiologic state of adaptation to a specific psychoactive substance characterized by the emergence of a withdrawal syndrome during abstinence, which may be relieved in total or in part by re-administration of the substance. Physical dependence is considered distinct from opioid use disorder.

Postoperative pain: Pain after a surgical procedure that is related to the procedure. The duration of post-operative pain is defined by the extent of the procedure and expected healing times, and may range from approximately a week to months.

Psychological dependence: A subjective sense, often accompanied by unwarranted fear of pain, of need for a specific substance, either for its positive effects or to avoid negative effects associated with its abstinence.

Subacute pain: Subacute pain is defined herein as pain lasting from 1 to 3 months. Often, this includes pain that is persisting beyond expected healing time and sometimes cannot be ascribed to a specific injury. Many researchers believe chronic pain features are present in this timeframe among those who develop chronic pain.

Tolerance: A state in which an increased dosage of a psychoactive substance is needed to produce a desired effect.

Withdrawal syndrome: The onset of a predictable constellation of signs and symptoms following the abrupt discontinuation of, or rapid decrease in, dosage of a psychoactive substance.

3.2. HISTORY OF OPIOIDS

The treatment of pain with opium (derived from the opium poppy) was described in the Ebers Papyrus more than 4,000 years ago. *Opiate* refers to natural opium alkaloids, while *opioid* refers to either natural or synthetic derivatives. Opioid use was largely unregulated until increased recognition of

morbidity from opioid use led to the passage of the Harrison Narcotics Tax Act in 1914, subsequently interpreted by courts to make it illegal for physicians to prescribe opioids to treat what was then termed "addiction." International laws to restrict the sale of opioids were promulgated in the 1930s (32).

Several decades ensued in the mid-20th century during which opioid use was minimized. During those decades, there was a strong preference for the prescription of weak opioids. In the 1980s, a trend towards wider opioid use emerged, including for nonmalignant pain. Pharmaceutical companies then marketed proprietary opioids to physicians and potential patients (33,36). The predominance of weaker opioids was replaced by strong opioids in the United States in the 1990s-2000s (63) (see Figure 2). Subsequently, the total paid schedule II* through IV prescription opioids increased and peaked in the United States in 2012, at 255 million prescriptions for a rate of 81.3 prescriptions per 100 persons (64).

Legislative and regulatory activities also helped drive the beginnings of the opioid epidemic (37). Beginning in the 1990s, there were a series of legal and disciplinary actions alleging that providers were undertreating pain (53,38-40). In 2000, the Veterans Administration launched the National Pain Management Strategy, adopting the increasingly common recognition of pain as the “5th Vital Sign” and calling providers “barriers to pain treatment” due to fear of patient addiction (i.e., opioid use disorder) and adverse effects (42,43). Also, in 2000, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) issued a pain management standard requiring recognition of the rights of patients to appropriate pain management (44,45).

After pain was made the fifth vital sign and JCAHO also took actions regarding the treatment of pain, patient satisfaction scores were widely implemented and linked to remuneration and/or incentives to providers. These changes caused another source of perceived and financial pressures to prescribe opioids (46-50,65). However, regular measurements of pain in clinical settings have not resulted in improved pain management (66-72). In response to the accumulating evidence of inefficacy of these measures and the concerns of adverse consequences, the American Medical Association voted to remove pain as the fifth vital sign in 2016 (48).

The prior actions have been thought to contribute to a sharp rise in drug overdose fatalities reaching 932,000 since 1999, most of which were opioid-related (73). By the 2010s, the magnitude of the opioid epidemic became widely known and actions to attempt to counter it were undertaken. FSMB produced revised guidelines for the management of chronic pain (74) and began to address opioid use for treatment of acute pain (75). JCAHO removed references to pain as the fifth vital sign (76). A large number of guidelines and policies have also been developed to address this epidemic (18,77-101). All states created “prescription monitoring programs” with controlled substances databases. Although the VA has not rescinded the 5th vital sign, VA guidelines in 2017 recommended against opioid use for treatment of chronic pain (102) and low back pain (103), which resulted in significant reductions in opioid use.

These actions significantly reduced opioids prescriptions by 47% since 2012, to 142 million prescriptions with the rate reduced to 43.3 per 100 persons in 2020 (64). However, the number of drug overdoses has continued to escalate, reaching 106,699 drug overdose deaths in 2021, largely due to illicit use of synthetic opioids. Of these, 80,411 involve any opioid, 16,706 involve a prescription opioid and 12,499 involve a benzodiazepine. This toll also includes nearly 1 million emergency department visits annually (104).

**Schedule II includes codeine, hydrocodone, hydromorphone, morphine, oxycodone, alfentanil, fentanyl, methadone, and sufentanil. Schedule III primarily includes barbiturates, but includes some opioids in low-dosage forms and buprenorphine. Schedule IV primarily consists of benzodiazepines, tramadol, pentazocine, and butorphanol. Schedule V includes low dose opioids in anti-tussive formulations and pregabalin.*

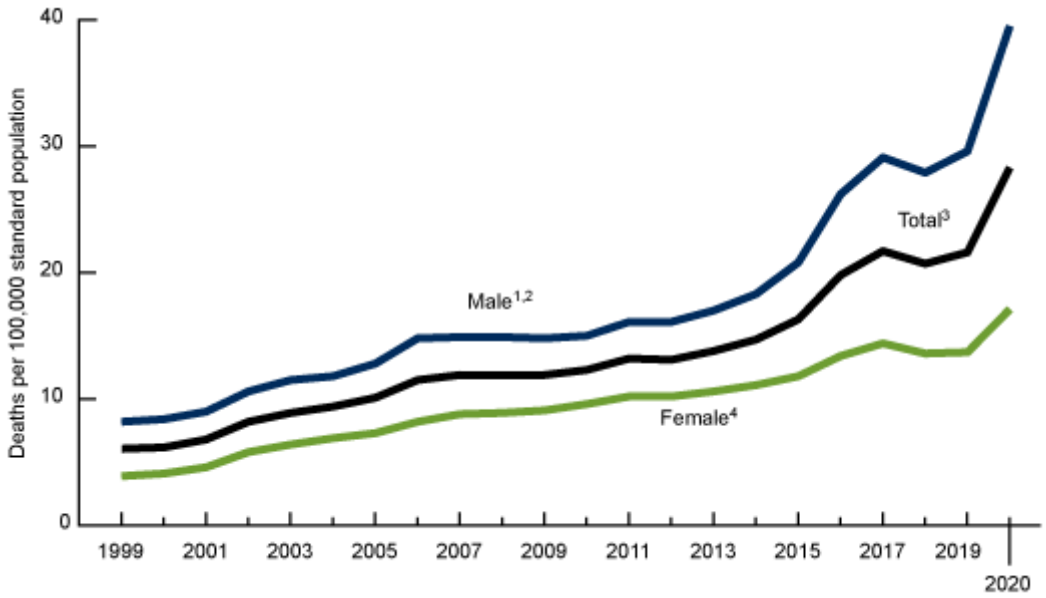
3.3. IMPACT

Opioid use increased sharply in the United States over the past three decades, well outpacing rates for other countries and was closely paralleled with a rise in opioids-related fatalities. Deaths related to opioid overdoses surpassed motor vehicle crashes as the cause of death in all states (67-70,73). This wave of opioid problems has been termed the first wave of the epidemic, having peaked in approximately 2012 (105).

While the rate of opioid prescriptions has fallen by 47% since 2012, these major state-level data mask significant differences when assessing county-level data. Approximately 70 US counties have 2020 prescription rates that are 3-fold higher, at more than 112.5 prescriptions per 100 persons, and are prominently overrepresented by economically impoverished areas, especially former and current coal mining counties (106). Additionally, since 2012, there was a rise in the death rate from heroin, peaking in approximately 2015 (105) that has been termed the second wave of the opioids epidemic.

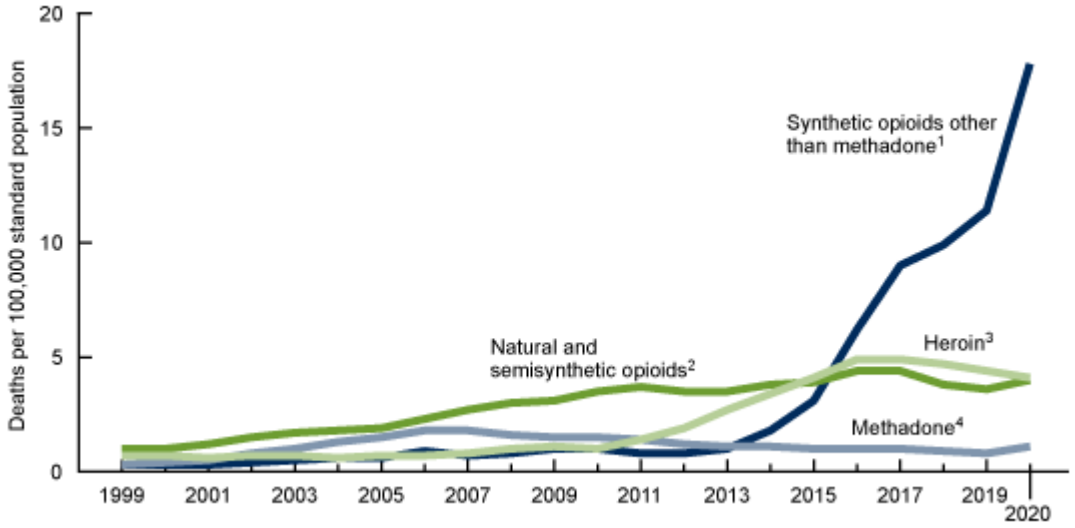
In contrast with the steep decrease in the rates of opioid prescriptions, the overall overdose rate has continued to climb throughout the 2010s and exceeded 100,000 in 2021 (35) (see Figure 1). These drug overdoses have been overwhelmingly driven by synthetic opioids (107) (see Figure 2), and the increases in fentanyl-related deaths with and without stimulants have been termed the third and fourth waves of the opioid epidemic (105) In contrast with the first and second waves related to prescription opioids and methadone, thus far there is no sign of abatement of the third and fourth waves (105)

Figure 1. National Drug-Involved Overdose Deaths by Sex



Source: Centers for Disease Control and Prevention, Multiple Cause of Death 1999-2020 on CDC WONDER Online Database, released 12/2021.

Figure 2. National Drug-Involved Overdose Deaths by Drug



Source: Centers for Disease Control and Prevention, Multiple Cause of Death 1999-2020 on CDC WONDER Online Database, released 12/2021.

3.4. OPIOID BENEFITS AND HARMS

BENEFITS

Over 120 randomized trials have reported consistent evidence of modestly reduced short-term acute, subacute, and chronic pain ratings associated with opioid use compared with placebo (108,109). Other comparative efficacy trials have largely failed to find superiority of opioids compared with other active treatments including NSAIDs (see evidence tables) (41). The magnitude of pain reduction is reportedly modest compared with placebo (i.e., 0.69 VAS pain scale reduction) (108). Furthermore, few of those trials lasted more than 1 month, and none were over 6 months in duration (41). These trials and details of the results are reviewed in this section.

ADVERSE EVENTS

Opioids have been associated with numerous adverse effects (see Table 2) (110-115), which differ somewhat based on the specific drug and route of administration. All of these have been associated with opioids, and the level of evidence for causal effects varies from high certainty to unproven.

Approximately 80% of patients initiating opioids experience some adverse effects and 33 to 80% do not finish clinical trials with opioids, primarily due to these adverse effects (the large range in estimates is in part due to trial design, such as whether a wash-out phase was included, length of treatment, and severity of pain) (116-119).

Opioid use is associated with elevated risks of emergency and other care. One-quarter to one-third of enrollees in both commercially insured and Arkansas Medicaid populations had an emergency department visit in the 12 months following chronic opioid therapy (120). Osteoarthritis patients receiving opioids compared to those receiving NSAIDs had increased risk of cardiovascular events, hospitalization, and overall mortality (121). A retrospective cohort of hospitalized Medicare recipients

which compared opioids with NSAIDs use at discharge found opioid-using patients had 64% higher risk of death (1.8% vs. 1.1%), 19% greater healthcare utilization, and any potential adverse effect (25.2% vs. 21.2%) (122).

Opioid-using patients undergoing surgery incur greater resource utilization (123), with much greater perioperative management challenges (124). Coronary artery bypass graft patients who use preoperative opioids are more likely to be readmitted within 6 months (125). Opioid use is associated with elevated risk of 1-year mortality after hip fracture, whereas osteoporosis medications were associated with reduced risk (126). Opioid-sparing perioperative approaches have been nearly universally associated with improved short- and long-term outcomes (see postoperative recommendations).

Opioids are also associated with lower return-to-work status (127), Higher opioid use compared with low or no use has been associated with worse activity interference and higher pain ratings (128). Opioid use is associated with greater disability (129-131). Disability is also increased among workers with pre-injury opioid use and/or benzodiazepine use (132).

A 3-year registry study found that of 233 patients enrolled, 39/227 (17.2%) completed the study, inferring high adverse effects. Forty-four percent had dose escalation within 3 months, inferring hyperalgesia or tolerance (133, 134).

Opioids have reportedly been associated with hyperalgesia and tolerance. Short-term use has been termed acute opioids tolerance, with evidence including an experiment showing tolerance as soon as within 2 hours of continuous IV remifentanil infusion (135) and another showing higher postoperative pain scores at 24 hours in the high-dose opioids group (136). These effects have been generally described within weeks of administration (137-139), purportedly through central sensitization. However, although tolerance is widely described, not all authors and studies agree that hyperalgesia occurs (137).

Adverse effects include gastrointestinal symptoms, which are common and include nausea, vomiting, delayed gastric emptying, and constipation (140-172).

Opioids cause sedation (140-172), clouding of consciousness or "mental fog," decreased concentration, slowed reaction time, problems with decision making, lack of impulse control, reduced spatial memory, impaired working memory, reduced flexibility for concept change, balance problems, dizziness, altered color vision, lack of coordination, myoclonus, muscle rigidity, muscle wasting, dysphoria, euphoria, hair loss, pruritis, and anaphylaxis (15, 173-200).

Opioids increase the risks of motor vehicle collisions (67-69, 72, 201), falls, and fractures (195-197, 202-205).

Opioids are associated with respiratory depression, including associations with central and obstructive sleep apnea (152, 154-157, 161-165, 169, 170, 175, 206, 207). Evidence suggests these effects are present regardless of opioid-naïveté (156, 208, 209). One study found an association with central sleep apnea with a dose-response relationship and a 15-fold risk at a daily MME of 200 mg (210). Sleep disturbance effects include suppression of rapid eye movement (183, 211). There was no demonstrated association between sleep disturbance and level of pain (212).

In overdose situations, some manifestation of anoxic brain injury has been found on imaging studies, with leukoencephalopathy commonly reported (213-220).

Opioid use has been associated with suppression of the immune system (221), including an increased risk of pneumonia (222) and invasive pneumococcal disease (223). Morphine has been postulated to affect tumor growth (224), although the overall quality of the data preclude a conclusion regarding whether opioids increase the risk of tumor spread (224-227). Immune stimulation with pro-aging effects has also been suggested (228).

Endocrinological effects include increases in growth hormone and prolactin; decreases in luteinizing hormone, estradiol oxytocin, and adrenocorticosteroids (229-231); subnormal testosterone levels by 74% (232-234); and 48-57% lower estrogen levels (235). Resultant effects including erectile dysfunction, reduced libido, oligomenorrhea, amenorrhea, bone loss, and infertility (185, 235-238).

Fetal effects of opioids include poor fetal growth, preterm birth, neonatal abstinence syndrome (239), and birth defects (240), including conoventricular septal defects, atrioventricular septal defects, hypoplastic left heart syndrome, spina bifida, and gastroschisis.

Chronic opioid therapy has been associated with an increased risk of cardiovascular outcomes (195-197), Methadone is known to prolong the QT interval (174, 241-243) and has been widely associated with cardiac dysrhythmias, polymorphic ventricular tachycardia, and sudden cardiac death.

Opioids at medium and high doses may acutely or chronically contribute to clinical depression, and increase perceived pain intensity. A large case series of 500 consecutive pain patients reported depression, anxiety, and somatization disorder in 59%, 64%, and 30% of the cases (244). A longitudinal study found that those who reported some opioid use "uniformly demonstrated higher pre-rehabilitation ratings of pain, disability, and depression" (127). Other studies suggest associations between opioid use and depression (51, 202, 245-249) and anxiety (51, 202, 247-249). A prospective cohort study found 7% of 768 consecutive chronic pain program patients produced a normal MMPI, 15% had conversion V, 9% were neurotic, and 69% had a disability profile (250). Aberrant psychological findings were also opioid dose-dependent, although that may be confounded by the apparent colinearity between psychological findings and opioid treatment. Patients with PTSD are more likely to be prescribed opioids and incur more adverse effects than those without PTSD (202, 251).

DEATHS ASSOCIATED WITH PRESCRIPTION OPIOIDS

Of the 106,699 (75.4%) total overdose deaths reported in 2021, opioids caused 80,411 deaths (252,253). Deaths have been reported among both those prescribed opioids and those obtaining opioids through illicit means and/or diversion. Prescription use recently became a minority cause of overdose-associated deaths, with an estimated 16,706 out of 80,411 (20.8%) opioid-associated overdose deaths in 2021, whereas a majority of cases were prescription-related in 2010 (2, 3, 110, 254-263). The most common medications associated with opioid-related deaths are fentanyl, other synthetic opioids, methadone, hydrocodone, and oxycodone, although there are significant regional variations (34, 252, 264-271). Long-acting oxycodone has been linked to increased mortality (272). Tramadol has been represented as a safer alternative, yet overdose deaths have also been associated with tramadol (273-280).

In a cohort study (2), the hazard ratios for all overdose events were 0.31 in those with no opioid usage, 1.0 in patients with a 1 to <20mg/d MED, 1.44 in those with 20 to <50mg/d MED, 3.73 in patients with 50 to <100mg/d MED, and 8.87 in those whose dosage was ≥ 100mg/day MED (see Figure 3). In those who had a serious overdose event, the hazard ratios were 0.19 for no opioid usage, 1.00 for 1 to <20mg/d, 1.19 for 20 to <50 mg/d, 3.11 for 50 to <100mg/d, and 11.18 for those whose dosage was ≥100mg/day. In a similar case cohort study by (3), the hazard ratios for those with chronic pain were 1.0 in patients with a 1 to <20mg/day dosage, 1.88 in those with a 20 to <50mg/day dosage, 4.63 in patients with 50 to <100mg/ day dosage, and 7.18 in those whose dosage was ≥100mg/day. In those who had acute pain, the hazard ratios were 1.00 for 1 to <20mg/day, 1.58 for 20 to <50mg/d, 4.73 for 50 to <100mg/day, and 6.64 for those whose dosage was ≥100mg/day.

Implementation of a 120mg/day MED maximum dose in 2007 in Washington State has been at least partially credited with decreases in the percentage of workers on Schedule II opioids, patient numbers over the limit, and the number of opioid-related deaths (257). However, the magnitude of that state's reduction was not large.

In a matched case-control comparison (281), 300 deaths occurred among 730,381 patients. This is 27.4 per 100,000 patients per year. It was also found that there was an association between risk and number of prescriptions, prescribers, and opioid daily dose. Six controlled substance prescriptions during 6 months quadrupled the risk of overdose deaths. The odds ratios for single peak prescriptions increased after 20 morphine milligram equivalents (MME)/day and increased until about 200 MME/day. Of those who were prescribed opioids, 34.2% had an average daily dosage above 60 MME/day, 23.6% had a daily dose above 120 MME/day and 17.3% above 200 MME/day. Among the 300 deceased patients, 66.3% of them had obtained opioids from two or more prescribers, 43.0% had prescriptions from three or more, and 13.7% had prescriptions from six or more.

At least one study has suggested no difference in the risk of respiratory depression in opioid-naïve patients compared to those on strong opioids (156), suggesting some additional corroborative evidence for the nearly identical dose-response curves in Figure 3.

A study assessing the means to decrease prescription opioid deaths reported a 14.0% drop in unintentional deaths from prescription opioid in 2008 compared to 2007 after the implementation of physician-targeted presentations (282).

SUICIDE

Opioids were reported to be among the most common substances found in decedents from suicide in studies by the Toronto Coroner's office (283-285). A non-randomized longitudinal study also found a threefold increased risk of suicidal thoughts among patients with chronic pain who were treated with opioids (286). However, whether prescription of an opioid causes an increased risk of suicide has not been shown among those with low-dose opioids and without mental health disorders (287-289).

OPIOID MISUSE

Prescribing opioids carries a risk of opioid use disorder; these risks may receive insufficient consideration and weighting of the risk/benefit analysis when prescribing opioids. The magnitude of risk of opioid use disorder is uncertain and has been estimated from 0-50% (290-294). Chronic opioid utilization for treatment of chronic non-cancer pain has increased greatly over the past three decades. The reasons for this are likely complex, with etiologies that may include increasing volumes of illicit opioids, socioeconomic considerations, pharmaceutical marketing, inaccurate information provided to prescribers, psychosocial determinants, differences in clinical practice and interindividual variation in biological pathways. However, there remains sparse knowledge about underlying mechanisms for the development of opioid misuse. Also, the tools used to stratify risk and monitor therapy may not be effective at addressing the core issues underlying opioid misuse (295-297).

Patients who have aberrant drug-related behaviors, psychosocial comorbidities, and a history of substance use are more likely to misuse prescription opioids and become addicted to them (298). Of the prescribed opioids, caution is particularly advised in prescribing long-lasting oxycodone for chronic pain due to higher risk of misuse, high cost, and high street value (174), although some data also suggest that oxymorphone is problematic as well (299,300).

Tolerance is a common occurrence, although generally not significantly problematic. Opioid use disorder and drug-seeking behaviors are less common (294, 301-306).

EVIDENCE FOR ADVERSE EVENTS

Please see the online evidence for adverse events associated with opioid use.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: adverse event; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 3619 articles in PubMed, 740 in CINAHL, 1117 in Cochrane Library, 34300 in Google Scholar, and 32 from other sources†. We considered for inclusion 16 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 32 from other sources. Of the 48 articles considered for inclusion, 48 epidemiological studies and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

RISK AND BENEFITS OF OPIOID USE

Please see the online evidence for the risks and benefits associated with opioid use.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: risks, benefits; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 4658 articles in PubMed, 850 in CINAHL, 98 in Cochrane Library, 39900 in Google Scholar, and 0 from other sources†. We considered for inclusion 4 from PubMed, 3 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 7 articles considered for inclusion, 0 randomized trials and 4 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

3.5. FINANCIAL COSTS ASSOCIATED WITH OPIOID USAGE

Opioids are associated with a higher rate of in-hospital adverse drug reactions, greater lengths of stay (1), and consequently higher hospitalization costs, although they are reportedly effective treatments. A randomized trial found that use of ketorolac resulted in fewer complications and lower costs than an opioid. There also is evidence that patient-controlled analgesia is more costly but not more effective for postoperative management. Opioids have been associated with greater workers' compensation claim costs and greater risk of catastrophic claims, although this relationship may be partially confounded by injury severity and psychopathology.

FINANCIAL COSTS ASSOCIATED WITH OPIOID USE

See the online studies on the financial costs associated with opioid use.

Rationale

A population-based, propensity score matched study comparing approximately 32 million respondents with and without an opioid prescription found annual total expenditures were $16,542 with and $7067 without an opioid prescription; this resulted in a total economic burden including healthcare costs, criminal justice, lose productivity and reduced quality of life of $524 billion (Bounthavong et al., 2021). Another estimate of the societal costs and economic burden of opioid use disorder and fatal opioid overdose exceeded $1 trillion dollars (Florence et al., 2021). A cross-sectional analysis of 2016-2017 commercial enrollment, health care, pharmacy claims and health risk assessment data evaluated the association of opioid use disorder and annual employee health care and productivity costs (Henke et al., 2020), and found the health care and productivity costs for employees with opioid use disorder were approximately $6,294 (among those who received pharmacotherapy) and $21,570 did not receive pharmacotherapy) more than employees without opioid use disorder.

Opioids also impact the cost of workers' compensation claims. with a study of Michigan indemnity claims during 2006-2010 showing an opioid prescription was associated with a 52.2% higher cost of a claim, a 1.76 times increase in claims costing $100,000 or more in the presence of short-acting opioids and 3.94 times with long-acting opioids (Hunt et al., 2019). A random sample of acute work related low back claims with and without opioid prescriptions suggested that morphine equivalent dose days may be a better predictor of total cost than MED alone (Merris et al., 2020).

Opioids were responsible for approximately 1 of every 80 emergency room visits in the US in 2016-17 costing $5B (Langabeer et al., 2021). A population-based study estimated there were 741,275 Americans hospitalized who had opioid use disorder in 2016; the average cost per discharge was $11,233 with the most frequent diagnoses as alcohol/drug misuse or dependence, psychosis and septicemia (Alemu et al., 2021). Opioid-dependent patients' costs for lower extremity bypass surgery were $7,032 higher than among those not dependent and included ~2 extra days of hospitalization (Aizpuru et al., 2020). Opioid use disorder patients have higher costs and emergency room visits within 90 days after open reduction internal fixation of ankle fractures (Allen et al., 2020). Women filling an opioid prescription within 12 months after a diagnosis of endometriosis incurred approximately $9,000 more in costs over the ensuing 12-month period (As-Sanie et al., 2020).

Preoperative opioid use, including tramadol, increases costs of total joint arthroplasty (Bell et al., 2021, Peratikos, 2020), lumbar discectomy (Jain et al., 2021), lumbar fusion (Tank et al., 2018), orthopedic surgeries (Cozowicz et al., 2017), ankle fracture surgery (Oladeji et al., 2021), aortic surgery (Clement et al., 2021), cardiac surgery (Dewan et al., 2019), major operating room procedures

(n=16,016,842) (Gupta, 2018), colorectal surgery (Jackson et al., 2021), emergency surgery (Kim, 2018), hip arthroscopy (Nazzal et al., 2021), and renal transplantation (Wise et al., 2021); opioid use also increases healthcare costs associated with osteoarthritis (Thakkar et al., 2021) (Zhao et al., 2019), acute pancreatitis (Shaikh et al., 2021), degenerative joint disease of the spine (Metfessel et al., 2019), migraines (Kangethe et al., 2020), and chronic pain conditions (Patel et al., 2020). Spinal cord stimulator implantation was associated with opioid reductions only among those who were able to continue stimulator therapy for at least 2 years (Fraifeld et al., 2021).

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: cost; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 995 articles in PubMed, 199 in CINAHL, 55 in Cochrane Library, 225,000 in Google Scholar, and 0 from other sources†. We considered for inclusion 34 from PubMed, 26 from CINAHL, 1 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 62 articles considered for inclusion, 6 randomized trials and 5 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

3.6. COMORBIDITIES

The contribution that comorbidities have with respect to the treatment of pain, especially chronic pain, is complex and varies. Much of chronic non-cancer pain is spine-related pain, and most chronic spine pain has no clearly defined etiology (see the ACOEM Low Back Disorders guideline). Evidence indicates that increasing co-morbidities, medical and mental, are associated with greater likelihood of complaints of chronic pain. Pre-morbid sexual, emotional, and physical abuse are associated with chronic nonmalignant pain. In individuals with both chronic pain and anxiety disorders, there is evidence that anxiety precedes the development of chronic pain. Comorbid depression appears more common after the development of chronic pain. Chronic long-term opioid usage is associated with a worse course of mental health conditions, especially depression. Depression and other mood disorders are associated with an increased risk of chronic pain and increased use of medical services including opioid as well as nonopioid pain relievers. Many have recommended practitioner awareness as well as pre-screening of candidates for opioid therapy due to the higher prevalence of psychiatric disorders and subsequent decreased effectiveness of treatment of those disorders if chronic opioids are prescribed.

There is no causal link established that insomnia causes chronic pain, or vice versa. Chronic pain (pre-sleep pain) does not reliably predict loss of sleep quality or sleep efficiency. Individuals with chronic pain have a higher prevalence of depression and depression is often associated with poor sleep quality and sleep inefficiency.

3.7. RISK EVALUATION AND MITIGATION STRATEGIES

The U.S. Food and Drug Administration (FDA) has suggested risk evaluation and mitigation strategies (REMS) with three components: a medication guide, elements to assure safe use, and a timetable for submission of assessments for extended-release and long-acting opioids (307). The medication guide would provide patients with more information about the safety and risks associated with their medication. Elements to assure safe use would focus on provider training specific to safe opioid prescribing, product information, and patient counseling. Evaluations should be implemented to determine the effectiveness of the REMS (308).

Opioids have long played an important role in the control of cancer-related and non-cancer pain. At the same time, they have contributed significantly to morbidity and mortality. According to the Centers for Disease Control and Prevention (CDC), “opioid analgesics, such as oxycodone, hydrocodone, and methadone, were involved in about 3 of every 4 pharmaceutical overdose deaths,” illustrating the importance of appropriate prescribing and patient monitoring (309). In an effort to address the magnitude of this public health crisis, the federal government developed the Risk Evaluation and Mitigation Strategies (REMS) program. The effectiveness of this program has recently come into question in a document published in 2013 by the Department of Health and Human Services Office of Inspector General entitled *FDA Lacks Comprehensive Data to Determine Whether Risk Evaluation and Mitigation Strategies Improve Drug Safety* (310).

Historically, based on a multi-agency effort to assure that the benefits of certain drugs outweighed their risks, FDA was authorized to require REMS for opioid analgesics. The final REMS for extended-release opioid medications were approved by FDA on July 9, 2012, as part of the White House’s plan to decrease misuse of prescription drugs. While REMS has targeted long-acting opioids; there is little evidence they are more hazardous than short-acting opioids.

The FDA's goal was for 60% of prescribers of extended-release (ER) and long-acting (LA) opioids to take REMS-adherent continuing education. However, between 2012 and 2016, only 27.6% had done so. Therefore, the FDA and manufacturers could not conclude whether there were meaningful improvements in inappropriate prescribing or improved patient outcomes (311). It has also been reported that internet-based, industry-funded REMS-compliant continuing medical education contain "messages that misrepresent scientific evidence and may foster overprescribing of opioids" (312). A correlation of reduced risk of deaths associated with extended-release (ER) and long-acting (LA) opioids was statistically significant in one of three states assessed (Washington), but non-significant in Florida and Oregon (313).

REMS are organized plans of action designed to monitor and manage drug risks, such as potential for opioid misuse, while allowing continued access for beneficial uses (as opposed to withdrawal from the market due to risk profiles). FDA mandates that drug manufacturers develop and oversee the REMS while the FDA’s responsibility is to review and approve the REMS. According to the FDA, the goal of REMS is to decrease significant adverse outcomes related to the use of extended-release (ER) and long-acting (LA) opioids. These adverse events include serious health outcomes such as “addiction, unintentional overdose, and death.” Significant events of this nature can arise from patient misuse and inappropriate or uniformed prescribing. In an attempt to address this issue, a key element of the opioid REMS was designed to ensure that all providers receive appropriate education on this topic to prevent untoward health effects for the purpose of maintaining safe patient access to opioids for pain control.

Within this context, FDA has identified three mechanisms that manufacturers may be required to include in the risk evaluation and mitigation process involving opioids: 1) use of a medication guide and/or a package insert; 2) elements to assure safe use (ETASU), and 3) communication plans. Risk management and evaluation strategies further require manufacturers to establish a timetable for

submission of risk assessments for brand name drugs including extended release and long-acting opioids. Under the ETASU section, FDA requires the manufacturer to assure that the prescribers of opioids have received proper training on the drug and have been supplied with appropriate patient education materials. Additionally, the manufacturer is required to notify the prescriber that REMS exists for a particular opioid and of the need for training.

The effectiveness of the original 1999 REMS was evaluated by FDA's Office of Inspector General in 2013. Concerns were identified related to the effectiveness of REMS mandated between the years 2008 and 2011. Findings of the study concluded that almost 50% of 49 REMS reviewed lacked data required by the assessment plan implemented by FDA with 14% meeting all required goals. The report stated that "FDA has not identified reliable methods to assess the effectiveness of REMS" (310). The Inspector General's Office made the following seven recommendations to address these findings, and the FDA accepted the first six:

1. Develop and implement a plan to identify, develop, validate, and assess REMS components.
2. Identify REMS that are not meeting their goals and take appropriate actions to protect the public health.
3. Evaluate the ETASUs of one REMS each year as required by Federal law.
4. Clarify expectations for sponsors' (drug manufacturer's) assessments in FDA assessment plans.
5. Ensure that assessment reviews are timely.
6. Identify incomplete sponsor assessments and work with sponsors to obtain missing information.
7. Seek legislative authority to enforce FDA assessment plans.

Providers play an integral role in the chain of pain control. As a result, they remain key stakeholders in all processes related to opioid prescribing and patient monitoring. Concerns by prescribers over REMS have arisen since its release as some prescribers opined of the burdensome need to take mandatory training classes, suggesting actions to stop prescribing opioids, and thus preventing patients from receiving pain medication (314). Additionally, REMS may require prescribers to receive certification or participate in certain programs prior to prescribing certain opioids creating added burdens. In response to these concerns, FDA has held public meetings inviting stakeholders to participate in commentary on the standardization of REMS.

REMS remains a work in progress and may be but one relatively weak tool to address the multi-factorial issue of opioid misuse and inappropriate prescribing.

3.8. MONITORING / AUDITING CRITERIA

The provider is recommended to assure:

1. Patients prescribed an opioid for acute pain are prescribed no more than 50mg MED. Target 90%.
2. Patients prescribed an opioid for acute pain are prescribed not more than 3 days for the initial prescription. Target 90%.
3. Patients prescribed a trial of an opioid for chronic pain should have documentation of ongoing compliance with active treatments (e.g., disorder-specific exercises), and at least 3 prior non-opioid medications that have been prescribed previously and failed. Target 100%.
4. Patients prescribed a trial of an opioid for chronic pain should have objective evidence of significant pain and improvement in function, using either objective evidence (e.g., return to work) or validated tools, to support continued opioid prescription. Target 90%.
5. Patients who are prescribed an opioid for chronic pain over 3 months should have a signed informed consent form and pain agreement. Target 100%.

6. Patients should be screened for aberrant and illicit drug use prior to initiating, or continuing, a prior opioid at the first visit. Target 100%.
7. Patients on an opioid should be prescribed at a morphine equivalent dose (MED) less than 50mg, unless a pain management evaluation finds that the benefits exceed the risks and there is documented incremental functional improvement beyond that at 50mg and up to a maximum of 90 MED. Target >98%.
8. Patients on an opioid at MED over 50mg are not taking benzodiazepine(s), unless a psychiatric consultation opines that the benefits exceed risks. Target 100%.
9. Patients who are in violation of their opioid agreement (e.g., illicit drugs, >1 prescriber, diverting drugs) should have the opioid weaned or stopped, or referred for Medical Assisted Treatment if OUD is suggested. (If the violation is due to OUD, patients are better served with referral for MAT than weaning or stopping their opioid; however, if the patient is diverting drugs, cessation with or without MAT referral is strongly recommended.) Target 100%.
10. Patients performing safety-sensitive jobs are not taking opioids. Target 100%.

[View also the Monitoring / Auditing Criteria for Chronic Pain]

4. TREATMENT RECOMMENDATIONS

4.1. COMPREHENSIVE HISTORY AND PHYSICAL EVALUATION

A comprehensive history and physical is recommended for all patients being considered for opioid therapy regardless of acuity, and is viewed as critical for the purposes of forming a holistic decision-making partnership with the patient to optimally approach pain management.

CONDUCTING A COMPREHENSIVE HISTORY AND PHYSICAL EVALUATION PRIOR TO PRESCRIBING OPIOIDS

Recommended

A comprehensive history and physical is recommended for all patients being considered for opioid therapy, regardless of acuity.

The comprehensive history and physical can be used to determine diagnoses, treatments to be trialed, function-based approaches, the degree to which indications are met, and the risk of opioid misuse. Strong risk factors from a large systematic review for opioid misuse include: any current or prior substance use, any mental health diagnosis, younger age, male sex, and high pain ratings (Kohns DJ, 2018, Hah JM, 2019, Cragg A, 2019, Klimas J, 2019, Turk DC, 2008) (Cheng et al., 2013, Han et al., 2017, Carey et al., 2018, Jones, 2012), with overall misuse estimated at an average of 40% among patients with chronic pain (Timmerman L, 2016). Evidence suggests that history and urine drug testing are the most sensitive indicators (see below).

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence High

Indications

All patients being considered for opioid therapy.

Benefits

Identification of functional status and goals. Identification of effective therapies not yet utilized, or for which compliance is needed to optimize treatment. Improved identification of more appropriate candidates for treatment with an opioid. Identification of patients at increased risk of adverse effects.

Harms

Negligible.

Frequency/Dose/Duration

All patients at baseline. May require only one evaluation for conditions of relatively short duration. Comprehensive evaluations are recommended to occur at least quarterly for patients with chronic pain who are treated with an opioid (see below for recommended contents of this evaluation). Screening should primarily rely on the history, discussion with family/caregivers, clinical records, PDMPs and toxicological testing; screening may include use of screening tool(s), such as COMM; ORT; Patient Health Questionnaire Ninth Edition; Patient Medication Questionnaire (PHQ-9); Cut down, Annoyed, Guilty, Eye-opener—Adapted to Include Drugs (CAGE-AID). However, the performance data for these questionnaire screening tools shows they do not well discriminate, there is no quality evidence or consensus that one tool is superior to the others, and CDC recommends against overly relying on them, as clinicians "should always use caution when considering or prescribing opioids and should not overestimate the ability of available risk stratification tools to rule out risks of long-term opioid therapy (CDC, 2022).

Rationale

Identification of pre-injury opioid and benzodiazepine use has been found to be an important predictor of opioid prescriptions and subsequent disability (Nkyekyer EW, 2018). Legitimate opioid use in adolescence has been found to be associated with subsequent opioid misuse (Miech et al., 2015). An analysis of all US veterans not having an opioid prescription in the prior 6 months evaluated in an emergency department at any VA facility in 2012 treated by low-quartile and high-quartile prescribers (n=57,738 and 86,393 patients, respectively) found variations in prescribing of 300% (6.4% vs. 20.8%), risks of opioid prescriptions for back pain and depressive disorders, and a trend towards more long-term opioid use among those treated by high-quartile prescribers (OR=1.11, p=0.056) (Barnett ML, 2019).

Appropriate pain management requires adequate knowledge about and assessments of a patient’s pain and function. It critically involves treatment of concomitant and/or confounding disorders, especially mental health disorders, whether acute, chronic, nonoperative, or operative (Menendez et al., 2015). Pain management often requires multiple pharmacological and nonpharmacological methods to safely and appropriately control pain, which should be evaluated (U.S. Food and Drug Administration, 2013, International Association of Industrial Accident Boards and Commissions, 2013, Federation of State Medical Boards, 2013, Gourlay et al., 2005). A comprehensive evaluation and documentation includes a patient's history, prior treatment, vocation, avocational activities, current functional level, past medical history, family history, social history including substance use (tobacco, alcohol, and illicit substances), history of impairing medication use, review of systems, laboratory testing, and imaging studies as appropriate (Chou et al., 2009, Federation of State Medical Boards, 2013, International Association of Industrial Accident Boards and Commissions, 2013, Gourlay et al., 2005, Webster, 2013, Jovey, 2002, Strudwick K, 2019, Hartwell M, 2021, Cheng et al., 2013, Carico et al., 2018, Compton WM, 2016, Gomes, 2017). History of an opioid overdose is associated with a 13-

fold risk of subsequent mortality (Ashburn et al., 2020, Ray et al., 2018). This systematic approach should result in a clear diagnosis to treat as evidence allows (International Association of Industrial Accident Boards and Commissions, 2013, Gourlay et al., 2005, Webster, 2013). In many cases of chronic pain, the most accurate diagnosis may be a symptom (e.g., chronic low back pain). An evidence-based treatment plan should focus on addressing that diagnosis. Obstacles for treatment and rehabilitation should be identified and addressed. A careful history will commonly reveal a lack of exhaustion of indicated non-opioid treatments that should be trialed and monitored, with compliance assured, prior to consideration of an opioid trial for subacute or chronic pain (see other ACOEM guidelines).

A history also provides the opportunity to educate a patient that opioids generally provide a pain reduction amounting to only 0.69 out of 10 on a pain rating scale (Busse JW, 2018), thus furthering an understanding of the risks and benefits of opioids. A comprehensive examination also may find evidence regarding physical and mental health conditions that are not optimized, and often appear to contribute to opioid prescriptions as a substitute to quality healthcare that addresses primary or contributing problems (Jerant et al., 2020, Vowles, 2022). The prescription drug monitoring program database should be carefully reviewed (Fink HA, 2018).

When considering an opioid prescription, the treating physician should have a clear, quantified treatment plan and functional goals (Washington State Department of Labor & Industries, 2010, International Association of Industrial Accident Boards and Commissions, 2013, Federation of State Medical Boards, 2013, Mahowald et al., 2005, Saper et al., 2006). "SMART" goals have been recommended: **S**pecific, **M**easurable, **A**chievable, **R**ealistic, and **T**ime-based. It is also recommended that the documentation include a discussion and plan for the "5 A's": **A**nalgesia (reduction in pain), **A**ctivity increase (improved in level of functional and meaningful activities, especially in work-related injuries returning to work, even part-time or gradually) (Reneman et al., 2002), **A**dverse effects (any adverse effects, especially constipation, dizziness, confusion and inability to function due to the opioid) (Moore et al., 2005), **A**berrant behaviors (self-dose escalation, poor compliance, continued 'pain behaviors' despite use of an opioid), and **A**ffect (mood changes, such as worsening of depression) (Federation of State Medical Boards, 2013, International Association of Industrial Accident Boards and Commissions, 2013).

If an opioid trial is planned for treatment of subacute or chronic pain, documentation should also include informed consent (International Association of Industrial Accident Boards and Commissions, 2013, Federation of State Medical Boards, 2013, Chou et al., 2009, Graziotti et al., 2002), including an agreed-on opioid treatment contract (for subacute or chronic pain patients), and monitoring results (see detailed sections below) (Chou et al., 2009, Federation of State Medical Boards, 2013, International Association of Industrial Accident Boards and Commissions, 2013). Provider and organizational barriers to implement this recommendation are few.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: Medical History Taking, Physical Examination; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 3147 articles in PubMed, 11 in CINAHL, 331 in Cochrane Library, 34800 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other

sources. Of the 1 article considered for inclusion, 0 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.2. WORKERS IN SAFETY-CRITICAL JOBS

Most of the literature addressing safety-critical work assesses risk of motor vehicle crashes; however, there is an increasing body of evidence on the risks of unintentional injuries, fractures, and cognitive function deficits. Many studies of drivers using opioids have been reported, including both epidemiological studies (61, 62, 66-69, 71-76, 102, 201, 315, 316) and experimental studies (61, 62, 77-81, 103, 104, 317, 318).

Opioid use among those performing safety-critical work is frequently restricted by regulations, statutes, or legal considerations. Driving simulator and experimental studies have suggested that opioid use is associated with driving-related impairments with acute exposures (61, 82, 103). After initiation of an ongoing opioid prescription, self-reported adverse effects markedly decline over days to weeks (83, 84). Most driving simulator and experimental studies of chronic opioid exposures have reported no indirect evidence of increased risk of crash (77-79, 81, 85-90, 104, 317). Yet, other evidence suggests cognitive compromise among those with chronic opioid use, especially decision-making (91, 92, 176). Some theorize that chronic pain itself causes cognitive decline, thus potentially confounding opioid use. However, the evidence does not appear to support this theory (93-97). Some literature reviews have concluded there is no increased risk of motor vehicle crash with chronic opioid use (66, 98-101, 317), while a more recent review has found both an increased risk of crash and a dose-response relationship (319).

USE OF OPIOIDS BY WORKERS IN SAFETY-CRITICAL JOBS

Not Recommended

Acute or chronic opioid use is not recommended for patients who perform safety-critical jobs. These jobs include the operation of motor vehicles, forklifts, overhead cranes, heavy equipment, or other modes of transportation; sharps work (e.g., knives); work with injury risks (e.g., heights); and tasks involving high levels of cognitive function and judgment. There are other non-opioid management strategies with less risk of impairment. Among those using opioids for post-operative pain, severe injuries or other appropriate uses, it is recommended that at least 3.3 half-lives (to clear 90% of the opioid) take place after cessation of the opioid prior to return to that worker's safety-critical job.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Moderate

Rationale

MOTOR VEHICLE CRASH RISK

Opioids are centrally acting drugs that produce analgesia while also causing sedation and otherwise hindering or impairing higher cognitive function (Dubois et al., 2010) (Moore et al., 2005) (Howard et

al., 2004) (Majdzadeh et al., 2009) (Bramness et al., 2012) (Dassanayake et al., 2011) (Orriols et al., 2009) (Strand et al., 2013) (Leung, 2011) (Bachs et al., 2009) (Corsenac et al., 2012) (Rohrig et al., 2021).

Licit use of both strong and weak prescription opioids has been consistently associated with an increased risk of motor vehicle collisions (MVCs). In the large epidemiological studies of working age-adults that were sufficiently powered to detect MVC risk associated with opioids, the estimates have ranged from 24% to more than 800% increased risk of MVC (Gomes et al., 2013) (Gibson et al., 2009) (Engeland et al., 2007) (Wickens et al., 2018) (Brubacher JR, 2021) (Yang et al., 2021) (Quinn et al., 2022) (Li et al., 2019) (Wickens et al., 2018) (Rudisill et al., 2016) (Chihuri et al., 2019) (Chihuri et al., 2017) (Mura et al., 2003) (Bramness et al., 2012) (Bachs et al., 2009) (Dubois, 2010) (Corsenac et al., 2012) (Monárrez-Espino J, 2016). A large database study reported no increased risk for patients with acute pain; however, it was unknown whether the patient was actually taking the opioid (Guan Q, 2021). A 1992 study of elderly patients found a lack of increased risk (Ray et al., 1992). A metanalysis of studies performed for this guideline found that among studies with data able to be combined, there was a doubling of crash risk associated with use of opioids (OR=2.0, 95% C.I. 1.59, 2.52) (see Figure 5).

In a study of 772,404 patients with an incident prescription of an opioid for non-cancer pain, 12,124 motor vehicle crashes were reported, along with the following: (1) an elevated risk of crash at doses under 60 MME, with an odds ratio of 3.86 (95% CI 3.54-4.21); (2) greater than threefold risk at higher-dose MME ranges; and (3) risks that were also elevated compared with prior periods of opioid nonuse (Quinn et al., 2022). A study of 36,642 drivers involved in 18,321 fatal two-vehicle crashes found prescription opioid use to be associated with a 2.18-fold risk of fatal crash (Chihuri et al., 2019). The risk of MVC is reportedly higher for methadone users compared to non-methadone users among patients with opioid use disorder (Yang et al., 2021, Bramness, 2012), as well as buprenorphine users (Corsenac et al., 2012). Prescription opioids have been found to increase fatal MVC risk by 72% compared with controls, independent of alcohol use (Li et al., 2019). Epidemiological studies have estimated that a 10% increase in opioid prescriptions results in a 1% increase in MVC fatalities (Betz et al., 2022).

In some population-based studies, the effects of prescription opioids compared with all opioid use (including illicit) are difficult to discern. One systematic review estimated that the prevalence of opioid use among fatally injured drivers rose approximately sevenfold, from 1% in 1995 to 7% in 2016 (Beaulieu et al., 2022). A similar sevenfold increase in opioid use among fatally injured drivers was found between 1995 and 2015 in another study of six states (California, Hawaii, Illinois, New Hampshire, Rhode Island, and West Virginia) (Chihuri S, 2017). Opioids were more recently found in 15% of fatal crashes in Ontario, Canada in 2015 (Woodall KL, 2015) and 14% in Maryland, USA in 2017, with the prevalence of opioids having risen among those fatally injured in crashes from 8.3% in 2006 to 14.1% in 2014 (Duren et al., 2019). Motor vehicle deaths associated with drug use outnumbered those associated with alcohol by 2016 in Milwaukee, with opioids (14%) following behind cannabinoids (29%) but statistically increasing over the 6-year study (Faryar et al., 2018). Australia also reported increases in opioid-related fatal vehicle crashes (Schumann J, 2021).

A study of Florida's experiences after the institution of a prescription drug monitoring program and new regulations for independent pain management clinics reported a 17% reduction in drug overdose deaths and a 9% reduction in motor vehicle crash deaths (Feder et al., 2020). Reductions in the proportions of motor vehicle crashes with injuries were especially noted after the Centers for Disease Control and Prevention's recommendations to reduce opioid prescriptions in 2016 (Jin et al., 2022). A correlational analysis from Florida associated the institution of their prescription drug monitoring program with reductions in drug-related fatal vehicle crashes (Tatar M, 2022), although cause and effect are speculative.

Unsafe driving actions (especially failure to stay in the lane) have been associated with opioid use that preceded fatal crashes (Dubois et al., 2010), which was similar to results of the previously described study of fatal two-vehicle crashes that also noted failure to stay in the lane as the most common error (Chihuri et al., 2019). There also is some evidence suggestive of a dose-response relationship with crashes (Gomes et al., 2013) (Bachs et al., 2009). Fentanyl has also been associated with increased risk of driving impairments, although much of that use may be illicit (Rohrig et al., 2021).

Some evidence suggests higher risk with acute opioid use, but risk remained elevated throughout treatment with an opioid; importantly, the findings of increased risks were reversed with opioid cessation (Gibson et al., 2009) (Hansen RN, 2017). This evidence appears to corroborate and complement a previously described study (Quinn et al., 2022), which also found elevated risk compared to pre-opioid treatment that persisted throughout opioid treatment. These findings strongly suggest opioids cause crashes instead of having an association with other factors, such as behavioral factors, that are responsible for the increased risk.

Driving simulator study data and other laboratory-based measures that attempt to infer crash risk conflict with the epidemiological data concerning crash risks, with most laboratory data suggesting a lack of increased risk (Chihuri S, 2017, Borgeat, 2010, Fishbain et al., 2002, Fishbain et al., 2003, Kress et al., 2005, Leung, 2011, Orriols et al., 2009, Strand et al., 2013) (Clemons et al., 1996) (Strand et al., 2013) (Menefee et al., 2004) (Jamison et al., 2003) (Tassain et al., 2003) (Sjogren, 1989) (Gaertner et al., 2006) (Sabatowski et al., 2003) (Dagtekin et al., 2007) (Tran et al., 2017). However, driving simulator studies are considered hypothesis-generating, and not the gold standard when there are numerous, largely consistent epidemiological studies to address risks (Verster et al., 2009). A driving performance study found a lack of driving impairment based on long-term amitriptyline use (van der Sluiszen, 2021).

Multiple other systematic reviews have found similar conclusions regarding the risk of crash associated with opioids (Chihuri S, 2017) (Elvik, 2013) (Kowalski-McGraw et al., 2017) (Tsai et al., 2023) (Verster et al., 2009). Unsurprisingly, based on the above data, it was recommended in 2017 to move several opioids to the mandatory (Tier I) testing category for investigation of drug-impaired motor vehicle fatalities, including buprenorphine, fentanyl, tramadol, and their metabolites (Logan et al., 2018).

INJURY RISKS

A large pharmacoepidemiological study found elevated risks of unintentional traumatic injuries, such as hip fracture or motor vehicle crashes, among patients who were newly prescribed hydrocodone, tramadol, and oxycodone and who were also prescribed another drug such as amoxicillin-clavulanate or telmisartan (Leonard et al., 2020). While not addressing risk among those using opioids chronically compared with non-use, a study of US veterans found a 31% elevated risk of accidents (i.e., accidents resulting in wounds/injuries, opioid-related and alcohol and non-opioid related accidents and overdoses, self-inflicted injuries) among those with an escalating opioid dose compared to those on stable doses; data supported a 21.7% increased risk of wounds/injuries 38.9% for self-inflicted injuries, and 66.7% for violence-related injuries (Hayes et al., 2020).

An increased risk of non-occupational falls has been reported in several other studies (Saunders et al., 2010) (Kamal-Bahl SJ, 2006, Ensrud KE, 2002, Söderberg KC, 2013, Richardson K, 2015, French DD, 2006) (Solomon et al., 2010) (Kelly et al., 2003) (Shorr et al., 1992), most of which were among the elderly. However, one case-crossover study of adults found the risk was highest among young adults, with a sevenfold risk of falls that was highest in the first week of opioid treatment. To date, a workplace-focused fall risk assessment associated with opioid use has not been reported. Systematic

reviews also have found an elevated risk of falls associated with use of opioids (Seppala LJ, 2018, Manias E, 2021, Yoshikawa A, 2020).

COGNITION

Randomized crossover trials have suggested cognitive impairment and/or sedation with feelings of impairments associated with the use of opioids (Kamboj et al., 2005, Babalonis et al., 2021). Cognitive deficits have been reported among patients with chronic opioid use for back pain (Schiltenwolf M, 2014), including slower information processing (Schiltenwolf M, 2014). Studies also report memory deficits (Jain G, 2014, Schiltenwolf M, 2014) and impairments in flexibility for concept change (Schiltenwolf M, 2014). Many studies have reported psychomotor slowing (Barker MJ, 2004, Anastassopoulos KP, 2012, Anastassopoulos KP, 2011, Pomara N, 2015). Systematic reviews of cognitive function are sparse and generally found modest reductions in memory, balance, reaction time, and attention (Akhurst J, 2021, Kurita GP, 2009, Allegri N, 2019, Block C, 2013, Higgins DM, 2018).

SUMMARY

Epidemiological studies are highly consistent that there is an estimated doubling of risk of motor vehicle crashes and there is an increased risk of falls from prescription opioid use. Evidence is also growing that other risks of opioids include cognitive function and memory impairments. Thus, the preclusion of safety-critical job functions while under treatment with opioids is recommended. For patients treated with opioids, sufficient time after the last dose is recommended to eliminate approximately 90% of the drug and active metabolites from their system, typically 3.3 half-lives (Metzner et al., 2009) (U.S. Department of Health and Human Services, 2017). Considerable caution is also warranted for patients consuming other CNS-depressant medications, such as benzodiazepines and sedating antihistamines, among whom opioids are not recommended.

Provider and organizational barriers to implement this recommendation are relatively few. However, there may be some patients taking opioids while employed in safety-critical jobs, and there are no validated tools to assess whether they can perform their job safely. There are other many other options for treatment (see other guidelines). There also are other options for opioid-dependent safety-critical workers, including naltrexone (Earley et al., 2017).

Evidence

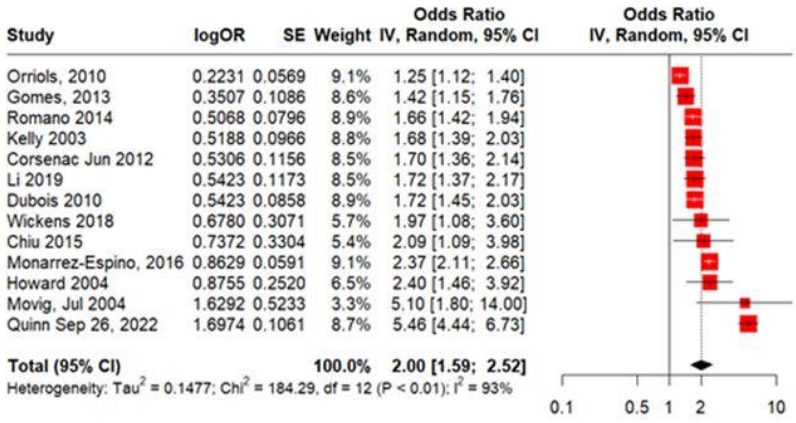
A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: safety-sensitive, safety-sensitive jobs, safety-sensitive work, safety-sensitive occupation; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 1 articles in PubMed, 2 in CINAHL, 3 in Cochrane Library, 123 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 0 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this

pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

For purposes of this guideline, a comprehensive synthesis with meta-analysis was performed to identify all relevant studies on safety-critical work. In all, 13 articles included sufficient data to allow for inclusion in this meta-analysis. Odds ratios were systematically aggregated according to findings delineated in the included studies. This compilation of studies was evaluated by subject matter experts to ascertain adherence to recognized methodological standards, including comparability of outcomes and opioid use measures. For enhanced clarity and interpretability, data were visualized using Microsoft Excel, employing the precise metrics provided by the individual studies. A large proportion of the potentially eligible studies were excluded due to the lack of the requisite case-control outcome data to calculate an overarching summary effect based on the reviewed literature (see Figure 4).

Figure 4. Meta-analysis of Safety-Critical Work Studies



4.3. ACUTE PAIN (UP TO 4 WEEKS)

The ACOEM guidelines, including this Opioids guideline, define *acute pain* as pain within the first month.

4.3.1. ACUTE NON-SEVERE PAIN

ROUTINE USE OF OPIOIDS FOR TREATMENT OF NONSEVERE ACUTE PAIN

Not Recommended

Routine opioid use is strongly not recommended for the treatment of nonsevere acute pain (e.g., low back pain, sprains, or minor/moderate injuries without signs of major tissue damage).

Strength of evidence Strongly Not Recommended, Evidence (A)
Level of confidence High

Benefits

Faster recovery, less debility, reduced accident risk, and reduced risk of dependency and risk of opioid use disorder.

Harms

May inadequately reduce acute, severe pain.

Rationale

For acute pain, there is quality evidence that other medications and treatments are at least equivalent if not superior to opioids. with no quality published evidence that an opioid is superior for treatment of acute pain to any of the following: multiple NSAIDs (Krebs EE, 2018) (Veenema et al., 2000) (Innes et al., 1998) (Ekman et al., 2006) (Clark et al., 2007) (Lovell et al., 2004) (Brown et al., 1986) (Muncie et al., 1986) (Chang et al., 2004) (Ekman et al., 2006) (Clark et al., 2007) (Lovell et al., 2004) (Veenema et al., 2000) (Innes et al., 1998) (Brown et al., 1986) (Muncie et al., 1986) (Chang et al., 2004) (Kumar et al., 2020), carisoprodol (Baratta, 1976) (Baratta, 1976), acupuncture (Grissa et al., 2016), and transcutaneous electrical nerve stimulation (TENS) (Ordog, 1987). There are many emergency department trials of very short-duration treatments (i.e., follow-ups of a few hours), which show minimal or no differences; therefore, they are also suggestive of non-inferiority of non-opioid approaches (Chang et al., 2006) (Chang et al., 2009) (Chang et al., 2009) (Chang et al., 2013) (Chang et al., 2011) (Chang et al., 2013) (Chang et al., 2013) (Turturro et al., 1998) (Turturro et al., 1991) (Jalili et al., 2012) (Bounes et al., 2010) (Marco et al., 2005) (Chang et al., 2006).

Quality evidence indicates that safety profiles are considerably worse for opioids. Studies also demonstrate worse functional outcomes for patients treated early with opioids (Webster et al., 2007) (Franklin et al., 2009) (Trevino et al., 2013) (Webster et al., 2007). Among trials for treatment of acute pain, ibuprofen was reportedly superior to codeine or acetaminophen for acute injuries, including fractures (Clark et al., 2007) (Clark et al., 2007). Diflunisal was equivalent to codeine for sprains, strains, and mild to moderate low back pain (LBP) (Muncie et al., 1986). Valdecoxib was better tolerated and trended towards greater pain relief than tramadol for ankle sprains (Ekman et al., 2006). Valdecoxib was equivalent to oxycodone as assessed by pain ratings, trended toward less rescue medication use, and had fewer adverse effects among patients with spine and extremity pain (Lovell et al., 2004). Tapentadol was found to be equivalent to morphine or oxycodone in one report of three randomized controlled trials (RCTs) (Viscusi et al., 2019). Global ratings for LBP showed carisoprodol is superior to propoxyphene and has fewer adverse effects (Baratta, 1976), although there are concerns about misuse of carisoprodol. A five-arm RCT of 600 emergency department patients with acute musculoskeletal pain found none of the analgesics (i.e., ibuprofen 400mg/acetaminophen 1g; ibuprofen 800mg/acetaminophen 1g; codeine 30mg/acetaminophen 300mg; hydrocodone 5mg/acetaminophen 300mg; oxycodone 5mg/acetaminophen 3225mg) to be superior to the other, although adverse effects among the opioids were worse, suggesting NSAIDs are preferable to opioids for initial treatment of pain (Bijur et al., 2021). The risk of mortality and other adverse reactions was greater among those prescribed an opioid compared with those prescribed an NSAID at hospital discharge (Herzig et al., 2021). An epidemiological study found worse outcomes among patients with work-related low back pain who were treated with an opioid in an emergency department, and recommended against use of an opioid for these patients (Lee et al., 2016).

Ketorolac was found to be equivalent for pain relief but superior to meperidine in terms of adverse effects for treating severe LBP (Veenema et al., 2000). Ketorolac was also superior to codeine/acetaminophen for acute LBP treated in emergency departments (Innes et al., 1998). Ketorolac appeared to be superior as a primary pain treatment supplemented with opioids compared with opioids alone for spine and joint procedures (Gora-Harper et al., 2001) (McNicol ED, 2021). An RCT found comparable pain efficacy but lower opioid requirements in the ketamine-treated arm for treatment of sickle cell crisis (Alshahrani et al., 2022). An epidemiological study found ketorolac use

for acute pain resulted in higher satisfaction than did opioid treatment (Pollack Jr et al., 2016). Diflunisal was reportedly superior to codeine/APAP for LBP (Brown et al., 1986).

There are no quality trials to suggest superiority of opioids to other active treatments, except for trials where the comparator was acetaminophen. An RCT comparing IV hydromorphone vs. IV acetaminophen for acute severe pain in the emergency department showed superiority of hydromorphone, although with adverse effects of nausea and vomiting (Barnaby et al., 2019); another trial in the same patient population found that the addition of acetaminophen to hydromorphone did not result in improved pain control (Bijur et al., 2020). An RCT found superiority of adding oxycodone to acetaminophen for treatment of acute musculoskeletal pain in the emergency department (Friedman et al., 2020). Another RCT of acetaminophen 1g IV vs. hydromorphone 0.5mg found hydromorphone statistically superior for pain reduction; however, the authors opined it was not clinically significant (Kolli et al., 2022). Long-term use of an opioid was found to be higher among recipients of a prescription from the higher prescribers in an emergency department (Barnett et al., 2017). Prolonged use of an opioid after an acute event has been associated with worse functional outcomes (Webster et al., 2007) (Franklin et al., 2009) (Trevino et al., 2013). Other systematic reviews have found similar results (Sin B, 2019, Gu HY, 2019).

Ketamine has been increasingly investigated for the treatment of acute pain. Trials found ketamine used as an adjunct to an opioid resulted in better pain control, but with worse problems of dizziness and light-headedness (Bowers et al., 2017, Hosseininejad et al., 2019). Comparative trials have both better pain control with ketamine (Mahshidfar et al., 2017), lower opioid consumption (Takieddine, 2017), and non-inferiority/comparable efficacy (Motov et al., 2019)(Tongbua, 2022)(Miller et al., 2015). A trial compared ketamine plus haloperidol (used to counter the ketamine adverse effect of agitation) compared with fentanyl for management of acute pain in the emergency department and found comparable efficacy for pain but lower adverse effects for the ketamine plus haloperidol (Moradi et al., 2022).

An epidemiological study of 357,884 patients found higher risks of chronic opioid use after treatment with tramadol (Thiels et al., 2019). A case series of 2,413 emergency department patients discharged with suspected urolithiasis found opioid prescriptions at discharge were associated with doubling of the risk of persistent pain (Wentz et al., 2021).

Thus, routine use of either weak or strong opioids for the treatment of acute pain is strongly not recommended.

For those necessitating use of an opioid, the lowest effective dose of a short-acting opioid is recommended for those with acute, severe pain uncontrolled by other agents such as NSAIDs (Cifuentes et al., 2010). Additionally, other non-opioid strategies should be considered before an opioid (e.g., muscle relaxants, ice/heat). Lower potency opioids are recommended when sufficient for pain relief and only in quantities sufficient for the pain (Bouida et al., 2019). A morphine equivalent dose limit of 50mg is recommended for the treatment of acute pain (Bohnert et al., 2011) (see Figure 3). Higher doses should be based on documented need and increased surveillance for adverse effects. PDMPs are recommended to be checked, although that alone will often fail to detect opioid use disorder (Hawk et al., 2018). NSAIDs or acetaminophen should generally accompany an opioid prescription. Considerable caution is recommended among those with other CNS-depressing medications such as benzodiazepines, or other risk factors for adverse effects, overdose, and death (Centers for Disease Control and Prevention, 2010) (Hall et al., 2008) (Wunsch et al., 2009) (Green et al., 2011) (Paulozzi et al., 2012) (Cheng et al., 2013) (Eriksen et al., 2006) (Atluri et al., 2004) (Shah et al., 2008) (Webster et al., 2011) (Dunn et al., 2010) (Paulozzi et al., 2009) (Grattan et al., 2012) (Manchikanti et al., 2004) (Nyhlen et al., 2011) (Hadidi et al., 2009) (Wysowski et al., 2006) (Wysowski,

2007) (Toblin et al., 2010) (Centers for Disease Control and Prevention, 2005) (Fareed et al., 2009) (Deyo et al., 2011) (Goodridge et al., 2010) (Dean, 2004) (Seal et al., 2012) (Mills et al., 2005). Due to risk of impairments and lost time from work (Volinn et al., 2009) (Dersh et al., 2008), a low-dose, low-potency opioid should be prescribed at night or while not working when possible (Gomes et al., 2013). If use goes beyond 3 days, a plan for cessation is generally needed. A taper may be necessary especially if higher doses are used and use is beyond 2 weeks.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: nonsevere acute pain; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 7 articles in PubMed, 4 in CINAHL, 0 in Cochrane Library, 4 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 0 articles considered for inclusion, 0 randomized trials and 0 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: Comparison; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 800 articles in PubMed, 3515 in CINAHL, 31 in Cochrane Library, 19,270 in Google Scholar, and 0 from other sources†. We considered for inclusion 12 from PubMed, 4 from CINAHL, 0 from Cochrane Library, 35 from Google Scholar, and 0 from other sources. Of the 21 articles considered for inclusion, 6 randomized trials and 12 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.3.2. ACUTE SEVERE PAIN

OPIOIDS FOR TREATMENT OF ACUTE, SEVERE PAIN

Recommended

Use of an opioid is selectively recommended for treatment of acute, severe pain (e.g., crush injuries, large burns, injury with significant tissue damage) uncontrolled by other agents, treatments and/or with functional deficits caused by pain (AMDG, 2015). They also may be indicated at the initial visit for a brief course for anticipated pain accompanying severe injuries (i.e., failure of other treatment is not mandatory), although they should be adjunctive to a co-prescription of NSAIDs whenever possible (Busse et al., 2020). Weak opioids may be indicated if there is true allergy to nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, other contraindications to an alternative medication, or insufficient pain relief with an alternative. A Schedule II opioid may be indicated for more severe pain that is not sufficiently addressed with other approaches. It is recommended to stop

or taper off opioid use ideally in 3 to 5 days. If use goes beyond 3-5 days, a plan for cessation is generally needed. A taper may be necessary especially if higher doses are used and use is beyond 2 weeks.

Long-term opioid use often begins with treatment of acute pain (Cheng et al., 2013, Durand et al., 2019). When an opioid is used for acute pain, clinicians should prescribe the lowest effective dose of an immediate-release opioid and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require the opioid. Because adverse effects and risks increase with dose, especially when greater than 50 mg morphine milligram equivalents (MME), the dose for acute pain should generally be approximately 20 mg MME and not exceed 50 mg MME for an individual who is not currently taking an opioid. A duration of 3 days or less will often be sufficient; more than 7 days will rarely be needed (Dowell D, 2016, Dowell et al., 2016, Dowell et al., 2022, Centers for Disease Control and Prevention, 2022). Acute and perioperative pain management is particularly challenging among patients who are already taking an opioid because the risks of overdose and fatality increase with dose, there is less efficacy among patients who are already taking an opioid, and there is a lower margin for error with higher doses (see also chronic pain recommendations).

Strength of evidence Recommended, Evidence (C)
Level of confidence High

Indications

Patients should meet all of the following:

1. Severe injury with a clear rationale for use (objective functional limitations due to pain resulting from the medical problem, e.g., extensive trauma such as forearm crush injury, large burns, severe radiculopathy). See examples of decision logic in Table 1. (Other indications beyond the scope of this guideline may include acute myocardial infarction or agitation interfering with acute trauma management.) Back pain and neck pain not due to major trauma (e.g., fractures) are not recommended to be treated with an opioid, as there are many effective strategies that should be implemented first and assessed for efficacy (e.g., directional stretching, progressive walking, NSAIDs, muscle relaxant at night, heat/ice; see Low Back Disorders Guideline), while there also is quality RCT evidence of lack of efficacy (Jones et al., 2023).
2. Other more efficacious treatments should have been instituted, and either were documented to have failed and/or have reasonable expectations of the immediate need for an opioid to obtain sleep the evening after the injury.
3. Prescription databases (usually referred to as Prescription Drug Monitoring Program (PDMP)) should be checked and not show evidence of concomitant prescriptions, conflicting opioid prescriptions from other providers, or evidence of misreporting. These databases include data from other states. Any of these are strong contraindications for a prescription, especially in the absence of severe objective injury. (Exceptions such as acute, severe trauma should be documented.) When the PDMP database and/or patient history indicates other opioid medication(s) have been recently used, yet there is need for a second prescription of an opioid, a few days of prescription at a low, additional dose (e.g., 20mg morphine equivalent dose (MED), not generally to exceed a total dose of 90mg MED) may be reasonable with close monitoring.
4. Non-opioid prescriptions (e.g., NSAIDs, acetaminophen) absent contraindication(s) should nearly always be the primary treatment and accompany an opioid prescription (Busse et al., 2020). Due to greater than 10-fold elevated risks of adverse effects and death, considerable caution is warranted among those using other sedating medications and substances, including benzodiazepines, anti-histamines (H1-blockers), and/or illicit substances (Green et

al., 2011) (Cheng et al., 2013) (Eriksen et al., 2006) (Atluri et al., 2004) (Carico et al., 2018). Patients should not receive an opioid if they use illicit substances unless there is objective evidence of significant trauma and at least moderate to severe injuries. Considerable caution is also warranted among those who are or have:

- older age (>65 yrs.)
- younger age, especially teenagers (Miech et al., 2015)
- pregnant
- sleep apnea
- psychiatric/mental health disorders (anxiety, depression, personality disorder, suicidal)
- drug-seeking behavior
- current or past substance use
- prior drug overdose
- consuming alcohol in combination with an opioid
- renal insufficiency
- hepatic insufficiency
- unemployed (10-fold risk of death) (Cheng et al., 2013) (Eriksen et al., 2006).

Due to elevated risk of death and adverse effects, caution is also warranted when considering prescribing an opioid for patients with any of the following characteristics: use of other psychotropic medications, family history of substance use disorder, current tobacco use, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), impulse control problems, thought disorders, chronic obstructive pulmonary disease (COPD), or recurrent pneumonia (Centers for Disease Control and Prevention, 2008) (Hall et al., 2008) (Wunsch et al., 2009) (Paulozzi et al., 2012) (Cheng et al., 2013) (Shah et al., 2008) (Webster et al., 2011) (Dunn et al., 2010) (Paulozzi et al., 2009) (Grattan et al., 2012) (Manchikanti et al., 2004) (Nyhlen et al., 2011) (Hadidi et al., 2009) (Wysowski et al., 2006) (Wysowski, 2007) (Toblin et al., 2010) (Centers for Disease Control and Prevention, 2005) (Fareed et al., 2009) (Deyo et al., 2011) (Goodridge et al., 2010) (Dean, 2004) (Seal et al., 2012) (Mills et al., 2005) (Washington State Department of Labor & Industries, 2010).

Additional risks and/or adverse effects are thought to be present from other comorbidities such as chronic hepatitis and/or cirrhosis (Walter et al., 2011), coronary artery disease, dysrhythmias, cerebrovascular disease, orthostatic hypotension, asthma, thermoregulatory problems, advanced age (especially with mentation issues, balance problems, fall risk, debility), osteopenia, osteoporosis, water retention, severe obesity, testosterone deficiency, erectile dysfunction, abdominal pain, gastroparesis, constipation, prostatic hypertrophy, oligomenorrhea, human immunodeficiency virus (HIV), ineffective birth control, herpes, allodynia, dementia, cognitive dysfunction and impairment, gait problems, tremor, concentration problems, insomnia, coordination problems, and slow reaction time. There are considerable drug-drug interactions that have been reported (see Appendices 2-3).

Patients should be educated on the proper storage and disposal of opioids at the time of the initial prescription and at every visit, as secondary fatalities from misuse and accidental poisonings of children, adolescents, and young adults are common.

Benefits

Improved short-term pain reduction by approximately 1 on 11-point pain rating scale (Busse et al., 2020).

Harms

Adverse effects are many and include: nausea, vomiting, delayed gastric emptying, constipation, bladder dysfunction, urinary retention, pruritus, drowsiness, sedation, respiratory depression, central sleep apnea, obstructive sleep apnea, euphoria, dysphoria, cognitive impairment, clouded consciousness, decreased concentration, reduced decision making, lack of impulse control, slowed reaction time, reduced coordination, balance problems, myoclonus, muscle rigidity, altered color vision, dizziness, euphoria, sexual dysfunction, anaphylaxis, motor vehicle crashes, falls, fractures, emergency department visits, and risk of hospitalization. Nonunion fractures have been associated with both NSAIDs and opioids suggesting these associations may be due to confounding (Tian et al., 2020).

Chronic use has been additionally associated with gynecomastia, reduced circulating testosterone, erectile dysfunction, infertility, amenorrhea, oligomenorrhea, preterm birth, neonatal abstinence syndrome, osteopenia, osteoporosis, coronary events, immune suppression, invasive pneumococcal disease, hair loss, tolerance, physical dependence, psychological dependence, opioid use disorder, suicide (high dose use), and death. Avocational and job-related safety-related issues are considerable (see separate recommendation on Safety-Critical Work) and require discussing with patients prior to prescribing (Cullen KL, 2018, Loisel P, 2002).

Use of an opioid is also associated with reduced return-to-work status, reduced function, and disability.

Opioids have worse risk-to-benefit ratios than NSAIDs (Busse et al., 2020).

Frequency/Dose/Duration

Generally, a low dose, low potency opioid should be prescribed at night or while not working (Gomes et al., 2013). The lowest effective, short-acting opioid doses are preferable for acute and perioperative pain as they tend to have the better safety profiles, less risk of escalation (Cifuentes et al., 2010), less risk of lost time from work (Volinn et al., 2009), and faster return to work (Dersh et al., 2008). Patient characteristics should be considered, such as age, race, ethnicity, gender/sex, body size, physical and cognitive disabilities, education level, socioeconomic status, immigration status, refugee status, and geography (urban vs. rural). For example, a low-dose opioid may be needed in the elderly who have greater susceptibility to the adverse risks of an opioid. Those of lower body weight may also require lower opioid doses. There is evidence of unconscious bias and racism impacting opioid prescriptions across diverse populations (e.g., (Kunins, 2020, Swift SL, 2019). However, in general, reductions in opioid prescriptions may be significantly beneficial. A short-acting opioid is recommended for treatment of acute pain and long-acting opioids are not recommended. Opioids should be used as required by pain, rather than in regularly scheduled dosing (except severe pain, such as extensive burns). Due to strong dose-dependent effects and fatality risks, doses for acute pain should generally be up to ~20mg MME and not exceed 50mg MME. Exceptions should be clearly documented (e.g., long-term prior use and thus accustomed to opioids), although caution is warranted as dose-response mortality risks do not reduce based on accustomization (see below).

Dispensing quantities should be only what is needed to treat the pain, because evidence shows that excessive prescriptions are common and the extra medication is rarely properly disposed of (Engstrom et al., 2022). Because evidence suggests duration is a greater risk for long-term opioid use than dose (Durand et al., 2019, Edlund et al., 2014) (Riva et al., 2020); duration beyond 7 days is a significant risk for disability at 1 year (Franklin et al., 2008), and subsequent opioid use disorder (Edlund et al., 2014), the first prescription should generally not exceed 3 days and rarely more than 7 days. An epidemiological study found that patients who were treated in the emergency department consumed a median of 10 tablets (Daoust et al., 2018). Emergency departments and urgent care clinics without

continuity should generally not dispense refills. At 3 to 7 days, continuity should either be established or in the process of establishment with reassessment recommended to ascertain curative treatment(s), function, progress, and other adjunctive treatments to consider.

If parenteral administration is required, ketorolac has demonstrated superior efficacy compared with opioids for acute severe pain (Veenema et al., 2000) (Innes et al., 1998), although ketorolac's risk profile may limit use for some patients. Meloxicam is another option. Use of an opioid is not recommended for management of spine pain, as there are many other, more efficacious interventions to be utilized for acute pain (see Low Back Disorders and Cervical and Thoracic Spine Disorders Guidelines). Parenteral opioid administration outside of obvious acute trauma or surgical emergency conditions is rarely required.

Indications for discontinuation

Resolution of pain, ongoing functional impairment without objective evidence of injury, sufficient improvement in pain, intolerance or adverse effects, non-compliance, surreptitious medication use, consumption of medications or substances advised to not take concomitantly (e.g., sedating medications, alcohol, benzodiazepines), or use beyond 2 weeks. Apparent need for an opioid beyond 2 weeks is an indication for re-assessment of the diagnosis and adequacy of compliance with non-opioid interventions shown to be successful.

Rationale

For acute pain, there is quality evidence that other medications and treatments are at least equivalent if not superior to opioids, and no quality published evidence that an opioid is superior for treatment of acute pain to any of the following: multiple NSAIDs (Krebs EE, 2018) (Veenema et al., 2000) (Innes et al., 1998) (Ekman et al., 2006) (Clark et al., 2007) (Lovell et al., 2004) (Brown et al., 1986) (Muncie et al., 1986) (Chang et al., 2004) (Ekman et al., 2006) (Clark et al., 2007) (Lovell et al., 2004) (Veenema et al., 2000) (Innes et al., 1998) (Brown et al., 1986) (Muncie et al., 1986) (Chang et al., 2004) (Kumar et al., 2020) (Bijur et al., 2021), carisoprodol (Baratta, 1976) (Baratta, 1976), acupuncture (Grissa et al., 2016), and transcutaneous electrical nerve stimulation (TENS) (Ordog, 1987).

There are many emergency department trials of very short-duration treatments using follow-ups of a few hours, with minimal or no differences; therefore, they are also suggestive of the non-inferiority of non-opioid approaches (Chang et al., 2006) (Chang et al., 2009) (Chang et al., 2009) (Chang et al., 2013) (Chang et al., 2011) (Chang et al., 2013) (Chang et al., 2013) (Turturro et al., 1998) (Turturro et al., 1991) (Jalili et al., 2012) (Bounes et al., 2010) (Marco et al., 2005) (Chang et al., 2006). Quality evidence indicates safety profiles are considerably worse for opioids. Studies also demonstrate worse functional outcomes for patients treated early with an opioid (Webster et al., 2007) (Franklin et al., 2009) (Trevino et al., 2013) (Webster et al., 2007). Among trials for the treatment of acute pain, ibuprofen was reportedly superior to codeine or acetaminophen for acute injuries, including fractures (Clark et al., 2007) (Clark et al., 2007). Diflunisal was equivalent to codeine for sprains, strains, and mild to moderate low back pain (LBP) (Muncie et al., 1986). Valdecoxib was better tolerated and trended towards greater pain relief than tramadol for ankle sprains (Ekman et al., 2006). Valdecoxib was equivalent to oxycodone as assessed by pain ratings, trended toward less rescue medication use, and had fewer adverse effects among spine and extremity pain patients (Lovell et al., 2004). Tapentadol was found to be equivalent to morphine or oxycodone in one report of three randomized controlled trials (RCTs) (Viscusi et al., 2019). Global ratings for LBP showed carisoprodol is superior to propoxyphene and has fewer adverse effects (Baratta, 1976), although there are concerns about misuse of carisoprodol. A five-arm RCT of 600 emergency department patients with acute musculoskeletal pain found none of the analgesics (i.e., ibuprofen 400mg/acetaminophen 1g;

ibuprofen 800mg/acetaminophen 1g; codeine 30mg/acetaminophen 300mg; hydrocodone 5mg/acetaminophen 300mg; oxycodone 5mg/acetaminophen 3225mg) to be superior to the other, although adverse effects among those prescribed an opioid were worse, suggesting NSAIDs are preferable to opioids for initial treatment of pain (Bijur et al., 2021). An epidemiological study found worse outcomes among work-related low back pain patients treated with an opioid in an emergency department, and recommended against use of opioids for these patients (Lee et al., 2016).

Ketorolac was found to be equivalent for pain relief, but superior to meperidine in terms of adverse effects for treating severe LBP (Veenema et al., 2000). Ketorolac was also superior to codeine/acetaminophen for acute LBP treated in emergency departments (Innes et al., 1998). Ketorolac appeared superior as a primary pain treatment supplemented with an opioid compared with use of an opioid alone for spine and joint procedures (Gora-Harper et al., 2001) (McNicol ED, 2021). An RCT found comparable pain efficacy but lower opioid requirements in the ketamine-treated arm for treatment of sickle cell crisis (Alshahrani et al., 2022). An epidemiological study found ketorolac use for acute pain resulted in higher satisfaction then opioid treatment (Pollack Jr et al., 2016). Diflunisal was reportedly superior to codeine/APAP for LBP (Brown et al., 1986). There are no quality trials to suggest superiority of opioids to other active treatments, except for trials where the comparator was acetaminophen (Bouida et al., 2019, Barnaby et al., 2019, Bijur et al., 2020, Friedman et al., 2021, Friedman et al., 2020, Kolli et al., 2022). An RCT comparing IV hydromorphone vs. IV acetaminophen for acute severe pain in the emergency department showed superiority of hydromorphone although with adverse effects of nausea and vomiting (Barnaby et al., 2019); another trial in the same patient population found addition of acetaminophen to hydromorphone did not result in improved pain control (Bijur et al., 2020). An RCT found superiority of adding oxycodone to acetaminophen for treatment of acute musculoskeletal pain in the emergency department (Friedman et al., 2020), and another trial in the same setting reported oxycodone/ibuprofen 600mg superior to ibuprofen 600/placebo but with ~3-fold greater adverse effects (Friedman et al., 2021). Another RCT of acetaminophen 1g IV vs. hydromorphone 0.5mg found hydromorphone statistically superior however, the authors opined it was not clinically significant (Kolli et al., 2022). Prolonged use of an opioid after an acute event has been associated with worse functional outcomes (Webster et al., 2007) (Franklin et al., 2009) (Trevino et al., 2013). Other systematic reviews have found similar results (Sin B, 2019, Gu HY, 2019). Ketamine has been increasingly investigated for treatment of acute pain. Trials found ketamine used as an adjunct to an opioid resulted in better pain control, but with worse problems of dizziness and light headedness (Bowers et al., 2017, Hosseininejad et al., 2019). Comparative trials have both better pain control with ketamine (Mahshidfar et al., 2017), lower opioid consumption (Takieddine, 2017), and non-inferiority/comparable efficacy (Motov et al., 2019)(Tongbua, 2022)(Miller et al., 2015). A trial compared ketamine plus haloperidol (used to counter the ketamine adverse effect of agitation) compared with fentanyl for management of acute pain in the emergency department and found comparable efficacy for pain but lower adverse effects for the ketamine plus haloperidol (Moradi et al., 2022). An epidemiological study of 357,884 patients found higher risks of chronic opioid use after treatment with tramadol (Thiels et al., 2019). A case series of 2,413 emergency department patients discharged with suspected urolithiasis found opioid prescriptions at discharge were associated with doubling of the risk of persistent pain (Wentz et al., 2021).

Thus, routine use of either a weak or a strong opioid for treatment of acute pain is strongly not recommended. The lowest effective dose of a short-acting opioid is recommended for those with acute, severe pain uncontrolled by other agents such as NSAIDs (Cifuentes et al., 2010). Additionally, other non-opioid strategies should be considered before use of an opioid (e.g., muscle relaxants, ice/heat). Lower potency opioids are recommended when sufficient for pain relief and dispensing only quantities sufficient for the pain are recommended (Bouida et al., 2019). A morphine equivalent dose limit of 50mg is recommended for treatment of acute pain (Bohnert et al., 2011) (see Figure 3).

Exceeding that should be based on documented need and increased surveillance for adverse effects. The relevant jurisdiction's PDMP database is recommended to be checked, although that alone will often fail to detect opioid use disorder (Hawk 2018). NSAIDs or acetaminophen should generally accompany an opioid prescription. Considerable caution is recommended among those with other CNS depressing medications such as benzodiazepines, or other risk factors for adverse effects, overdose and death (CDC, 2010) (Allen et al., 2021) (Park et al., 2020) (Green et al., 2011) (Paulozzi et al., 2012) (Cheng et al., 2013) (Eriksen et al., 2006) (Clement et al., 2021) (Shah et al., 2008) (Webster et al., 2011) (Dunn et al., 2010) (Paulozzi et al., 2009) (Grattan et al., 2012) (Manchikanti et al., 2004) (Nyhlen et al., 2011) (Hadidi et al., 2009) (Wysowski et al., 2006) (Wysowski, 2007) (Toblin et al., 2010) (CDC, 2005) (Fareed et al., 2009) (Deyo et al., 2011) (Goodridge et al., 2010) (Dean, 2004) (Seal et al., 2012) (Mills et al., 2005). Due to risk of impairments and lost time from work (Volinn et al., 2009) (Dersh et al., 2008), a low dose, low potency opioid should be prescribed at night or while not working when possible (Gomes et al., 2013). If use goes beyond 3 days, a plan for cessation is generally needed. A taper may be necessary especially if higher doses are used and use is beyond 2 weeks.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: Acute Pain; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 477 articles in PubMed, 170 in CINAHL, 613 in Cochrane Library, 35700 in Google Scholar, and 0 from other sources†. We considered for inclusion 33 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 35 articles considered for inclusion, 22 randomized trials and 7 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.3.3. INITIAL SCREENING

INITIAL SCREENING OF PATIENTS PRIOR TO INITIATION OF OPIOIDS

Recommended

An initial screening of patients is recommended prior to the initiation of opioid treatment. More detailed screening is recommended in the following cases: 1) patients with an acute severe injury who require continuation of an opioid beyond 2 weeks; and 2) patients for whom there is consideration of opioid initiation for severe pain but no objective evidence.

Screening should include history of depression, anxiety, catastrophizing, personality disorder, other psychiatric disorder, substance use, sedative use (e.g., antihistamine/anti-H1 blocker), benzodiazepine use, opioid dependence, alcohol misuse, current tobacco use, other substance use, chronic obstructive pulmonary disease, sleep quality, sleep apnea, posttraumatic stress disorder, other psychotropic medications, (severe) obesity, cognitive impairment, balance problems/fall risk, osteoporosis, and renal failure (see Appendix 1).

For patients who screen positive, especially to multiple criteria, the following are recommended: 1) greater scrutiny for the appropriateness of opioid use (may include psychological evaluation); 2) consideration of consultation and examination(s) for complicating conditions and/or appropriateness of use of an opioid; and 3) if an opioid is prescribed, more frequent assessments for compliance, achievement of functional gains, adverse effects, and symptoms and signs of aberrancy. The clinician should use responses to the screening tools as alerts to unexplored areas and pursue further discussions with the individual patient regarding the new areas revealed.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence High

Benefits

Improved identification of more appropriate candidates for opioid prescriptions. Identification of patients at increased risk of adverse effects. In cases where the patient has elevated but potentially acceptable risk, screening may alert the provider to improve surveillance for complications and aberrant behaviors.

Harms

Negligible. If a consultation is needed, modest costs are incurred.

Rationale

Many opioid screening tools, as well as a generic review of opioid misuse risk factors, are typically used. Some screening tools have been validated for the detection of aberrant use, mostly in patients with chronic pain. Prior evaluation has shown poor discriminant ability for the Opioid Risk Tool, Screener and Opioid Assessment for Patients with Pain-Revised, and the Current Opioid Misuse Measure in emergency department patients (Chalmers et al., 2019). No quality studies indicate pre-treatment screening results are associated with improved outcomes. Yet, it has been suggested that pre-screening is effective (Cheatle et al., 2018). Furthermore, high-risk patients seem less likely to be prescribed an opioid, which produces a systematic bias in scientific literature. There is strong reason to believe that screening (and acting on screening results) may result in reduced adverse effects and risks. Thus, pre-treatment screening is recommended.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: screening prior to opioid initiation; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 149 articles in PubMed, 0 in CINAHL, 18 in Cochrane Library, 2 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 0 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If

relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.3.4. MAXIMUM DAILY DOSE

MAXIMUM DAILY ORAL OPIOID DOSES FOR PATIENTS IN ACUTE PAIN

Recommended

For opioid-naïve patients with acute pain, the recommended maximum daily oral dose based on the risk of overdose/death is 50 mg MME (Bohnert et al., 2011). (*Statistical significance is present for acute and chronic pain at and above 50 mg per day of oral morphine equivalent dose, or MME.)* Only the dose, frequency, and numbers of pills required should be dispensed.

In rare cases with documented functional improvement, higher doses may be considered; however, the risks are substantially higher and greater monitoring is also recommended (see Subacute/Chronic Opioid recommendations). Lower doses should be used for patients at higher risk of dependency, opioid use disorder, or other adverse effects. Monitoring is also recommended and consultation may be considered for those patients on higher doses.

Strength of evidence Recommended, Evidence (C)
Level of confidence Moderate

Benefits

Reduced risk for adverse physical, mental, and cognitive effects; dependency; opioid use disorder; and opioid-related overdoses and deaths.

Harms

Theoretical potential to undertreat pain in some patients.

Rationale

A population-based study of 154,684 patients analyzed the risks among patients taking opioids compared with no use of opioids. The study documented a dose-response relationship between opioid dose and overdose/deaths, which also suggested largely identical relationships whether the opioid use was acute or chronic (Dunn et al., 2010, Bohnert et al., 2011). The risks were markedly elevated beyond 50 mg MME (Bohnert et al., 2011). A study of Ohio worker's compensation cases also found dose-response relationships between opioid dose and deaths, especially above 120 mg MED, although deaths were 1.5- to 3.2-fold elevated above 40 mg MED (Freeman A, 2022).

A large Veterans Affairs (VA) study found a dose-response relationship with fourfold risk of serious prescription opioid-related toxicity or overdose among those taking 100 mg MME compared with a low opioid dose (Zedler B, 2014). Other studies with a low-dose group for comparison have found similar dose-response relationships, which were naturally reduced by using a low dose instead of a no-dose comparison group (Gomes, 2011).

Other large studies also report higher incidence of complications with higher doses (Quinn et al., 2022). A dose-response increase in the risk of suicide with increased opioid dose starting above 20 mg MME has been reported, rising to a hazard ratio of 2.15 (95% CI 1.64, 2.81) at >100 mg MME (Ilgen MA, 2016). An increased risk of overdose among those with depression that is a dose-response

relationship has been reported, with a more than 50% increased risk among those using at least 100 mg MME (Turner BJ, 2015).

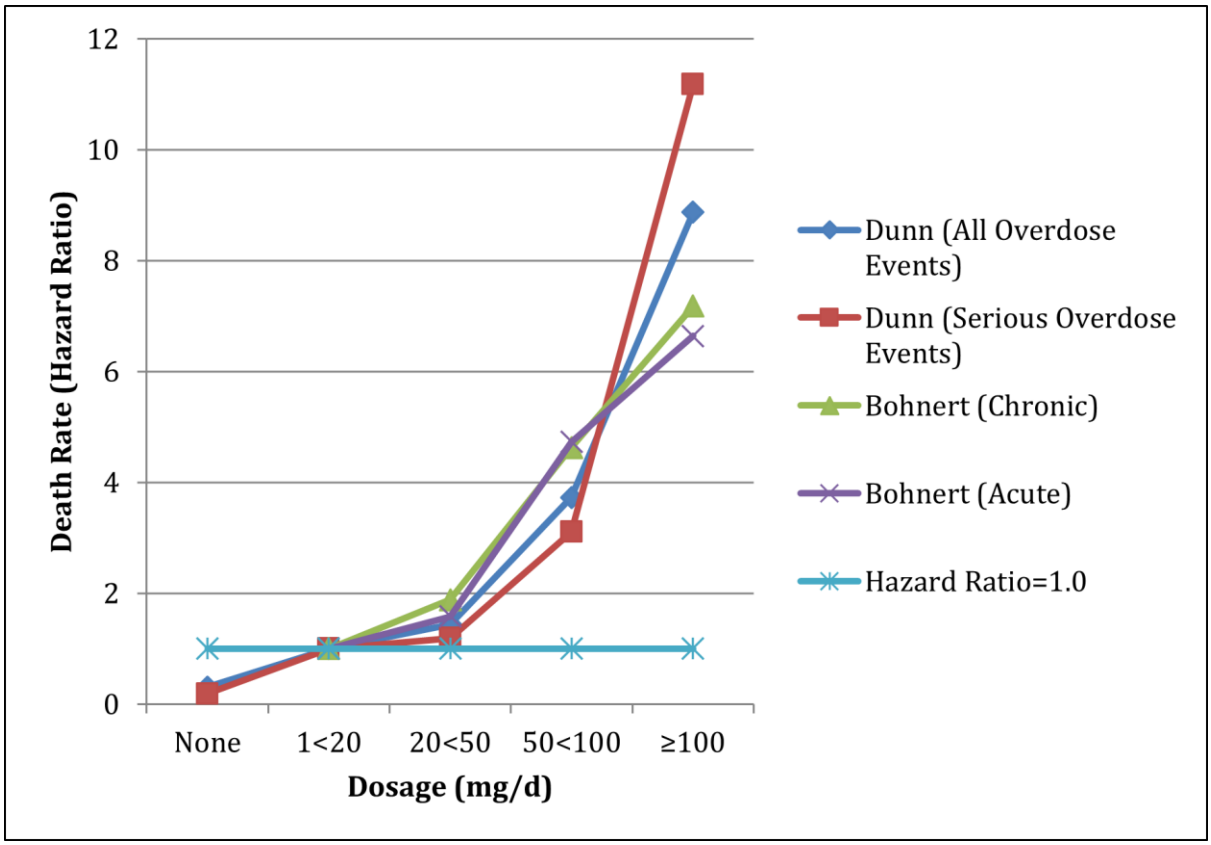
CDC recommendations in 2022 removed references to dose-response risks in recommendation statements, while retaining dose-response data in discussion sections (Dowell et al., 2022). Because there is large-scale evidence of a strong dose-response relationship and the data and relationship for chronic use largely duplicate the data for acute use, this suggests there is quality evidence on which to form evidence-based guidance. Importantly, there does not appear to be a reduction in mortality/overdose risk with chronic use compared with the same dose for acute pain treatment use. The lowest effective dose is recommended. Generally, 20 mg MME is advised as a reasonable dose for acute pain (up to 50 mg MME). Acute and perioperative pain use beyond 50 mg MME is generally not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: maximum daily oral dosing, maximum oral dosing, acute pain; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 226 articles in PubMed, 0 in CINAHL, 105 in Cochrane Library, 0 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 0 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Figure 3. Death Rate (Hazard Ratio) vs. Morphine Equivalent Dosage (mg/day)*



Adapted from (2) and (3).

**Statistical significance present for acute and chronic pain at and above 50 mg per day of oral morphine equivalent dose.*

4.4. SUBACUTE (1-3 MONTHS) AND CHRONIC PAIN (3+ MONTHS)

For purpose of the ACOEM guidelines, including this Opioids guideline, *subacute pain* includes pain lasting from 1 to 3 months. Often, this includes pain that is persisting beyond expected healing time and sometimes cannot be ascribed to a specific injury. Many researchers believe chronic pain features are present in this timeframe among those who develop chronic pain.

Pain lasting more than 3 months is defined as *chronic*. Chronic pain has also been sometimes defined as persisting beyond expected healing time and not clearly ascribable to a specific injury or area of tissue pathology.

Individuals who are prescribed opioids on a chronic basis have a high risk of death, which has been estimated at 20.8% over approximately 5 years in an opioid registry (although not all are opioid-related fatalities) (4). Thus, the decision to continue opioids on a long-term basis and/or to initiate a opioid trial should be carefully considered.

4.4.1. OPIOID USE

OPIOID PRESCRIPTIONS FOR SUBACUTE AND CHRONIC NONMALIGNANT PAIN

Not Recommended

Opioid use is moderately not recommended for treatment of subacute and chronic nonmalignant pain. Opioid prescription should be patient-specific and limited to cases in which other treatments are insufficient and criteria for opioid use are met (see below).

Strength of evidence Moderately Not Recommended, Evidence (B)
Level of confidence High

Benefits

Less debility, fewer adverse effects, reduced accident risks, lower risks of dependency, opioid use disorder, overdoses, and deaths.

Harms

May inadequately treat severe subacute or chronic pain.

Indications for discontinuation

Opioids should be tapered and discontinued (see Tapering) based on lack of functional benefit (International Association of Industrial Accident Boards and Commissions, 2013), resolution of pain, improvement to the point of not requiring opioids, intolerance or adverse effects, non-compliance, surreptitious medication use, medication misuse (including self-escalation and sharing medication), aberrant drug screening results, diversion, consumption of medications or substances advised to not take concomitantly (e.g., sedating medications, alcohol, benzodiazepines) (FDA, 2016) (Dasgupta et al., 2016).

Rationale

There are no long-term trials documenting superiority of opioids to NSAIDs, and comparisons with placebo demonstrate only modest efficacy (0.69/11 points; Busse 2018) (Meske et al., 2018). There is quality evidence that other medications and treatments are at least equivalent if not superior for subacute or chronic pain, such as NSAIDs (Pavelka et al., 1998) (O'Donnell et al., 2009) (Parr et al., 1989) (Jamison et al., 1998) (DeLemos et al., 2011, Krebs EE, 2018, Ouncharoen, 2018), clonidine (Siddall et al., 2000), and flupirtine (Li et al., 2008). There is conflicting evidence regarding whether antidepressants have equivalency (Khoromi et al., 2007) (Raja, 2002). Safety profiles are considerably worse for subacute and chronic use of opioids.

There are no quality trials to suggest superiority of opioids to other common active treatments (Beaulieu et al., 2008, Ouncharoen, 2018). One trial suggests morphine is superior to benztropine for pain, but not function (Moulin et al., 1996). Among trials for treatment of subacute or chronic pain, one trial failed to find superiority of morphine to nortriptyline for treatment of chronic lumbar radiculopathy (Khoromi et al., 2007). Another found neither morphine nor mexiletine superior to placebo (Wu et al., 2008). Another found celecoxib superior to tramadol for chronic LBP (O'Donnell et al., 2009). Diclofenac was superior to dextropropoxyphene/APAP for treatment of hip or knee osteoarthritis (Parr et al., 1989). Diclofenac was approximately equivalent to tramadol in another trial (Pavelka et al., 1998). Naproxen was equivalent to oxycodone for treatment of chronic LBP (Jamison et al., 1998). Few trials primarily targeted patients with subacute pain; these patients are included in the chronic pain section due to the speed with which dependency can arise. The main exception is one trial finding flupirtine was equivalent to tramadol for subacute LBP (Li et al., 2008). Buprenorphine has been recently explored for treatment of chronic pain (Rauck et al., 2016, Gimbel et al., 2016).

There are no trials documenting improved objective functional outcomes, with more than 100 studies documenting many adverse effects (see evidence table for Adverse Events) (Moore et al., 2005). There is quality evidence that opioids are associated with reduced pain thresholds (Edwards et al., 2011). Thus, there is strong evidence that other medications and treatments should be used prior to consideration of an opioid prescription for chronic/subacute pain patients (Saper et al., 2006).

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: Subacute pain, acute pain, chronic pain, non-malignant pain; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 135 articles in PubMed, 51 in CINAHL, 391 in Cochrane Library, 44,100 in Google Scholar, and 0 from other sources†. We considered for inclusion 6 from PubMed, 1 from CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 10 articles considered for inclusion, 5 randomized trials and 5 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

OPIOID TRIAL FOR SUBACUTE OR CHRONIC SEVERE PAIN

Recommended

The use of an opioid trial is recommended if other evidence-based approaches for functional restorative pain therapy have been used and documented to have provided inadequate improvement in function (Federation of State Medical Boards, 2013, International Association of Industrial Accident Boards and Commissions, 2013). An opioid trial is then recommended to assess for efficacy of treatment for function and pain that are both affected by subacute or chronic severe pain, such as the inability to work due to any of the following: chronic severe radiculopathy, chronic severe peripheral neuropathies, complex regional pain syndrome (CRPS), and severe arthroses. Ongoing opioid treatment beyond the trial period should be dependent on the results of the opioid trial, particularly regarding functional improvement (Reneman et al., 2002).

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Patients should meet all of the following:

1. A complete history and physical should be done, if not previously accomplished. A detailed screening for comorbidities is recommended when considering an opioid prescription for treatment

of chronic pain. This includes an assessment of function, review of systems, medication review, physical examination, and screening. An abbreviated screening for substance use disorder, psychiatric illnesses, illicit drug use, and use of other sedating medications is recommended when considering an opioid prescription for treatment of acute pain.

2. Reduced function is attributable to the pain. Pain or pain scales alone are insufficient reasons for prescribing opioids for chronic pain (Administration, 2013) (Mahowald et al., 2005) (Reneman et al., 2002) (Eriksen et al., 2006) (Gross et al., 2003) (Reneman et al., 2007) (Brouwer et al., 2005) (Buelow et al., 2009) (Schiphorst Preuper et al., 2008) (Smeets et al., 2007) (Morasco et al., 2013) (Fox et al., 1979) (Hartrick et al., 2003) (Lund et al., 2005). Examples of functions to assess at baseline and track prospectively at each office visit include: working status, modified duty/limitations, maximum weight lifted, numbers of repetitions performed, walking distance, activities of daily living, ability to complete household chores, and sports participation (see the ACOEM Initial Approaches to Treatment guideline).

3. Both function and pain treatment goals should be established before an opioid trial of 1 to 3 weeks is attempted. Before initiating opioids, there should be plans for discontinuation in the event the goals are not met. Opioids should only be continued beyond the opioid trial period if both goals are met and these outweigh risks to patient safety (CDC, 2016). Assessment of function and pain should be documented at each office visit. There should be at least 30% improvement in both function and pain to continue opioid treatment.

4. A severe disorder warranting potential opioid treatment is present [e.g., CRPS, severe radiculopathy, advanced degenerative joint disease (DJD)] (U.S. Food and Drug Administration, 2013).

5. Other more efficacious treatments have been documented to have failed (U.S. Food and Drug Administration, 2013). Other approaches that should have been first utilized include physical restorative approaches, behavioral interventions, self-applied modalities, non-opioid medications (including NSAIDs, acetaminophen, topical agents, norepinephrine adrenergic reuptake blocking antidepressants or dual reuptake inhibitors; also antiepileptic medications particularly for neuropathic pain) and functional restoration. For LBP patients, this also includes [i] fear avoidant belief training and ongoing progressive aerobic exercise, and strengthening exercises. For CRPS patients, this includes progressive strengthening exercise. For DJD, this includes NSAIDs, weight loss, aerobic and strengthening exercises.

6. Be engaged in an ongoing active exercise program and comply with that prescription.

7. Be prescribed a non-opioid prescription(s) (e.g., NSAIDs, acetaminophen) absent a contraindication. Such non-opioids should nearly always be the primary pain medication and accompany an opioid prescription (CDC, 2016) (De Heer et al., 2018). Other medications to consider include topical agents, norepinephrine adrenergic reuptake blocking antidepressants or dual reuptake inhibitors; also antiepileptic medications particularly for neuropathic pain).

8. The lowest effective dose should be used (Cifuentes et al., 2010). Weaker opioids should be used whenever possible (Volinn et al., 2009) (Dersh et al., 2008). Meperidine is not recommended for chronic pain due to bioaccumulation and adverse effects.

9. Low-dose opioids may be needed in the elderly who have greater susceptibility to the adverse risks of opioids. Those of lower body weight may also require lower opioid doses.

10. Dispensing should be only what is needed to treat the pain and reduced function. (*A previous trial of a muscle relaxant is generally recommended. However, if an opioid trial is contemplated, cessation of all CNS-depressing medications including muscle relaxants is advisable.)*

11. Patients should be periodically reminded to not take benzodiazepines, alcohol, diphenhydramine (included in many OTC medications), other sleep medication, or use other sedating medications.

12. Patients should be educated on the proper storage and disposal of opioids at the time of the initial prescription and at every visit, as secondary fatalities from misuse and accidental poisonings of children are common.

13. If an opioid trial is successful and there is a decision to transition to long-term opioids, extended-release/long-acting opioids may be selectively used. Long-acting opioids should be used on a scheduled basis, rather than as needed (U.S. Food and Drug Administration, 2013). As-needed opioids should generally be avoided for treatment of chronic pain, although limited use for an acute painful event (e.g., burns, major tissue damage) is reasonable. Sublingual fentanyl is not recommended for treatment of subacute or chronic pain. Caution is warranted with fentanyl patches due to unpredictable absorption.

14. Prescription databases (usually referred to as PDMP) should be checked for conflicting opioid prescriptions from other providers or evidence of misreporting.

15. Due to greater than 10-fold elevated risks of adverse effects and death, considerable caution is warranted among those using other sedating medications and substances including benzodiazepines, antihistamines (H1-blockers) (Cheng et al., 2013), and/or illicit substances (Green et al., 2011) (Cheng et al., 2013) (Eriksen et al., 2006) (Atluri et al., 2004).

Patients should not receive opioids if they use illicit substances unless there is objective evidence of significant trauma or at least moderate to severe injuries.

Considerable caution is also warranted among those who are:

- older (>65 yrs.),
- pregnant,
- sleep apnea,
- psychiatric/mental health disorders (anxiety, depression, personality disorder, suicidal),
- drug-seeking behavior,
- current or past substances use,
- consuming alcohol in combination with opioids,
- renal insufficiency,
- hepatic insufficiency, and who are
- unemployed (10-fold risk of death) (Cheng et al., 2013) (Eriksen et al., 2006).

Due to elevated risk of death and adverse effects, caution is also warranted when considering prescribing an opioid for patients with any of the following characteristics: other psychotropic medications, current tobacco use, attention deficit hyperactivity disorder (ADHD), PTSD, impulse control problems, thought disorders, COPD, or recurrent pneumonia (CDC, 2008) (Allen et al., 2021) (Park et al., 2020) (Paulozzi et al., 2012) (Cheng et al., 2013) (Shah et al., 2008) (Webster et al., 2011) (Dunn et al., 2010) (Paulozzi et al., 2009) (Grattan et al., 2012) (Manchikanti et al., 2004) (Nyhlen et al., 2011) (Hadidi et al., 2009) (Wysowski et al., 2006) (Wysowski, 2007) (Toblin et al., 2010) (CDC,

2005) (Fareed et al., 2009) (Deyo et al., 2011) (Goodridge et al., 2010) (Dean, 2004) (Seal et al., 2012) (Mills et al., 2005).

Additional risks and/or adverse effects are thought to be present from other comorbidities such as chronic hepatitis and/or cirrhosis (Walter et al., 2011), coronary artery disease, dysrhythmias, cerebrovascular disease, orthostatic hypotension, asthma, thermoregulatory problems, advanced age (especially with mentation issues, balance problems, fall risk, debility), osteopenia, osteoporosis, water retention, severe obesity, testosterone deficiency, erectile dysfunction, abdominal pain, gastroparesis, constipation, prostatic hypertrophy, oligomenorrhea, human immunodeficiency virus (HIV), ineffective birth control, herpes, allodynia, dementia, cognitive dysfunction and impairment, gait problems, tremor, concentration problems, insomnia, coordination problems, and slow reaction time. There are considerable drug-drug interactions that have been reported (see Appendices 2-3).

16. Attempt to wean twice a year to lower than 90mg MED if patients were previously prescribed those doses (Huffman et al., 2017, Huffman et al., 2013).

Benefits

Improved short-term pain ratings. Theoretical potential to improve short-term function impaired by a painful condition.

Harms

Adverse effects are many and include: nausea, vomiting, delayed gastric emptying, constipation, bladder dysfunction, urinary retention, pruritus, drowsiness, sedation, respiratory depression, central sleep apnea, obstructive sleep apnea, euphoria, dysphoria, cognitive impairment, clouded consciousness, decreased concentration, reduced decision making, lack of impulse control, slowed reaction time, reduced coordination, balance problems, myoclonus, muscle rigidity, altered color vision, dizziness, euphoria, sexual dysfunction, anaphylaxis, motor vehicle crashes, falls, fractures, emergency department visits, and risk of hospitalization. Chronic use has been additionally associated with gynecomastia, reduced circulating testosterone, erectile dysfunction, infertility, amenorrhea, oligomenorrhea, preterm birth, neonatal abstinence syndrome, osteopenia, osteoporosis, coronary events, immune suppression, invasive pneumococcal disease, hair loss, tolerance, physical dependence, psychological dependence, opioid use disorder, suicide, and death. Avocational and job-related safety-related issues are considerable (see separate recommendation on Safety-Critical Work) and require discussing with patients prior to prescribing (Cullen KL, 2018, Loisel P, 2002). Use of an opioid is also associated with reduced return-to-work status, reduced function, and disability. Opioids have worse risk-to-benefit ratios than NSAIDs (Busse et al., 2020).

Frequency/Dose/Duration

Opioid use is generally initiated as a “trial” to ascertain whether the selected opioid produces functional improvement. Opioid use is generally prescribed on a regular basis (Von Korff et al., 2011) (Von Korff et al., 2011), at night or when not at work (Kress et al., 2005). Only one opioid is recommended to be prescribed in a trial. More than one opioid should rarely be used. Lower opioid doses are preferable as they tend to have the better safety profiles, less risk of dose escalation (Cifuentes et al., 2010), less work loss (Volinn et al., 2009), and faster return to work (Dersh et al., 2008) (Dersh et al., 2008). Tapentadol has been advocated as a preferred strategy by some due to its dual action that includes norepinephrine reuptake inhibition (Afilalo et al., 2013), although the quality of evidence to support its superiority is poor (Kress et al., 2014, Iwaki et al., 2021). Patients should have ongoing visits to monitor efficacy, improvement in functional status (e.g., return to work),

adverse effects, compliance and surreptitious medication use. Opioid prescriptions should be shorter rather than longer duration (Cifuentes et al., 2012).

Indications for discontinuation

Opioids should be discontinued based on lack of functional benefit (Commissions, 2013), resolution of pain, improvement to the point of not requiring opioids, intolerance or adverse effects, non-compliance, surreptitious medication use, medication misuse (including self-escalation and sharing medication), aberrant drug screening results, diversion, consumption of medications or substances advised to not take concomitantly (e.g., sedating medications, alcohol, benzodiazepines) (FDA, 2016) (Dasgupta et al., 2016).

Rationale

There are no long-term trials documenting efficacy of opioids. There is quality evidence that other medications and treatments are at least equivalent if not superior for treatment of subacute or chronic pain [e.g., NSAIDs (Pavelka et al., 1998) (O'Donnell et al., 2009) (Parr et al., 1989) (Jamison et al., 1998) (DeLemos et al., 2011, Krebs EE, 2018, Ouncharoen, 2018), clonidine (Siddall et al., 2000), and flupirtine (Li et al., 2008). There is conflicting evidence regarding whether antidepressants have equivalency (Khoromi et al., 2007) (Raja, 2002). There is evidence of modest superiority of opioids to placebo (Meske et al., 2018). Safety profiles are considerably worse for subacute and chronic use of opioids.

There are no quality trials to suggest superiority of opioids to other common active treatments (Beaulieu et al., 2008, Ouncharoen, 2018, Skelly et al., 2020, Farrar et al., 2022, McDonagh et al., 2020) (Chou et al., 2020). One trial suggests morphine is superior to benztropine for pain, but not function (Moulin et al., 1996). Among trials for treatment of subacute or chronic pain, one trial failed to find superiority of morphine to nortriptyline for treatment of chronic lumbar radiculopathy (Khoromi et al., 2007). Another found neither morphine nor mexiletine superior to placebo (Wu et al., 2008). Another found celecoxib superior to tramadol for chronic LBP (O'Donnell et al., 2009). Diclofenac was superior to dextropropoxyphene/ APAP for treatment of hip or knee osteoarthritis (Parr et al., 1989). Diclofenac was approximately equivalent to tramadol in another trial (Pavelka et al., 1998). Naproxen was equivalent to oxycodone for treatment of chronic LBP (Jamison et al., 1998). Few trials primarily targeted subacute pain patients, and these patients are included in the chronic pain patient section due to the speed with which dependency can arise. The main exception is one trial finding flupirtine was equivalent to tramadol for subacute LBP (Li et al., 2008). Buprenorphine has been recently explored for treatment of chronic pain (Rauck et al., 2016, Gimbel et al., 2016).

There are no trials documenting improved objective functional outcomes, with more than 100 studies documenting many adverse effects (see evidence table below) (Moore et al., 2005). There is quality evidence that opioids are associated with reduced pain thresholds (Edwards et al., 2011). Thus, there is strong evidence that other medications and treatments should be used prior to consideration of an opioid prescription for chronic/subacute pain patients (Saper et al., 2006).

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: Chronic pain; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical

study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 1327 articles in PubMed, 732 in CINAHL, 108 in Cochrane Library, 35100 in Google Scholar, and 0 from other sources†. We considered for inclusion 14 from PubMed, 3 from CINAHL, 2 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 19 articles considered for inclusion, 1 randomized trials and 14 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: Comparison; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 800 articles in PubMed, 3515 in CINAHL, 31 in Cochrane Library, 19,270 in Google Scholar, and 0 from other sources†. We considered for inclusion 12 from PubMed, 4 from CINAHL, 0 from Cochrane Library, 35 from Google Scholar, and 0 from other sources. Of the 21 articles considered for inclusion, 6 randomized trials and 12 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.4.2. INITIAL SCREENING

SCREENING PATIENTS PRIOR TO INITIATION OF OPIOIDS

Recommended

Screening of patients is recommended prior to initiating a trial of opioids for treatment of subacute or chronic pain. Screening should include history of depression, anxiety, personality disorder and personality profile (Dersh et al., 2008) (Hartrick et al., 2012) (Kidner et al., 2010) (Dersh et al., 2008) (Hartrick et al., 2012) (Kidner et al., 2010) (Pestka et al., 2018), other psychiatric disorder, substance use history, sedative use (e.g., antihistamine/anti-H1 blocker) (Webster et al., 2011) (Webster et al., 2011), benzodiazepine use, opioid dependence, alcohol misuse, current tobacco use, other substance use, family history, COPD, sleep quality, sleep apnea, PTSD, other psychotropic medications, (severe) obesity, cognitive impairment, balance problems/fall risk, osteoporosis, and renal failure (see Appendix 1). For patients who screen positive, especially to multiple criteria, the following are recommended:

- Greater scrutiny for appropriateness of opioids (may include psychological and/or psychiatric evaluations to help assure opioids are not being used instead of appropriate mental health care)
- Consultation and examinations for complicating conditions and/or appropriateness of opioids, including by a pain specialist
- Consultation with an addiction/opioid use disorder specialist if there is a history of substance use disorder
- More frequent assessments for compliance, achievement of functional gains, urine drug testing, checks of the prescription drug monitoring database, review of the medical records, and symptoms and signs of aberrant use if opioids are prescribed

Strength of evidence Recommended, Evidence (C)
Level of confidence High

Benefits

Identification of patients at increased risk of adverse effects. Improved identification of more appropriate and safe candidates for treatment with opioids. This should reduce adverse effects. In cases where the patient has elevated but potentially acceptable risk, this may alert the provider to improve surveillance for complications and aberrant behaviors.

Harms

Negligible. If a consultation is needed, additional costs are incurred.

Rationale

Many different tools are used for opioid screening, and some have been validated for the detection of aberrant use (mostly among patients with chronic pain). No quality studies have suggested that pretreatment screening results in improved outcomes among patients with subacute and chronic pain. Yet, with evidence of successful detection of aberrancy, there is strong reason to believe that screening and acting on screening results may also result in reduced risks of adverse effects and risks. Thus, pretreatment screening is recommended.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: patient screening, chronic pain; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 329 articles in PubMed, 734 in CINAHL, 58 in Cochrane Library, 35,500 in Google Scholar, and 0 from other sources†. We considered for inclusion 3 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 1 randomized trials and 2 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.4.3. MAXIMUM DAILY DOSE

MAXIMUM DAILY ORAL OPIOID DOSE FOR PATIENTS WITH SUBACUTE AND CHRONIC PAIN

Recommended

The maximum daily oral dose of opioids recommended for patients with subacute or chronic pain based on risk of overdose/death is 50 mg MED (Dunn et al., 2010) (Bohnert et al., 2011). In cases with

documented functional improvements occurring with use greater than 50 mg MED, subsequent doses up to 90 mg may be considered (Dowell D, 2016); however, risks of death are much greater and more intensive monitoring is then also recommended. Lower doses and/or non-opioid strategies should be considered in high-risk patients.

Caution appears warranted because the risk of dose escalation has been reported in all patients. Even patients enrolled in a “hold-the-line" (stable dose) prescribing strategy treatment arm experienced an approximately 17% increase in dose over 12 months compared with 79% in the liberal escalating-dose arm (Naliboff et al., 2011) (Naliboff et al., 2011). Extrapolated linearly, the hold-the-line prescribing strategy would result in average doses over 50 mg within approximately 3.5 years, whereas the liberal policy would exceed 50 mg in approximately 11 months.

For patients whose daily consumption is more than 50 mg MED, greater monitoring is recommended, including the following:

- At least monthly to not more than quarterly appointments, with greater frequencies during trial, during dose adjustments, and for patients with greater co-morbid risk factors and conditions;
- At least semiannual attempts to wean below 50 mg MED if not off the opioid;
- At least semiannual documentation of persistence of functional benefit;
- At least quarterly urine drug testing (see drug testing section); and
- At least semiannual review of medications, particularly to assure no sedating medication use (e.g., benzodiazepine, sedating anti-histamines). After stability with lack of aberrancy of at least 2 years, reductions to twice yearly are a reasonable option.

Strength of evidence Recommended, Evidence (C)
Level of confidence High

Benefits

Reduced risk for adverse effects, dependency, opioid use disorder and opioid-related deaths.

Harms

None in a short-term trial. For patients with chronic pain, there is a theoretical potential to undertreat pain and thus impair function. However, there is no quality literature currently available to support that position.

Rationale

A population-based study of 154,684 patients analyzing risks among those taking opioids compared with no use of opioids documented a dose-response relationship between opioid dose and overdose/deaths, while also suggesting largely identical relationships whether the opioid use was acute or chronic (Bohnert et al., 2011, Dunn et al., 2010), with risks elevating markedly beyond 50 mg MME (Bohnert et al., 2011). A large VA study found a dose-response relationship with a fourfold risk of serious prescription opioid-related toxicity or overdose among those taking 100 mg MME compared with a lower opioid dose (Zedler B, 2014). Other studies with a low-dose group for comparison found similar dose-response relationships, which were naturally reduced by using a low dose instead of no-dose comparison group (Gomes, 2011)). Other large studies also reported a higher incidence of complications with higher doses (Quinn et al., 2022, Planelles et al., 2019). A dose-response increase in the risk of suicide with increased opioid dose starting above 20 mg MME has been reported, increasing to a hazard ratio of 2.15 (95% CI 1.64, 2.81) at >100 mg MME (Ilgen MA, 2016). An increased

risk of overdose among those with depression that is a dose-response relationship has been reported, with a more than 50% increased risk among those using at least 100 mg MME (Turner BJ, 2015). CDC recommendations in 2022 removed references to dose-response risks in recommendation statements, while retaining dose-response data in discussion sections (Dowell et al., 2022).

Because there is large-scale evidence of a strong dose-response relationship and the data and relationship for chronic use largely duplicate the data for acute use, this suggests there is quality evidence on which to form evidence-based guidance. Importantly, there does not appear to be a reduction in mortality/overdose risk with chronic use compared with the same dose for acute pain treatment use. The lowest effective dose is recommended. Generally, 20mg MME is advised as a reasonable dose for acute pain, up to 50mg MME. Acute and perioperative pain use beyond 50mg MME is generally not recommended.

In cases with documented functional improvements occurring with use above 50 mg MED, subsequent doses up to 90 mg may be considered (Dowell D, 2016). However, the risk of death increases approximately 10-fold at 90 mg MME, so more intensive monitoring is also recommended. Lower doses and/or non-opioid strategies should be considered in high-risk patients.

Caution appears to be warranted in all patients. Evidence of the risk of dose escalation was present even among patients enrolled in a stable-dose treatment arm; these patients experienced an approximately 17% increase in dose over 12 months compared with 79% in the liberal-escalating dose arm (Naliboff et al., 2011). Extrapolated linearly, a stable-dose prescribing strategy would result in average doses over 50 mg within approximately 3.5 years, whereas the liberal policy exceeded 50 mg in approximately 11 months.

For patients whose daily consumption is greater than 50 mg MME, increased monitoring is recommended, including the following:

- At least monthly to not more than quarterly appointments with greater frequencies during trial, dose adjustments, and with greater co-morbid risk factors and conditions
- At least semiannual attempts to wean below 50 mg MME if not off the opioid
- At least semiannual documentation of persistence of functional benefit
- At least quarterly urine drug testing (see Drug Testing section)
- At least semiannual review of medications, particularly to assure no sedating medication use (e.g., benzodiazepine, sedating antihistamines)

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from July 2013 to March 2022 using the following terms: Maximum Daily Dose, Daily Dose, Subacute Pain, Chronic Pain; analgesics, opioid, narcotics, opioid, opiate, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 368 articles in PubMed, 9 in CINAHL, 215 in Cochrane Library, 8460 in Google Scholar, and 0 from other sources†. We considered for inclusion 21 from PubMed, 0 from CINAHL, 4 from Cochrane Library, 3 from Google Scholar, and 0 from other sources. Of the 28 articles considered for inclusion, 10 randomized trials and 8 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.4.4. OPIOID ROTATION

OPIOID ROTATION

Sometimes Recommended

Rotation of opioids is selectively recommended.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Patients on opioids for subacute or chronic pain who appear to lose evidence of efficacy or experience intolerable adverse effect(s) (Chen, 2012) (Braden et al., 2010) (Portenoy et al., 2007) (Currow et al., 2011). May be reasonable to also rotate from one opioid to a second opioid on a one-time basis when there was no opioid trial, there is lack of evidence of efficacy, and there is concern there could be benefit demonstrated with a different opioid. Caution is warranted in converting to methadone, as there is no safe and dependable conversion table. Caution is also warranted with opioid rotation as deaths have been reported (Webster et al., 2012), and thus careful monitoring is recommended.

Benefits

Identify if there is objective evidence of improvement on a different opioid. Potential to regain function if prior opioid appears to have become ineffective.

Harms

Deaths have been reported (Webster et al., 2012). Requirement to reduce dose during rotation, and thus likely report increased pain. If not cautious, may become another means for dose escalation.

Frequency/Dose/Duration

Generally, opioid rotation should be an infrequent requirement. If becomes more frequent need, there is consideration for adherence to the functional exercise requirements, as well as increasing drug screening surveillance to assure proper use and not misuse. Morphine equivalent dose is recommended to be reduced by 50% when rotating from one opioid to another (Chen, 2012) (Currow et al., 2011). Rotation schedules are typically accomplished over 3 to 10 days (Choquette et al., 2008)(Quang-Cantagrel et al., 2000). Functional gains should be carefully tracked. If there are no functional gains, further taper and complete cessation of the opioid is generally indicated.

Rationale

There are no quality studies showing efficacy of opioids rotations (Gatti et al., 2009) (Thomsen et al., 1999) (Chou et al., 2009) (Quang-Cantagrel et al., 2000) (Freye et al., 2007) (McNicol ED, 2021). There are epidemiological studies describing opioids rotation (Baschirotto et al., 2020, Corli et al., 2019, Kovacevic et al., 2020, Lehmann et al., 2021, Okayama et al., 2019, Reddy et al., 2017, Smith et al., 2020, Tan, 2020). Some epidemiological studies reported lower pain scores and improved pain attributed to opioids rotation (Legakis et al., 2021, Corli et al., 2019). There are studies of switching to buprenorphine (Chung et al., 2019, Oldfield et al., 2018, Veldman, 2022). Opioids rotations are thought to be successful in a some patients. This involves reduction in MED and then rotation to another opioid. Functional gains should be carefully tracked.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: opioid rotation, opioid switching; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 323 articles in PubMed, 38 in CINAHL, 87 in Cochrane Library, 34600 in Google Scholar, and 0 from other sources†. We considered for inclusion 16 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 18 articles considered for inclusion, 3 randomized trials and 4 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.5. POSTOPERATIVE PAIN (UP TO 4 WEEKS)

Oral opioids are commonly prescribed after most surgeries, including sinus surgery (320), major non-cardiac surgical procedures (321), mastectomy and immediate breast reconstruction (IBR) (322) (323), coronary artery bypass graft surgery (324), major abdominal surgery (abdominal laparoscopic, abdominal hysterectomy, bowel resection, or radical hysterectomy) (325-328), orthopedic surgery (329), foot and ankle surgery (330-334), and molar extraction (63). Pre-operative opioid use is associated with increased peri-operative morbidity, increased mortality, and clinically challenging management (335).

4.5.1. OPIOID USE

LIMITED USE OF OPIOIDS FOR POSTOPERATIVE PAIN

Recommended

Limited use of opioids is recommended for postoperative pain management as adjunctive therapy to more effective treatments. Preoperative screening for adverse opioid-related outcomes and risk factors is recommended. Re-screening is recommended for patients who appear to need ongoing opioids for more than 4 weeks postoperatively (see the separate recommendation for Screening).

Yet, many quality randomized controlled trials (RCTs) of diverse minor to major surgical procedures have consistently shown that outcomes are superior when opioids are reduced, if not obviated, through the use of non-opioid treatment strategies. These RCTs document equivalent if not superior outcomes with opioid-sparing strategies and/or worse outcomes with higher opioid usage (Ayoub et al., 2021, Grandizio et al., 2021, Moutzouros et al., 2021, Papoian et al., 2020, Jildeh et al., 2021, Hartwell et al., 2020, Yeo, 2022, Nguyen, 2019, Fedrigon, 2021, Akinbade et al., 2018, Waelkens et al., 2021, Burns et al., 2021, Shutze et al., 2018, Tangtiphaiboontana et al., 2021, Syed et al., 2018, Cortez et al., 2019, Forlenza et al., 2020, Zusmanovich et al., 2020, Lu et al., 2020, Sharbel et al., 2020).

Evidence suggests that higher pain ratings are associated with both opioid use and subsequent chronic opioid use (Hsia et al., 2018). A study of 357,884 patients found higher risks of chronic opioid use after treatment with tramadol (Thiels et al., 2019), and another found higher risks of chronic use when larger volumes of opioids were provided (Young, 2021). An RCT of codeine/acetaminophen vs. tramadol/acetaminophen found the codeine to be superior for dental abscesses (Santini, 2016).

There is also quality evidence that an opioid-centric educational program reduces postoperative opioid use with earlier termination of opioid use, including 6.8-fold higher discontinuation rates among those with preoperative opioid usage (Syed et al., 2018). Opioid-tapering protocols for the postoperative period have been reported (Joo et al., 2020).

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence High

Indications

For postoperative pain management, a brief prescription of short-acting opioids as an adjunct to more efficacious treatments. Nonselective NSAIDs may be used after the risk of bleeding is no longer a concern (e.g., COX-2 inhibitors). More efficacious treatments also include therapeutic exercises, such as progressive early ambulation, especially for moderate to extensive procedures (e.g., arthroplasty, fusion).

Opioids are generally not needed for minor surgical procedures; for the exceptions, only a short course of a few days is indicated. Wound laceration repairs often require no opioids. Evidence suggests perioperative pregabalin, especially in younger patients, and/or regional anesthetic blocks and/or neuraxial anesthesia instead of solely using oral opioids results in superior knee arthroplasty functional outcomes with less venous thromboses (Nader et al., 2012).

Additional considerations include the following:

1. Non-opioid prescriptions (e.g., NSAIDs, acetaminophen) should nearly always be the primary treatment and accompany an opioid prescription (Jones et al., 2022, Langford et al., 2022, Moore et al., 2015, Wu et al., 2022) (Burns et al., 2021) (Liu et al., 2018) (Nguyen, 2019) (Waelkens et al., 2021) (Collaborative, 2018, Moore et al., 2013). Perioperative ketorolac, celecoxib, other NSAIDs, and ketamine have been successfully used to spare opioid use (Lopez et al., 2021, Moore et al., 2015, Langford et al., 2022, Jones et al., 2022, Ayoub et al., 2021, Hartwell et al., 2020, Jildeh et al., 2021, Papoian et al., 2020, Moutzouros et al., 2021, Grandizio et al., 2021) (Fedrigon, 2021) (Yeo, 2022) (Dastan, 2020). Computerized programs may also assist in optimal management (Webster et al., 2011). Early rehabilitation is also a strategy shown to be effective. Opt-in opioid prescription strategies have also been shown to reduce opioid consumption (Zhu et al., 2021).

2. Planning for opioid use to treat postoperative pain should begin during the preoperative assessment, emphasizing a minimal effective dose strategy. Evidence among spine fusion patients suggests worse outcomes with preoperative opioid use (Bhattacharjee et al., 2020); thus, aggressive rehabilitative strategies may be warranted.

3. Prescription databases (usually referred to as PDMP) should be checked for other opioid prescriptions.

4. Due to greater than 10-fold elevated risks of adverse effects and death, considerable caution is warranted among those using other sedating medications and substances, including benzodiazepines, anti-histamines (H1-blockers) (Cheng et al., 2013), and/or illicit substances (Green et al., 2011) (Cheng et al., 2013) (Eriksen et al., 2006) (Atluri et al., 2004). Patients should not receive opioids if they use illicit substances, unless there is objective evidence of significant trauma or at least moderate-severe injuries.

Considerable caution is also warranted among those who are or have the following:

- older (>65 yrs.)
- pregnant
- sleep apnea
- psychiatric/mental health disorders (anxiety, depression, personality disorder, suicidal)
- drug-seeking behavior
- current or past substance use
- consuming alcohol in combination with opioids
- renal insufficiency
- hepatic insufficiency
- unemployed (10-fold risk of death) (Cheng et al., 2013) (Eriksen et al., 2006)

Due to elevated risk of death and adverse effects, caution is also warranted when considering prescribing an opioid for patients with any of the following characteristics: other psychotropic medications, current tobacco use, attention deficit hyperactivity disorder (ADHD), PTSD, impulse control problems, thought disorders, COPD, or recurrent pneumonia (Centers for Disease Control and Prevention, 2008) (Hall et al., 2008) (Wunsch et al., 2009) (Paulozzi et al., 2012) (Cheng et al., 2013) (Shah et al., 2008) (Webster et al., 2011) (Dunn et al., 2010) (Paulozzi et al., 2009) (Grattan et al., 2012) (Manchikanti et al., 2004) (Nyhlen et al., 2011) (Hadidi et al., 2009) (Wysowski et al., 2006) (Wysowski, 2007) (Toblin et al., 2010) (Centers for Disease Control and Prevention, 2005) (Fareed et al., 2009) (Deyo et al., 2011) (Goodridge et al., 2010) (Dean, 2004) (Seal et al., 2012) (Mills et al., 2005).

Additional risks and/or adverse effects are thought to be present from other comorbidities such as chronic hepatitis and/or cirrhosis (Walter et al., 2011), coronary artery disease, dysrhythmias, cerebrovascular disease, orthostatic hypotension, asthma, thermoregulatory problems, advanced age (especially with mentation issues, balance problems, fall risk, debility), osteopenia, osteoporosis, water retention, severe obesity, testosterone deficiency, erectile dysfunction, abdominal pain, gastroparesis, constipation, prostatic hypertrophy, oligomenorrhea, human immunodeficiency virus (HIV), ineffective birth control, herpes, allodynia, dementia, cognitive dysfunction and impairment, gait problems, tremor, concentration problems, insomnia, coordination problems, and slow reaction time. There are considerable drug interactions that have been reported (see Appendices 2-3).

Inpatient management may moderate these recommendations provided there is careful monitoring, although these same management issues then apply post-discharge.

5. For patients taking opioids chronically prior to surgery, preoperative consultations with anesthesiology and/or pain management are generally needed because postoperative management is often quite challenging and postoperative dosing may be high (Prabhakar NK, 2022, Ward EN, 2018, Harrison TK, 2018, Selvamani BJ, 2022, Sritapan Y, 2020, Larach DB, 2022, VA Pharmacy Benefits Management Services, 2022).

6. Ongoing prescriptions of opioids after the immediate postoperative period should generally be for patients who have undergone a major surgery or have other condition(s) necessitating opioids. Most patients should be making progress towards functional restoration, pain reduction, and weaning off opioids. Patients who have not progressed should be carefully evaluated for physical complications or psychiatric comorbidity, adherence to active treatments, and pending development of opioid use disorder or dependency.

7. Patients should be educated on the proper storage and disposal of opioids at the time of the initial prescription and at every visit, as secondary fatalities from misuse and accidental poisonings of children are common.

Benefits

Multiple RCTs have shown lower use of opioids is associated with superior outcomes and postoperative pain control. Some studies suggest reduced or no opioid use strategies also improve functional outcomes in the postoperative population. One study found preoperative opioid use was associated with a higher risk of early knee arthroplasty revision (Bedard NA, 2018).

Harms

The adverse effects of opioids are many, including worse functional outcomes, delayed recovery, higher complications, and higher costs. Preoperative use of opioids and/or benzodiazepines is associated with increased morbidity, mortality and challenging clinical management (Menendez et al., 2015, Hozack et al., 2019, Anderson et al., 2020).

Adverse effects also include: nausea, vomiting, delayed gastric emptying, constipation, bladder dysfunction, urinary retention, pruritus, drowsiness, sedation, respiratory depression, central sleep apnea, obstructive sleep apnea, euphoria, dysphoria, cognitive impairment, clouded consciousness, decreased concentration, reduced decision making, lack of impulse control, slowed reaction time, reduced coordination, balance problems, myoclonus, muscle rigidity, altered color vision, dizziness, euphoria, sexual dysfunction, anaphylaxis, motor vehicle crashes, falls, fractures, emergency department visits, and risk of hospitalization. Chronic use has been additionally associated with gynecomastia, reduced circulating testosterone, erectile dysfunction, infertility, amenorrhea, oligomenorrhea, preterm birth, neonatal abstinence syndrome, osteopenia, osteoporosis, coronary events, immune suppression, invasive pneumococcal disease, hair loss, tolerance, physical dependence, psychological dependence, opioid use disorder, suicide, and death. Avocational and job-related safety-related issues are considerable (see separate recommendation on Safety-Critical Work) and require discussing with patients prior to prescribing (Cullen KL, 2018, Loisel P, 2002).

Frequency/Dose/Duration

For moderate and major surgeries, opioids may be needed on a scheduled basis in the immediate postoperative period. Other postoperative situations may be sufficiently managed with an as-needed opioid prescription schedule. Provision of opioids sufficient to participate in therapeutic exercise (e.g., progressive ambulation) and allow sleep may be needed, although there are other, less problematic strategies for sleep management.

The lowest effective dose of a short-acting opioid should be used, as well as weaker opioids if possible (Volinn et al., 2009) (Dersh et al., 2008) (Jenkin et al., 2021). Short-acting opioids are recommended for treatment of acute pain. Long-acting opioids are not recommended for postoperative use, especially in the opioid-naive patient population. High-dose use at night is not recommended due to respiratory depression and disruption of sleep architecture. Higher doses have also been associated with higher risk of longer-term opioid use (McCarthy et al., 2021). Low-dose opioids may be needed in the elderly who have greater susceptibility to the adverse risks of opioids. Lower opioid doses should generally be prescribed among those of lower body weight.

Oliceridine, an IV-administered G protein-biased ligand designed to activate mu receptors differently than typical opioids, reportedly has fewer adverse effects than typical opioids. It has been trialed for treatment of pain (Bergese et al., 2019) (Bergese et al., 2020). A RCT found comparable efficacy with MS and with less nausea, vomiting and hypoventilation but a higher rate of hypotension (Singla et al., 2017). A series of randomized trials of oliceridine for treatment of moderate to severe post-surgical pain including post-bunionectomy pain, post-abdominoplasty pain, found comparable efficacy at 0.35 mg and 0. 5mg of oliceridine with morphine 1mg (Viscusi, 2019, Singla et al., 2019, Ayad et al., 2020, Brzezinski et al., 2021, Hammer et al., 2021, Beard et al., 2021). Another RCT of oliceridine vs. morphine found similar results (Singla et al., 2017). An experimental trial with painful stimulus showed evidence of less respiratory drive reduction and less nausea with oliceridine than morphine, although there was evidence of some respiratory depression (Soergel, 2014, Dahan et al., 2020). Another experimental trial also reported less risk of respiratory depression (Simons et al., 2023). A dose-ranging phase 2 trial of oliceridine 2 mg and 3 mg IV every 3 hours suggested the potential for greater pain reductions than with morphine 4 mg every 4 hours (Viscusi E.R., 2016). Most of the literature was produced by one research study group. A cost analysis suggested cost reductions with oliceridine compared with IV morphine, although it largely depended on the estimated costs and rates of adverse effects (Simpson et al., 2021).

There are many studies documenting that patients do not use a large proportion of prescribed opioids (Balceniuk et al., 2020, Boyd et al., 2020, McEntee et al., 2021, Patanwala et al., 2020, Qian et al., 2019, Solouki et al., 2019, Ngombu et al., 2020, Blegen et al., 2021, Chan et al., 2020, Kamdar et al., 2021, Limbach et al., 2020, Linnaus et al., 2022, Lovecchio et al., 2019); thus, dispensing should be only what is needed to treat the pain. One study suggested 5 oxycodone 5-mg pills for knee arthroscopy (Kamdar et al., 2021), 15 oxycodone 5mg/325mg APAP (Locketz et al., 2019), 3 for partial mastectomy (Limbach et al., 2020), 47 for bilateral mastectomy (Limbach et al., 2020), and another suggested 15 doses for otorhinolaryngological surgery (Kim, 2019). (Generally, this should be sufficient to cover 2 weeks of treatment. Prescriptions of 90-day supplies in the postoperative setting are not recommended among those not using chronic opioids.) Weaning should begin as soon as function is recovering and pain is subsiding. Subsequent weaning to as-needed opioid use is recommended. Tapering is generally required if the use has been continuous and over 2 weeks duration.

Indications for discontinuation

The physician should discontinue the use of opioids based on sufficient recovery, expected resolution of pain, lack of efficacy, intolerance or adverse effects, noncompliance, surreptitious medication use, self-escalation of dose, or use beyond 3 to 5 days for minor procedures, and 2 to 3 weeks for moderate/less extensive procedures. Use for up to 3 months may occasionally be necessary during recovery from more extensive surgical procedures (e.g., spine fusion surgery). However, with rare exceptions, only nocturnal use is recommended in months 2 to 3 plus institution of management as discussed in the subacute/chronic guidelines below. For those requiring opioid use beyond 1 month, the subacute/chronic opioid use recommendations below apply.

Rationale

The treatment of postoperative pain with opioids is a longstanding medical practice, and most of the literature parallels that for the use of opioids to treat acute pain (see evidence table). However, recent evidence is considerably changing this practice. While not eliminating use of opioids, accruing recent evidence is resulting in major changes in practice to effect better outcomes by reducing use, daily doses, and durations of opioid treatment. There also is robust evidence that preoperative use of opioids results in worse outcomes, including prolonged hospitalizations, increased complications, and higher costs (see Financial Considerations) (Jain et al., 2011).

Evidence is suggesting that reduced use of postoperative opioids results in superior outcomes, and many trials are showing superiority of non-opioid-based approaches most typically with NSAIDs (Akinbade et al., 2018, Nguyen, 2019, Fedrigon, 2021, Jivraj et al., 2020) (Niebler et al., 2016, Tamboli et al., 2020). A trial found superior range of motion and fewer venous thromboses after continuous femoral nerve catheters analgesia instead of solely using oral narcotics (Nader et al., 2012). One RCT showed that less opioid use was associated with modestly improved long-term knee range-of-motion among those treated with pregabalin vs. no pregabalin for 14 days plus epidural and opioid management after total knee arthroplasty (Buvanendran et al., 2010). Another study found worse 1-year outcomes in ACL reconstruction patients consuming higher quantities of opioids (Forlenza et al., 2020). Hip surgery outcomes were worse among those with preoperative and postoperative opioid use (Zusmanovich et al., 2020), and another study of hip arthroplasty found higher opioid use preoperatively to be associated with increased risk of revision (Bedard et al., 2018). An RCT among rotator cuff repair patients found lower pain scores, and reduced postoperative opioid consumption among those treated with ibuprofen while also achieving comparable 1-year outcomes (Tangtiphaiboontana et al., 2021). An opioid-sparing approach that included ketorolac and fewer oxycodone pills for post-shoulder arthroplasty patients found equivalent pain relief, less opioid consumption and higher satisfaction (Jones et al., 2022). Another study of shoulder arthroplasty patients found worse outcomes among those with pre-operative opioids, including worse pain, lower satisfaction and higher revision rates (Lu et al., 2020). Tapering of remifentanil at the end of surgery was superior to discontinuation after thyroidectomy (Han et al., 2015). Earlier discontinuation of an epidural catheter was associated with lower use of opioids after spine surgery (Joo et al., 2020) and periacetabular osteotomy (Cunningham et al., 2020). An epidemiological study found opioid-use was associated with increased pain at rest, and increased pain while walking (Aasvang et al., 2016). Preliminary evidence suggests stellate ganglion blockade results in less opioids and superior outcomes in head and neck cancer operative patients (Sharbel et al., 2020). A propensity-matched comparison study of colorectal surgery patients found preoperative opioids to be associated with higher post-operative opioid use, higher costs and higher 30-day re-admission rates (Cortez et al., 2019). A trial comparing ketorolac with opioids for ureteroscopy found ketorolac superior and associated with less days of confinement to bed (Fedrigon, 2021). A trial of obstetrics and gynecology surgeries found

addition of acetaminophen to opioids resulted in lower opioid usage and decreased hospitalization costs (Hansen RN, 2017).

Thus, quality evidence suggests opioids may have deleterious postoperative effects other than when used as adjuncts. Additional differences from the acute pain recommendations include that NSAIDs have been administered at the time of surgery without undue complications (Chang et al., 2004) (Silvanto et al., 2002) (Sell et al., 2004) (Gimbel et al., 2001) (Dahl et al., 1995) (Ittichaikulthol et al., 2010), although these studies would likely be underpowered for rare complications.

Epidemiological studies also suggest lower opioid doses result in superior functional improvements. One study found lower doses of opioids were associated with improved walking distances among lumbar spine surgery patients (Aoyagi et al., 2020). Use of liposomal bupivacaine was found to reduce opioid use and improved outcomes among Medicare outpatient surgery patients (Dobson, 2021). Opioid-free anesthesia was found to be superior to opioid-based anesthesia for pancreatic surgery in an epidemiological study with regards to complication rate and pain (Hublet, 2022). A multi-modal pain management strategy was reportedly superior to an opioid-based post-operative management plan for total joint arthroplasties (Hyderi, 2021). A report of 3 RCTs found tapentadol was equivalent to oxycodone or morphine (Viscusi, 2019). Earlier tapering of remifentanil at the end of thyroidectomy was associated with lower pain scores (Han et al., 2015) and success has also been reported after earlier epidural discontinuation after periacetabular osteotomy (Cunningham et al., 2020).

Recent RCT evidence also suggests that many patients do not generally need opioids, including for arthroscopic meniscectomies, ACL reconstructions, dental surgery, ureteroscopy, outpatient otolaryngology surgery, sinus surgeries, and thyroidectomies (Aoyagi et al., 2020, Hartwell et al., 2020, Moutzouros et al., 2021, Jildeh et al., 2021, Papoian et al., 2020, Yeo, 2022, Nguyen, 2019, Fedrigon, 2021, Akinbade et al., 2018) (Nguyen, 2019). Three RCTs of non-opioid vs. opioid-based analgesia for ACL reconstruction, meniscus surgery, and thyroidectomy found equivalent if not better pain scores and patient outcomes (Papoian et al., 2020, Jildeh et al., 2021, Moutzouros et al., 2021). An RCT among arthroscopic partial knee meniscectomy patients of multimodal pain management (acetaminophen, aspirin, naproxen) with an optional oxycodone prescription vs. the same medications plus an included oxycodone prescription found comparable pain control; 37% of patients did not need any opioids, and there was less use of oxycodone among those not automatically prescribed oxycodone (Hartwell et al., 2020). A trial among sinus surgery patients treated with acetaminophen scheduled use, with either ibuprofen or oxycodone rescue, found only 26-37% needed rescue opioids (Ayoub et al., 2021). One trial found earlier recovery after ureteroscopy with ketorolac than oxycodone (Fedrigon, 2021).

Among patients on preoperative opioids, guided opioid tapering in the postoperative period has been reportedly successful (Hah et al., 2020) (Uhrbrand et al., 2021). Among those on buprenorphine, two studies have reported conflicting results, with one reporting reduced perioperative opioid consumption than if buprenorphine is discontinued (Quaye et al., 2020) while another reported no reduction in opioid dosing requirements (Komatsu et al., 2022). Recommendations generally are to maintain buprenorphine and add agonists as necessary (Buresh et al., 2020). Successful discontinuation of chronic opioid use after spinal cord stimulation implantation was largely among those on a median dose of 30mg MME (Simopoulos et al., 2019), although recent population-based evidence suggests spinal cord stimulation does not reduce opioids use on average over two years (Dhruva et al., 2023).

It is also recommended to dispense only what is needed, and not 30- day, 90-day, or other lengthy treatment supplies, to avoid either overmedication and/or diversion. Also, closely monitored inpatient settings may somewhat moderate the cautions about the recommended dose limits and overdoses. However, the evidence that early ambulation is critical to functional recovery while also limiting

complications is overwhelming; therefore, oversedation, remains a concern. For patients on chronic opioids preoperatively, especially moderate to high doses, consultation with a physician experienced in managing these complex cases may be necessary.

Thus, evidence suggests both a role for an increasingly selective use of opioids postoperatively, while also minimizing the need, dose, and duration for opioid treatment.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: Pain, Postoperative; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 7859 articles in PubMed, 2860 in CINAHL, 205 in Cochrane Library, 37400 in Google Scholar, and 0 from other sources†. We considered for inclusion 24 from PubMed, 10 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 34 articles considered for inclusion, 8 randomized trials and 4 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: Comparison; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 800 articles in PubMed, 3515 in CINAHL, 31 in Cochrane Library, 19,270 in Google Scholar, and 0 from other sources†. We considered for inclusion 12 from PubMed, 4 from CINAHL, 0 from Cochrane Library, 35 from Google Scholar, and 0 from other sources. Of the 21 articles considered for inclusion, 6 randomized trials and 12 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.5.2. INITIAL SCREENING

SCREENING AMONG SURGICAL PATIENTS PRIOR TO OPIOID INITIATION

Recommended

Screening is recommended for surgical patients prior to the initiation of opioids for postoperative pain (up to 4 weeks).

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence High

Indications

All patients undergoing surgery.

Benefits

Determine preoperative opioid use and plan postoperative pain management.

Harms

Negligible

Rationale

There are no quality studies of screening perioperative patients (see also the screening recommendation for patients with acute pain). Patients using opioids preoperatively have considerably worse outcomes and incur higher costs. Screening allows determination of preoperative opioid use, stratification of the degree of chronic opioid use among opioid-naive patients (Larach et al., 2021, Zhang, 2020), and planning for postoperative pain management; thus, screening is recommended.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: screening, post operative; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 736 articles in PubMed, 0 in CINAHL, 715 in Cochrane Library, 30700 in Google Scholar, and 0 from other sources†. We considered for inclusion 11 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 11 articles considered for inclusion, 11 epidemiological studies and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.5.3. MAXIMUM DAILY DOSE

MAXIMUM DAILY ORAL OPIOID DOSE FOR POSTOPERATIVE PAIN

No Recommendation

There is no quality evidence for dose limits for postoperative patients using opioids. Because there are no quality data and there is no reason that dose limits for postoperative use would differ from acute pain, maximum doses are recommended to be adopted from evidence for the treatment of acute pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is no quality evidence for dose limits for postoperative patients using opioids, and thus there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: maximum daily dosage; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 53 articles in PubMed, 5 in CINAHL, 223 in Cochrane Library, 33900 in Google Scholar, and 0 from other sources†. We considered for inclusion 3 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 4 from other sources. Of the 7 articles considered for inclusion, 3 epidemiological studies and 4 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.6. DIAGNOSTICS AND MONITORING

Opioid treatment agreements are widely used to assist patients in understanding treatment parameters, goals, expectations, compliance, and screening expectations, as well as to monitor patients on opioids. A systematic review found weak evidence of efficacy for these agreements (336). Commonly, these agreements include provisions for urine drug testing for assessing compliance for use of that particular opioid, as well as ascertaining other illicit substance use (336). Finding either type of urine drug testing discrepancy (presence of an unexpected substance and/or absence of an expected opioid/metabolite) is normally considered grounds for referral to an addiction/opioid disorder specialist, supportive opioid tapering, and/or opioid cessation.

Drug testing most commonly measures drugs, or their metabolites, in urine or hair. There is expanding use of this diagnostic tool in pain management and addiction medicine. Urine is most commonly assayed. Hair testing may also be used, primarily for its advantage of assessing drug(s) use over a longer timeframe, and baseline screening, although it cannot be used for acute toxicity and its interpretation is frequently, considerably more difficult.* With the common 1” to 1.5” (2-3cm) scalp hair specimen evaluates a ‘window of detection’ of drug use over roughly the past 3 months. Depending on the hair source and length, the ‘window of detection’ may be as long as 1 year. Thus hair testing is used only to evaluate for the use of drugs not prescribed by or reported to the treating physician. The “window of detection” is too long to determine if the person is actually currently (still) taking the prescribed opioids(s).

For most opioids, the "window of detection" by urine drug testing is approximately 3 days. This varies a bit based on genetic variations in cytochrome P450 enzyme phenotypes, and thus the half-life of variability of opioids. Generally, drugs are detectable in urine for 5-6 medication half-lives. Thus, urine is the usual specimen collected for compliance testing. Specific metabolite testing for the opioid being prescribed is a necessity to determine if the prescribed medication is being used. Urine testing that fails to find the drug prescribed (assuming the test chosen is capable of detecting the drug prescribed) indicates one of five options: absence of recent use (indicating no need for the medication while also potentially indicating diversion), exhausting the supply of opioid before the appointment, a dilute urine sample, an immunoassay test that does not cross-react with that particular opiate or is not sufficiently sensitive to detect the drug level, or pharmacogenetic variability in drug metabolism (e.g., ultra-rapid metabolizer).

The NIDA-5 measures the cocaine metabolite benzoylecgonine, marijuana metabolites (principally delta-9 tetrahydrocannabinol), some opiates (e.g., codeine, morphine, 6-monoacetyl morphine [a heroine metabolite], amphetamines (methamphetamine, amphetamine, MDMA (3,4 methylenedioxy-methamphetamine) MDA (3,4 methlyenedioxypamphetamine), MDEA (3,4 methylenedioxy-N-ethylamphetamine), and phencyclidine (PCP) (337). Many commercial laboratories do NIDA 5 testing, and offer "expanded panel" tests that will detect commonly used opioids including oxycodone, hydrocodone, oxymorphone, hydromorphone, tramadol, Fentanyl, carisoprodol, barbiturates, benzodiazepines, etc. Thus, it is important to decide which panel will provide the best assessment for a specific situation. In general, the NIDA 5 is insufficient for monitoring opioid use, even if the patient is to be taking only a natural opiate due to insufficient coverage of other opioids. The NIDA 5 was developed to detect heroin use in US Military troops in Vietnam in the 1960s, and not for detecting use of either most current prescription and illicit opioids. To be useful, one must choose a test that the laboratory represents will detect the presence of the opioid being prescribed, assuming the patient is actually taking and not diverting the medication. It is also important that the test chosen is able to detect the drugs that might be used surreptitiously, and that increase the risk of accidental overdose mortality (e.g., benzodiazepines, barbiturates, etc.).

The prescriber is able to verify whether other prescribers are prescribing (other) controlled substances both in that state and in other states. Patients who are using both prescribed opioids and non-prescribed additional controlled substances usually have a substance use disorder, and further prescriptions for opioids are generally inappropriate. Such patients should be provided supportive care and either tapered from the opioid(s) or referred to a physician specializing in addiction medicine or psychiatry.

The NIDA-5 drug testing panel is commonly the extent of required testing for many federally regulated safety-sensitive employees[†]; these employees generally should not be taking opioids if in a safety-sensitive work status. This drug testing panel also is the most common test done by private employers as a pre-employment drug test. The opiates in this test detect heroin, but do not detect the new synthetic and semi-synthetic pharmaceutical opiates.

Multiple laboratories conduct urine drug testing. Each laboratory offers testing for the basic five categories, but typically also offers "expanded panel" tests capable of detecting many more classes of drugs.

Naturally, testing for more classes of drugs costs more per test. The choice of which test to order depends on what medications are being prescribed, and on what substances are potentially available for the patient to misuse. The prescribing physician must consult with the laboratory to determine which drugs are detectable by which tests, and then choose a test that would detect each prescribed controlled substance, and a test that would detect what other drugs the person might be misusing. Certification as a Medical Review Officer (MRO) is quite helpful with this decision making and monitoring (338,339).

Urine drug testing should be done in federally certified laboratories, which use a two-step process. The initial screening test is generally an enzyme-mediated immunoassay. Negative immunoassays conclude testing for a specific drug or drug class. However, the screening test method frequently cross-reacts with other drugs. Thus, the immunoassay screening test has the possibility that positive tests are true positives, but also the possibility that positive tests are false positives due to cross-reacting substances.

If the screening test is positive, the certified laboratories perform the second step, which is gas chromatography-mass spectroscopy (GC-MS). This test is more expensive, but detects the unique chemical fingerprint of every specific chemical. With GC-MS, there are no false-positive tests.

Proper interpretation of test results requires an understanding of the metabolism of medications (340). Hydrocodone is metabolized to hydromorphone (Dilaudid) before excretion, and the urine drug test of individuals taking hydrocodone thus usually detects both hydrocodone and a lower concentration of hydromorphone. If the last dose of hydrocodone was taken near the limit of the approximately 3-day window of detection, patients prescribed and taking just hydrocodone may test negative for hydrocodone (all metabolized), but still positive in low concentration for hydromorphone.

"Quick test" kits that use the screening immunoassay method permit in-office point-of-collection testing. While it may seem useful to have immediate urine drug screen results, immunoassays are subject to false-positive results and may not test for all the classes of medications/drugs for which the prescribing physician should be testing. Thus, urine drug testing is usually done by sending the urine sample to certified laboratories for testing that includes both screening immunoassay and confirmatory gas chromatography-mass spectroscopy testing.

Urine drug testing is also recommended by the Federation of State Medical Boards in its *Model Policy on the Use of Opioid Analgesics in the Treatment of Chronic Pain*. Urine drug testing of patients being prescribed chronic opioids is part of proper medical practice and should be a covered expense.

Correlating concentrations of substances in various body substances among opioid-related deaths with the adverse event is quite challenging and beyond the scope of this guideline.

**There are legal cautions of which to be aware. For example, in some states where all records are unavailable to employers, results from drug screenings may inadvertently be released to an employer. This may result in an employee's termination and could be interpreted as a HIPAA violation. Another example is drug use more than 3 months previously, having undergone opioid use disorder treatment, with subsequent termination that may be interpretable as a violation of the ADA.*

†An employer may require a wider battery beyond the NIDA 5 panel at the employer's discretion.

4.6.1. OPIOID TREATMENT AGREEMENTS

USE OF AN OPIOID TREATMENT AGREEMENT (OPIOID CONTRACT, DOCTOR/PATIENT AGREEMENT, INFORMED CONSENT)

Recommended

The use of an opioid treatment agreement (opioid contract, doctor/patient agreement, or informed consent) is recommended to document patient education, understanding, acknowledgement of potential benefits, adverse effects, and agreement with the expectations of opioid use (see Appendix 1) (Chou et al., 2009) (Boards, 2013) (Starrels et al., 2010) (Wiedemer et al., 2007) (Goldberg et al., 2005) (Manchikanti et al., 2006) (Manchikanti et al., 2006) (Chelminski et al., 2005) (Ives et al., 2006) (Hariharan et al., 2007) (Compton et al., 2008) (Burchman et al., 1995) (Vaglienti et al., 2003) (Brooks

et al., 2023). If consent is obtained, it is recommended that appropriate family members be involved in this agreement.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Indications

Patients treated with opioids beyond 4 weeks. Treatment agreements may be indicated in the acute phase for patients at high risk of opioid misuse.

Benefits

Educates the patient and significant others that these medications are high risk, with numerous adverse effects. It allows for a more informed choice and provides a framework for initiation of a trial, monitoring, treatment goals, compliance requirement, treatment expectations, and conditions for opioid cessation. Should reduce risk of adverse events and opioid-related deaths, although that remains unproven to date.

Harms

Generally negligible. However, treatment agreements may have stigma related to their implementation, drug testing components, and utilization, as well as inappropriate abandonment (Ho, 2017, Payne R, 2015, Helft PR, 2014).

Rationale

There is evidence that many patients do not adhere to prescribed treatment (even with an opioid agreement) (Wiedemer et al., 2007). However, these agreements are felt to be needed and are recommended to be coupled with a drug-screening program (Chou et al., 2009) (Boards, 2013) (Wiedemer et al., 2007) (Michna et al., 2007). These agreements also alert patients to the availability of data that will be accessed from across state lines via prescription drug monitoring program (PDMP) databases. Drug screening may identify both aberrant use as well as other substance use (Wiedemer et al., 2007) (Michna et al., 2007).

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: Informed consent; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 437 articles in PubMed, 80 in CINAHL, 165 in Cochrane Library, 35300 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 0 articles considered for inclusion, 0 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search,

and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.6.2. URINE DRUG TESTING

URINE DRUG TESTING FOR PATIENTS PRESCRIBED OPIOIDS

Recommended

Baseline and random urine drug testing, qualitative and quantitative, is recommended for patients prescribed opioids for the treatment of subacute or chronic pain to evaluate presence or absence of the drug, its metabolites, and other licit and illicit substance(s) use (Gudin et al., 2020, Kolla et al., 2019, Nugent et al., 2017).

In certain situations, other screenings (e.g., hair, particularly for information regarding remote use (Lees et al., 2012) (Politi et al., 2007) (Lamoureux et al., 2009) (Cooper et al., 2012) (Kulaga et al., 2009) (Appenzeller et al., 2007) or blood (for acute toxicity) may be appropriate.

More frequent screening at least quarterly has been associated with reductions in aberrancy and improve patient compliance (Gudin et al., 2020, DiBenedetto et al., 2019, Knezevic et al., 2017), as has lowered cutoffs for liquid chromatography/mass spectroscopy for screening results (Krock et al., 2017). Screening tools and questionnaires have not been found to be effective substitutes (Morasco et al., 2021). There are toxicological and other details beyond the scope of this guideline (see, e.g., (Swotinksy, 2021)).

Strength of evidence Recommended, Evidence (C)
Level of confidence High

Indications

All patients on opioids for subacute or chronic pain.

Benefits

Identifies aberrant medication(s) and licit/illicit substance(s) use. Such uses are high-risk for opioid events including fatalities. It provides objective evidence to cease an opioid trial or provide supportive treatment while tapering the opioid. Identifies patients who may be diverting medication (those screening negative for prescribed medication).

Harms

No adverse clinical effects if properly interpreted.

Frequency/Dose/Duration

Initial screening is recommended at baseline with either urine or hair testing. Urine drug testing is recommended intermittently with the frequency determined by the patient history which may be supplemented by a screening tool and the morphine equivalent dosing level. For details beyond the scope of this guideline, see, e.g., (Swotinksy, 2021).

Those with high risk screening results and/or MED more than 50mg are recommended to be screened randomly at least 4 times a year and at termination (Gudin et al., 2020). Those with low risk screening results and MED<50mg are recommended to be screened randomly twice yearly. Non-random testing twice yearly at the time of prescription refills for those at MED doses under 50mg and without a history of aberrancy, substance use disorder, and/or use of other sedatives (e.g., benzodiazepines) is a suboptimal management approach, but may be necessary in some settings. Federal guidelines recommend at least 8 tests a year among those utilizing opioid treatment programs (Substance Abuse and Mental Health Services Administration, 2013) (Federal Drug Administration, 2012).

Screening should also be performed "for cause" (e.g., provider suspicion of substance misuse including over-sedating, drug intoxication, motor vehicle crash, other accidents and injuries, driving while intoxicated, premature prescription renewals, self-directed dose changes, lost or stolen prescriptions, using more than one provider for prescriptions, non-pain use of medication, using alcohol for pain treatment or excessive alcohol use, missed appointments, stockpiling of medications, and selling and/or diverting medications).

Standard urine drug/toxicology screening processes should be followed; it is recommended to consult a qualified medical review officer (MRO) (Auerbach, 2007) (Jortani et al., 2012) (Heit et al., 2004). If there is an aberrant drug screen result (either positive for unexpected drugs or unexpected metabolites or unexpectedly negative results), there should be a careful evaluation of whether there is a plausible explanation (e.g., drug not tested, drug metabolite not tested, laboratory cutpoint and dosing interval would not capture the drug/metabolite, laboratory error). In the absence of a plausible explanation, those with an aberrant drug test showing an unexpected drug should have supportive treatment while the opioid is discontinued if the expected opioid/metabolite is missing (International Association of Industrial Accident Boards and Commissions, 2013) (Larochelle et al., 2018), or referred to addiction/opioid use disorder specialist and/or weaned for other aberrant findings due to opioid treatment agreement/contract violation and high risk of overdose (Commissions, 2013).

Rationale

Only drug testing has been found successful to detect aberrancy, including illicit substance use and prescribed substances misuse and non-use. Questionnaires and screening tools have not been found to be clearly effective (Morasco et al., 2021). However, both point-of-care screening and laboratory-based immunoassay tests are subject to false negative and false positive results. Opioid treatment agreements include provisions for urine drug testing for assessing compliance for use of that particular opioid, as well as ascertaining other illicit substance use. A systematic review found low quality evidence of efficacy of these tests (Starrels et al., 2010). More frequent screening at least quarterly has been associated with reductions in aberrancy and improved patient compliance (Gudin et al., 2020, DiBenedetto et al., 2019, Knezevic et al., 2017), while another retrospective analysis of UDTs collected between 2008-2011 found more frequent testing ($\geq$ 5) was observed to be associated with higher rates of adherence to prescribed medications (Yee et al., 2014). Lowered cutoffs for liquid chromatography/mass spectroscopy for screening results have also been associated with improved patient compliance (Krock et al., 2017).

Several medications may result in false-positive urine drug test results, as shown with examples in Table 3 (Vincent EC, 2006). In cases where false-positive results may be suspected, a careful review of the patient's medications is recommended. For further confirmation, mass spectroscopy/gas chromatography is recommended (Shafiq Q, 2010). Marijuana issues are further complicated by legal medical and/or recreational use in a majority of states (National Conference of State Legislatures, 2023), although they are contraindicated for safety-critical work and still illegal under federal law; this

is especially relevant for safety-critical workers in the transportation workforce (e.g., interstate truck drivers). For other details beyond the scope of this guideline, see, e.g., (Swotinksy, 2021).

Baseline and random urine drug testing, qualitative and quantitative, is recommended for patients prescribed opioids for the treatment of subacute or chronic pain to evaluate presence or absence of the drug, its metabolites, and other substance(s) use (Gudin et al., 2020, Kolla et al., 2019, Nugent et al., 2017). Confirmatory testing by a laboratory with GC/MS or LC/MS is recommended to be utilized for the following conditions: (1) POC testing was negative for the expected/prescribed medication/metabolites, (2) POC testing was positive for opioid/metabolites that were not prescribed by the treating physician, or (3) POC testing indicated illicit substances. A comprehensive drug panel may be appropriate when initiating care for a patient, however repeated testing with, e.g., broad 50-drug panels needs to be justified medically.

In certain situations, other screenings (e.g., hair particularly for information regarding remote use (Lees et al., 2012) (Politi et al., 2007) (Lamoureux et al., 2009) (Cooper et al., 2012) (Kulaga et al., 2009) (Appenzeller et al., 2007) or blood (for acute toxicity) may be appropriate. Either type of urine drug testing discrepancy (presence of an unexpected substance and/or absence of an expected opioid/metabolite) is normally considered grounds for referral to an addiction/opioid use disorder specialist, supportive opioid tapering, and/or opioid cessation.

Urine drug testing is non-invasive, has low adverse effects, is high cost, but has evidence of efficacy where there is no alternative to detect both compliance and use of illicit substance(s); thus, it is recommended both at baseline and periodically while there is ongoing opioid treatment for subacute and chronic pain. It is recommended that frequency be based on MED, risks, and other factors outlined above.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: Substance Abuse Detection; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 139 articles in PubMed, 109 in CINAHL, 58 in Cochrane Library, 35200 in Google Scholar, and 0 from other sources†. We considered for inclusion 6 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 7 articles considered for inclusion, 0 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.6.3. SCREENING TOOLS

A clinical interview is the most important method to identify risk for aberrant drug-related behaviors (341-343). However, it is neither systematic nor efficient. Its quality also is heavily reliant on the healthcare provider.

Many screening methods have been developed, but no proven substitute for the clinical interview exists yet. Although there are some comparative data, no quality comparative trials have identified the best tool to predict one or more measures of aberrancy (344-346).

Research has largely focused on four screening tools: the Screener and Opioid Assessment for Patients with Pain (SOAPP) and its revised version (SOAPP-R), the Pain Medication Questionnaire (PMQ), the Opioid Risk Tool (ORT), and the Current Opioid Misuse Measure (COMM). All four of these tools have undergone validation, including a demonstrated ability to predict aberrancy in one or more studies. However, a systematic review concluded that the available tools are not highly predictive (347).

The SOAPP was designed to reflect the consensus of experts and determine the circumstances/characteristics related to aberrant drug use through a self-administered screening tool for patients with chronic pain. The self-reported items for the SOAPP were generated based on the concept mapping results, literature, and clinical experience of the patients (348-351). However, SOAPP-R and other versions were created later to improve limitations of the original assessment (352-356). The SOAPP-R has undergone partial validation (357,356), yet the likelihood ratios are unhelpfully near 1 (see Appendix 1). A randomized, placebo-controlled experimental study for morphine found that higher SOAPP-R scores predicted a greater desire to take morphine again, increased feelings of sedation and improvement, and greater reductions in sensory low back pain (358). Patients presenting for surgery who were taking preoperative opioids or illicit opioids were found to have higher SOAPP-R scores (359). Studies suggest that the tool is predictive of opioid prescriptions at discharge among emergency department patients (360), prescriptions among emergency department patients at 6 and 12 months (343), post-operative opioid use (361), and aberrancy (349,362,363).

Another assessment tool is COMM, which is also a self-reported instrument. COMM was developed to complement other screening assessments tools for opioid misuse (364,357). The tool has been reportedly predictive of aberrancy (365,366) and substance use disorder (367). One study suggested that COMM was inferior to SOAPP for identifying opioid prescriptions at 6 and 12 months in an emergency department (343).

The Opioid Risk Tool (ORT) is also widely used to attempt to identify aberrancy (368-370). It has been found to predict the quantity of postoperative opioids consumed in orthopedic trauma patients, aberrancy among surgical patients (371), and prolonged risk among post-arthroplasty patients (372). It also reportedly identifies the degree to which an emergency department patient would be willing to share prescribed opioids with others (373). However, other studies found it was not predictive for which patients would use opioids 6 weeks after trauma (374) or the need for discharge opioids after elective colorectal surgery (375). The tool also was unable to detect aberrancy in emergency department patients (357) or opioid dependence after arthroscopic rotator cuff repair and shoulder surgery (376,361), and it was not strongly predictive of aberrancy in another study (377). The ORT has been used to stratify pharmacist interventions with patients, but there is no validation for this approach (378).

A fourth tool is the Pain Medication Questionnaire (PMQ). It has also undergone partial validation to show an ability to predict aberrancy (379-383).

Numerous other tools include the Prescription Drug Use Questionnaire (384,385), Brief Risk Inventory, Brief Risk Interview (386,387), Opioid Compliance Checklist (388,389), Brief Risk Questionnaire (390), DIRE score (391), Prescription Opioid Misuse Index (392), Screening Tool for Addiction Risk (STAR) (393), Prescription Opioid Therapy Questionnaire (341), and CAGE-AID/Opioid (394) (see Appendix 1), Pain Assessment and Documentation Tool, Brief Risk Interview, and Addiction Behaviors Checklist are

reportedly helpful to identify future aberrant drug-related behaviors, although there is considerably less robust literature supporting them.

GENETIC FACTORS

Genetic polymorphisms have been shown to affect opioid metabolism, including COMT, OPRM1, and OPRK1, with randomized experimental trial evidence suggesting there are differences by both the pain type of the opioid and the pain mechanism (e.g., pressure pain vs. heat vs. ischemia) (395). There also is evidence that different polymorphisms affect the metabolism of different opioids (396) and dropout rates during treatment (397). Consequent pharmacodynamic differences in opioid reversal agents (398), high-dose requirements (399,400), and complications of opioids have been reported (401). Cytochrome-blocking drugs and cytochrome-inducing pharmaceuticals also influence efficacy and toxicity.

Opioid deaths have been associated with CYP2D6 and OPRMI gene variations, with the CYP cytochromes (CYP 3A4/3A5, CYP 2D6, CYP 2C9, CYP2D9) responsible for metabolism through the cytochrome P450 system, and genetic variations impairing opioid metabolism (see Appendix 3) (396, 398, 399, 400-407). Another study found the genotype for 5-HTTLPR in the SLC6A4 gene to be modestly associated with dropout rate for methadone and buprenorphine/naloxone (397) As one example of potential clinical impacts, there is a strong tendency for those of Chinese ancestry, as well as some Caucasians, to poorly metabolize codeine to morphine.

It has been recommended that CYP2D6 pharmacogenetic testing be performed to improve oxycodone efficacy (408), as well as tramadol, codeine, and methadone prescribing (396,409).

Currently, screening for genetic risks prior to opioid treatment is not in widespread use. While the evidence for pharmacogenomic testing in opioid prescriptions is rapidly growing, the evidence-based roles are yet to be clearly defined in quality publications to show that testing impacts meaningful outcomes (396,402,403, 406).

SCREENING TOOLS TO IDENTIFY RISK FOR ABERRANT DRUG-RELATED BEHAVIORS

No Recommendation

Evidence suggests that the history is more important than screening tools for the detection of aberrancy (Michna, 2004, Moore et al., 2009). Evidence does not suggest the superiority of one screening tool over another; thus, there is no recommendation for or against specific screening tools.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

Electronic medical record clinical decision support software has been found to result in a modest increase in urine drug screens and referrals to therapy, although most major outcomes such as hospitalization and percentage over 90MME were not affected (Lu et al., 2020). However, evidence suggests that the history is more important than screening tools for the detection of aberrancy (Michna, 2004, Moore et al., 2009), and thus there is no recommendation for or against specific screening tools.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: aberrant drug-related

behaviors, aberrant drug-taking behavior, screening; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 12 articles in PubMed, 7 in CINAHL, 2 in Cochrane Library, 340 in Google Scholar, and 0 from other sources†. We considered for inclusion 4 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 6 from Google Scholar, and 0 from other sources. Of the 11 articles considered for inclusion, 2 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.7. DISCONTINUATION AND TAPERING OF OPIOIDS

DISCONTINUATION AND TAPERING OF OPIOIDS

Recommended

Supportive care while rapidly discontinuing opioids is recommended for most acute pain and post-operative patients. Patients treated for acute pain who are opioid-naïve should generally require no tapering. Patients with acute pain treated with continuous opioids over 50mg MED for longer than 2-3 weeks duration may benefit from brief tapering over 3 to 7 days. Longer tapers are recommended for those on opioids for longer periods of time, especially in the presence of physical dependency, and often require far greater coordination, adaptation, monitoring and supportive care to avoid overdose, aberrancy and abandonment (FDA, 2019).

Discontinuation, yet with ongoing supportive coordinated care, is also recommended for subacute and chronic pain patients who:

- used opioids on a chronic basis, and
- [any one of] lacked demonstrated functional gain, non-compliance, aberrant drug screening results and/or diversion, adverse effects (e.g., cognitive impairment, falls, poor judgment, untreated obstructive sleep apnea, central sleep apnea, psychological disorders, and concurrent use of sedative hypnotic and/or depressant medications such as moderate- or high-dose benzodiazepines and diphenhydramine)] (Commissions, 2013) (FDA, 2016) (Freire C, 2022) (Dowell D, 2016). In epidemiological studies, the most common reason for opioid cessation is aberrancy (Husain et al., 2019, Lovejoy et al., 2016).

Discontinuation is not recommended for the small subset of patients who show increased function with low to moderate doses of opioids and have little or manageable adverse effects, or who show reduced function with tapering (see the recommendations for subacute and chronic pain).

Immediate discontinuation without tapering is recommended for those who have a urine drug screen (UDS) showing unexpected absence of the prescribed drug. Among those with urine drug testing results showing non-prescribed licit or illicit substance(s) use, discontinuation is recommended, although tapering may be advisable if in addition to the aberrancy, the opioid is thought to be taken

as prescribed (e.g., rather than partially diverted) and the dose is over 50 mg MED. Supportive care is recommended for all of these situations to avoid overdose, aberrance and abandonment.

Tapering off buprenorphine is generally not done, as it is commonly used to treat opioid use disorder. However, when buprenorphine is tapered, it is more challenging (Sigmon et al., 2013, Fiellin et al., 2014). Yet, it is noteworthy that a majority of patients prescribed buprenorphine will reportedly discontinue the medication over a couple years after initiating it (Lovejoy et al., 2016, Hasan et al., 2021).

Strength of evidence Recommended, Evidence (C)
Level of confidence High

Indications

Discontinuation with tapering is recommended for subacute and chronic pain patients who used opioids on a chronic basis, and demonstrated any of the following: lack of functional gain, non-compliance, aberrant drug screening results and/or diversion, and/or among those in whom risks outweigh benefits (e.g., cognitive impairment, falls, poor judgment, untreated obstructive sleep apnea, central sleep apnea, psychological disorders, and concurrent use of depressant medications such as benzodiazepines and diphenhydramine) (CDC, 2022, VA Pharmacy Benefits Management Services, 2022, Joint Commission, 2013, Freire C, 2022). Generally, no tapering is needed to discontinue opioid use for most acute and postoperative patients. However, abrupt tapers among patients on chronic opioid treatment is not recommended unless there is evidence the patient is not taking the opioid and/or there are significant adverse effects (CDC, 2022).

Benefits

Improved pain, pain tolerance, function, and quality of life while reducing risk of adverse events and opioid-related deaths (Compton et al., 2022, Harden et al., 2015, McPherson et al., 2018, Muzzio et al., 2021, Fenton et al., 2021, Hill et al., 2020, Mackey et al., 2020).

Harms

None for either acute/post-operative patients undergoing abrupt or rapid opioid discontinuation, as well as for most patients managed with gradual tapers. Patients with tapering from long-term and higher-dose opioids may be at increased risk for overdose and mental health crisis (Agnoli et al., 2021). Fatalities have been reportedly associated with tapering, particularly those with opioid use disorder (Kennedy et al., 2022). Theoretical potential to worsen functional gain through cessation of opioid treatment, although evidence suggests most patients either improve or do not worsen while tapering (Fenton et al., 2021, Hill et al., 2020). Abrupt cessation in the presence of physical dependency is not advisable as tapering strategies are recommended, and a retrospective study reported higher risk of overdoses among those on high dose, long-term opioids (>90MME) compared with gradual tapers (DiPrete, 2022).

Frequency/Dose/Duration

A process is not generally needed for most acute and post-operative patients undergoing abrupt or rapid opioid discontinuation. For other patients, a process is recommended:

1. Develop a patient-centered tapering plan. Elements of the plan include:

- agreement to taper,

- education on potential symptoms during the taper,
- return visits for regular evaluation, education, assessment of function and assurance
- monitor for withdrawal symptoms, e.g., using scales such as Subjective Opiate Withdrawal Scale (SOWS,) Clinical Opiate Withdrawal Scale (COWS)
- return visits for intolerable symptoms with consideration of a pause in the taper, and
- other treatments to be changed or substituted.

2. The provider should be supportive and engaged in the patient's care, management and concerns. It is advised to not 'abandon' the patient. It is recommenced to engage the patient and optimize treatment with other active therapies during taper as indicated for the specific disorder treated (e.g., progressive active exercises, cognitive behavioral therapy, education, psychiatric consultation, psychiatric medication). Consider judicious use of passive therapies (e.g., acupuncture, TENS, manipulation) as adjuncts in assisting tapering when there is evidence of efficacy for that specific disorder (see disorder-specific ACOEM guidelines). Consider behavioral health support before and during a taper, especially although not limited to affective disorders.

3. **Rate of tapering.** Duration of a taper is largely empirical, dependent on dose, duration of use, and informed and supportive patient decision-making (CDC 2022). Rates of the taper vary. Rates of tapering have been slowed over the past 20 years (Barrett AK, 2022). The rate of tapering is increasingly thought to be important with faster rates having some evidence of higher dropouts (Kurita et al., 2018) and overdoses (DiPrete, 2022), although some patients may prefer faster tapers and the direction of the dose is most important. Besides personal preference, faster tapers may be implemented in inpatient and more controlled settings, or when use has been for a shorter period of time. Rapid tapers may also be needed for those with patient safety issues (e.g., discovery of combined high-dose opioids and benzodiazepines, near-fatal overdoses). Brief negotiated pauses in the rate of a taper can be successful.

There are few quality trials; thus it is unsurprising that there are many regimens recommended by numerous entities. A study of 595,078 patients receiving high-dose opioid therapy (>50MME) found that 26.7% experienced sustained dose reductions and 9.3% experienced complete discontinuation, with rates of taper of >10-40% per month (62.0%) and 40+% (36.1%) (Nataraj et al., 2022). The following are among the options for those on opioids for longer durations and/or at higher doses and are more recent tapering regimens:

- 10% per month (CDC 2022)
- 10% per week or less until 30% of the original dose is reached; then 10% per week of the remaining dose (HHS, 2019)
- 5-20% of original dose every 4 weeks completed over several months to years (VA, 2017)
- 5-20% of original dose per week, especially for those with non-adherence, high-risk medication-related behaviors, drug diversion, illegal activities, and/or other high risks (VA, 2017)
- No more than 10-25% every 2 to 4 weeks (FDA, 2019)
- 10% of original dose every 5-7 days until 30% of original dose reached, then weekly decrease by 10% of the remaining dose (Berna C, 2015)
- 6 months, gradual (Barrett AK, 2022)
- 3 months, gradual (Barrett AK, 2022)
- 1 month, gradual (Hundley L, 2018)

The following are among the options for those on opioids for shorter durations and/or at lower doses, and have been developed more remotely:

- 10% per day (American Academy of Pain Medicine, 2005)

- 20% every 3-5 days (American Academy of Pain Medicine, 2005)
- 10% per week (Washington State Department of Labor & Industries, 2010, Kral, 2006)
- 25% per week (American Academy of Pain Medicine, 2005)
- 20-50% per day until lower doses reached (e.g., oxycodone CR 30mg, then decrease dose by 10mg/day every 2-5 days (VA, 2010)
- 2.5-10mg/week as an outpatient (Substance Abuse and Mental Health Services Administration, 2013).

A pilot study found a 22-week taper support intervention was effective; it included psychiatric consultation, psychiatric medication med. if indicated, opioid dose tapering, and 18 weekly meetings with a physician assistant to educate, explore motivation for tapering and CBT-based learning pain self-management skills (Sullivan et al., 2017).

Other agents are used when weaning is challenging, and/or dependence and opioid use disorder issues are more complex and commonly include naltrexone, methadone, buprenorphine and clonidine (see below). While death during acute withdrawal is rare in those dependent on opioids alone, death during (withdrawal) tapering is a possibility in those dependent on multiple medications (e.g., opioids and benzodiazepines, carisoprodol, and anticonvulsants) and especially among those also on benzodiazepines. Those patients with unstable cardiovascular disease and polypharmacy dependence should be considered for in-patient detoxification under the supervision of an addiction/opioid use disorder specialist. For those using chronically high doses with difficulty tapering and/or undue anxiety, referral to a psychologist may also be helpful to address anxiety and behavioral issues.

4. Educate the patient that tapering will produce symptoms. These include anxiety, emotional distress, hyperalgesia, experiencing pain in new areas. These are expected and not contraindications to a taper, although if intolerable, may be a rationale for a brief pause in a taper.

5. **When to pause or cease tapering.** The taper should be stopped if there is objective worsening of function, excessive withdrawal, and/or intolerance. After stabilization, resumption of the taper should generally be attempted. However, if there is a plateau level where function is achieved, that dose should be noted in the records and maintained for an ongoing basis. There is consideration for reattempting tapering in subsequent months or years.

Indications for discontinuation

Tapering should be paused for those who develop significant withdrawal symptoms and signs. Decline in function may also signal a need to pause a taper.

Rationale

There are many studies that have described various methods of tapering opioids. However, there are no high and few moderate quality studies among the desired target population to define the best methods. The clinical approach is therefore somewhat empirical. Rates of tapers recommended have been considerably lengthened over the past 20 years.

A systematic review of opioid tapering and discontinuation studies found the overall quality of evidence to be poor, with literature suggesting among those tapered there was some evidence of improvements in pain, function and quality of life among some of the patients (Frank et al., 2017). Transitioning to non-pharmaceutical pain management and/or only an NSAID or acetaminophen or complete cessation of analgesics is/are generally indicated. Among those successfully tapered off opioids, there were improvements in functional measures, such as feeling more rested (Kurita et al.,

2018). However, this is tempered by concerns for adverse effects, including increased risk of overdoses and suicide.

A moderate-quality RCT found opioid tapering to be successful in high-risk trauma patients (Berube, 2022). A trial of an educational intervention found greater reductions in opioids compared with a usual care group, with 29% vs 7% successful discontinuations (Sandhu HK, 2023). Another trial of pain coping plus taper support and usual care compared with usual care alone ineffective (Wartko PD, 2023). Two-thirds of 113,618 patients who initiated opioid tapering sustained long-term reductions (Fenton et al., 2021). A state-mandated opioid dose reduction in Maine was found to not result in worsening pain, with 20% improving and 51% not experiencing a clinically significant change despite dose reductions (Hill et al., 2020). Patients on high-dose opioids also have been shown to attain improved experimental pain tolerance without declines in function or quality of life when opioids are tapered (Compton et al., 2022). Fibromyalgia patients also experienced improved pain measures while opioids were tapered during an interdisciplinary pain program (Cunningham et al., 2016). Multiple other epidemiological studies report successful dose tapering, including lack of increased pain or worsened function (Harden et al., 2015, McPherson et al., 2018, Muzzio et al., 2021). However, patients rapidly tapered who were on high-dose, long-term opioids (>90MME) were found in a retrospective study to have higher risk of overdoses compared with gradual tapers (DiPrete, 2022). Cessation of care has also been reported related to opioid tapering (Nataraj et al., 2022, Perez et al., 2020). Higher initial doses predicted higher likelihood of requiring buprenorphine transition (Sturgeon et al., 2020). Tapering support is reportedly helpful (Sullivan, 2017). Cognitive behavioral therapy as a sole treatment in one study has not been found helpful to reduce opioid prescriptions (DeBar et al., 2022). A propensity-matched random sample of 12+month opioid users in the VA found that 81% vs. 68% of those discontinued were due to clinician decisions related to aberrant behaviors among those with/out substance use disorders (Lovejoy et al., 2016).

Tapering is recommended if the opioid was used at a moderate or high level (e.g., above 50-90mg* MED) on a chronic basis. Consultation with an addiction/opioid use disorder specialist or psychiatrist is generally recommended for complex patients (e.g., high-dose patients, prior withdrawal problems, complex psychosocial confounders, complicating medical conditions).An RCT comparing the addition of nurse care management electronic registry and academic detailing, to electronic tools found the most common rates for discontinuation was misuse (65%, mostly detected by urine drug testing) (Husain et al., 2019). There is one moderate-quality pilot trial of a supportive group compared with usual care for tapering suggesting some efficacy (Sullivan et al., 2016). An RCT of simulated treatment approaches among chronic pain patients found the most receptivity to the taper off pain medications and participate in a CBT-based pain self-management program compared with staying on current medications or changing to a different pain medication (Ashton-James CE, 2019).

The rate of long-term success of tapers and discontinuation is also somewhat unclear, with a database study suggesting that high-dose opioid use predicts long-term opioid use (Martin et al., 2011). Some tapers are relatively unspecified (Nilsen et al., 2010) (Murphy et al., 2013). Tapers with buprenorphine also vary widely (Dreifuss et al., 2013) (Orman et al., 2009) (Weiss et al., 2011) (Dunn et al., 2011) (Westermeyer et al., 2012). Naltrexone or naloxone are also sometimes used as adjunct agents (Webster et al., 2011) (Weiss et al., 2011) (Jones et al., 2011) (Ling et al., 2012) (Farahmand et al., 2012) (Webster et al., 2012) (Fiellin et al., 2013) (Fiellin et al., 2006) (Fudala et al., 1998) (Krupitsky et al., 2011) (Krupitsky et al., 2012) (Mannelli et al., 2012) (Veenema et al., 2000) (Muncie et al., 1986) (Chang et al., 2004) (Eriksen et al., 2006) (Atluri et al., 2004) (Shah et al., 2008) (Webster et al., 2011) (Dunn et al., 2010) (Paulozzi et al., 2009) (Paulozzi et al., 2012) (Grattan et al., 2012). Discontinuation rates are low in the VA system and are low among the tobacco use disorders population (Vanderlip et al., 2014). There are many trials and other studies among heroin, licit, illicit and other undefined opioid users which use widely varying rates of detoxification mostly ranging from approximately 2 to 10 days

up to indefinite but lower dose maintenance. There also are additional studies on prevention and treatment of opioid dependence. These studies are beyond the scope of these guidelines. There are a few studies on detoxifying opioid using, non-abusing inpatients that are also beyond the scope of this guideline (Pederson et al., 2000) (Parran et al., 2002) (Parran et al., 2000). There are few barriers to implementing this recommendation. However, among those with demonstrated functional gains from low dose use of opioids, tapering is not recommended. Complex patients may need referral to a program for treatment of opioid use disorder, which may be geographically limited.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from July 2013 to March 2022 using the following terms: drug tapering, tapering, discontinuation; analgesics, narcotics, opioid, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 1191 articles in PubMed, 310 in CINAHL, 448 in Cochrane Library, 35100 in Google Scholar, and 0 from other sources†. We considered for inclusion 24 from PubMed, 15 from CINAHL, 0 from Cochrane Library, 8 from Google Scholar, and 0 from other sources. Of the 47 articles considered for inclusion, 12 randomized trials and 6 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.8. TREATMENT OF DEPENDENCY AND OPIOID USE DISORDER

Most tapering of opioids can be safely accomplished with no adjunctive or alternative medications (see above). However, medications may be selectively used for more difficult opioid tapers, as well as for treatment of opioid dependency and substance use disorder. Often, the same medications are used for both of these purposes; these medications include buprenorphine, clonidine, and naltrexone (5,6,7,8,9,10,11). Methadone is rarely used for tapering and is almost exclusively used for maintenance. Detailed guidance on the treatment of substance use disorder is beyond the scope of this guideline.

MEDICATIONS FOR OPIOID USE DISORDER

Sometimes Recommended

There are multiple pharmaceutical agents, combinations of agents, and formulations that are used to treat patients with opioid use disorder, including for detoxification and maintenance. These include buprenorphine, buprenorphine/naloxone, methadone; methadone/lofexidine; extended-release naltrexone. Naloxone is sometimes used as an adjunct primarily to attempt to deter misuse. Buprenorphine has been primarily used to treat opioid use disorder. However, it has also been used in some trials to treat pain, among those already using opioids (Gimbel et al., 2016) and those not using opioids (Rauck et al., 2016, Widenka et al., 2020).

These medications are selectively recommended for treatment of opioid use disorder. Choice of medication is per prescriber preference(s) for patient needs and expectations.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Moderate

Indications

Selective use among those with opioid use disorder, in a state of withdrawal at the time of initiation, and/or with a high risk of recidivism and for whom risks of tapering are felt to outweigh risks of maintenance therapy. Detailed deliberations are essential for those who either perform safety-critical work, or anticipate doing so, as maintenance therapy may preclude employment, and thus tapering and discontinuation may be preferred by, and for those individuals. There are many requirements that should be met, e.g., medical history, psychiatric history, substances use history, evaluation of family support, psychosocial support, prescription drug monitoring program access and monitoring, drug testing, other lab testing, and an integrated approach to address the medical, mental health and social needs of the patient (SAMHSA, 2023).

Benefits

Reduced risk of opioid misuse, cravings, reduced opioid misuse, overdoses and deaths.

Harms

Nausea, vomiting, constipation, abdominal pain, sleepiness, fatigue, CNS depressive symptoms, dizziness, pruritis, skin rash, headache, and confusion. Overdose may occur, but typically occurs in combination with alcohol, benzodiazepines, and other CNS depressants. There is some evidence for an increased risk of motor vehicle crashes; thus, other accidents are likely as well (see the recommendations on Safety-Sensitive work). Preclusion from performing safety-critical work in some industries and employment settings.

Frequency/Dose/Duration

Per manufacturer's recommendations. Buprenorphine is preferred to be combined with naloxone to prevent diversion. Advised to concomitantly include psychosocial support. Initiating dose is dependent on many factors including opioid use history, last use, type of opioid(s) used, severity of withdrawal symptoms, and the clinical presentation. Maintenance dosing goals are once-daily use with no withdrawal between doses. Altered management is advised if, e.g., there are signs of non-compliance, diversion, and/or other substances use (SAMHSA, 2023). Altered management may include shorter prescription supplies, observed dosing, more frequent appointments, and clear communications regarding future expectations, management requirements, and consequences. Signed agreements including all of these elements are highly recommended, both for initiation, as well as after evidence of aberrancy.

Indications for discontinuation

Non-compliance, diversion, especially if occurring after measures taken to attempt to (re)gain compliance. Intolerance, or significant adverse effects. May also need to discontinue if a job requires it, typically for safety-critical work, such as new employment.

Rationale

Multiple RCTs have assessed the use of buprenorphine with and without naloxone for the treatment of opioid use disorder (Wang, 2018, Socias et al., 2018, Law et al., 2017, Lofwall et al., 2018, Lintzeris et al., 2002, Lintzeris et al., 2013, Lintzeris et al., 2021, Walsh, 2017, Ahmadi et al., 2018, Lee et al., 2018, Haight et al., 2019, Ling et al., 2019, Andorn et al., 2020, Jutras-Aswad et al., 2022, D'Onofrio, 2017, Stein, 2019, Jain et al., 2018, Sullivan, 2017, Ahmadi et al., 2003, Amass et al., 2004, Assadi et al., 2004, Bickel et al., 1988, Chawarski et al., 2005, Collins et al., 2005, Dunn et al., 2015, Hopper et al., 2005, Janiri et al., 1994, Kakko et al., 2007, Kakko et al., 2003, Kamien et al., 2008, Ling et al., 1998, Ling et al., 2009, Magura et al., 2009, Marsch et al., 2016, Mattick et al., 2003, McAnulty et al., 2022, Nigam et al., 1993, Wright et al., 2011, Ziaaddini et al., 2010, O'Connor et al., 1997, Oreskovich et al., 2005, Petitjean et al., 2001, Schottenfeld et al., 2008, Seifert et al., 2005, Sigmon et al., 2013, Soyka et al., 2008, Umbricht et al., 2003, Rudolph, 2021, Fiellin et al., 2014, Marsch et al., 2016).

Trials have also assessed methadone (Socias et al., 2018, Law et al., 2017, Nunes Jr et al., 2021, Bickel et al., 1988, Kakko et al., 2007, Kamien et al., 2008, Magura et al., 2009, Seifert et al., 2005, Soyka et al., 2008, Umbricht et al., 2003, Mattick et al., 2003, McAnulty et al., 2022, Petitjean et al., 2001, Wright et al., 2011, Schwartz, 2011, Schwartz, 2012, Schwartz, 2014, Schwartz, 2017) (Larochelle et al., 2018).

Extended-release naltrexone has been successfully used in multiple RCTs for detoxification (Bisaga et al., 2018, Tanum, 2017, Lee et al., 2018, Nunes Jr et al., 2021, Sullivan et al., 2017, Greiner, 2021, Shulman, 2021, Ruglass, 2019, Latif, 2018).

Clonidine has been infrequently used (Collins et al., 2005, Janiri et al., 1994, Nigam et al., 1993, O'Connor et al., 1997, Umbricht et al., 2003, Ziaaddini et al., 2010). Buspirone has been used as an adjunctive medication for buprenorphine-assisted opioid withdrawal (Bergeria et al., 2022).

One large study of Medicaid claims suggested longer maintenance of buprenorphine was associated with a lower likelihood of being seen in an emergency department, although more than two-thirds of patients on buprenorphine at least 6 months were not included in the analyses for various reasons (Williams et al., 2020). Another report on the same source database found 28.4% discontinued buprenorphine within a month and 64.6% discontinued within 180 days, with discontinuation of lower dose, male, younger age, minority race/ethnicity, capitated insurance, comorbid substance use disorders, hepatitis C, opioid overdose history, and inpatient care (Samples et al., 2018). Another large study of claims data reported 75% of patients discontinued buprenorphine/naloxone within 2 years of initiating treatment (Hasan et al., 2021).

Comparative trials are few and those available do not suggest superiority of one agent to the others.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: pharmaceutical agent; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 507 articles in PubMed, 84 in CINAHL, 32 in Cochrane Library, 33600 in Google Scholar, and 3 from other sources†. We considered for inclusion 22 from PubMed, 0 from CINAHL, 0 from Cochrane

Library, 13 from Google Scholar, and 3 from other sources. Of the 38 articles considered for inclusion, 3 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

BUPRENORPHINE FOR OPIOID TAPERING

Sometimes Recommended

Buprenorphine is selectively recommended for adjunctive treatment in opioid tapering.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Indications

Most patients are weaned without use of an adjunctive controlled substance medication. Buprenorphine is sometimes used for detoxification from high-dose opioids and is recommended for select cases with opioid use at over 50-90 mg MED for at least 3 months duration (Dowell D, 2016). Buprenorphine is also recommended for the treatment of opioid use disorder. Prior to initiation, patients should be off short-acting opioids for at least 24 hours and off long-acting opioids for 48-72 hours. Buprenorphine dose is titrated to achieve stability, after which patients may undergo weaning or, for patients with opioid use disorder, maintenance with buprenorphine / naloxone. Patients should be off opioids for 5-7 days prior to beginning buprenorphine-naltrexone medication assisted treatment. As treatment of these conditions is behaviorally and medically challenging, most are treated by addiction/opioid use disorder specialists (e.g., high-dose patients, prior withdrawal problems, complex psychosocial confounders, complicating medical conditions). When there are complex medical issues (e.g., significant cardiovascular disease), inpatient treatment may be indicated. There are safety -critical job concerns to consider regarding the use of buprenorphine (see recommendations for Safety-Sensitive Work).

Buprenorphine is generally not recommended for those with no demonstrated functional gain from opioid prescriptions; non-compliance; use of illicit substances; use of alcohol with opioids; and/or adverse effects of opioids (e.g., cognitive impairment, falls, poor judgment, untreated sleep apnea, psychological disorders, use of benzodiazepines). Transitioning to only an NSAID or acetaminophen or complete cessation of analgesics is/are generally preferable to substitution with buprenorphine.

Buprenorphine is not indicated for tapering from opioid use for acute pain or post-operative use, other than potentially with selective use among those post-operative with use that became high dose and chronic (>3 months).

Benefits

May help reduce opioid withdrawal symptoms. Reduced risk for misuse and diversion when using combined buprenorphine/naloxone.

Harms

Buprenorphine/naloxone may precipitate opioid withdrawal. Sedation, daytime fatigue, overdose, fatalities, however the risk of fatalities is considerably lower than with methadone. There is potential for misuse (Cassidy et al., 2014). There is increased risk for safety including motor vehicle crash and other injuries (Hegmann et al., 2014, Rudisill et al., 2016)(Hazle et al., 2022),

Frequency/Dose/Duration

Buprenorphine is generally thought to be better prescribed as combined with naloxone to reduce misuse and diversion potentials (Substance Abuse and Mental Health Services Administration, 2013). Monotherapy with buprenorphine is recommended for treatment during pregnancy and when converting from methadone treatment; subsequently, transfer to buprenorphine/naloxone is recommended.

Indications for discontinuation

Resolution of pain, non-tolerance, significant sedating effects that carry over into the daytime, or other adverse effects.

Rationale

Most literature addressing methadone and buprenorphine are for use among those with opioid dependency and especially for those with opioid use disorder.

Buprenorphine has been shown to increase adherence to treatment and reduce risk of illicit opioid use among patients with opioid use disorder (Zacny, 2005) (Iezzi et al., 2004) (Berryman et al., 2013) (Hart et al., 2000) (Moriarty et al., 2011). Buprenorphine may be used for opioid use disorder, although it should be prescribed by experienced and licensed providers. It should be taken as directed, not started/stopped or used with other medications or dietary supplements without advice of the provider. Providers should be aware of the adverse effects including overdose, fatalities, respiratory depression, and dysrhythmias. Buprenorphine is not recommended in workers with safety-sensitive jobs (Gomes et al., 2013) (Gibson et al., 2009) (Engeland et al., 2007) (Dubois et al., 2010) (Majdzadeh et al., 2009) (Bachs et al., 2009) (Corsenac et al., 2012) (Bramness et al., 2012) (Movig et al., 2004). Clinicians should offer or arrange evidence-based treatment (usually treatment with buprenorphine in combination with behavioral therapies) for patients with opioid use disorder (Dowell D, 2016).

Buprenorphine appears to be considerably safer than methadone due to its partial agonist effects. Yet, while appearing safer, it may cause respiratory depression with high doses (Yassen et al., 2007) (Dahan et al., 2006) (van Dorp et al., 2006) and has been associated with some risk of fatalities in most (Anchersen et al., 2009) (Hakkinen et al., 2012) (Pelissier-Alicot et al., 2010) (Lai et al., 2006) (Kintz, 2002) (Romelsjo et al., 2010) (Soyka et al., 2006) (Ho et al., 2009) but not all studies especially with use of sedatives (Bauer et al., 2008). It requires training of the prescriber and is expensive (Berland et al., 2012). Naltrexone has been used in both oral and implantable forms, as a means of treating problematic opioid use, but only after tapering has been completed. However, while it has been associated with reduced risk, it also does not eliminate risk (Kelty et al., 2012). Evidence supporting supervised compared with at-home administration of medication is poor (Saulle R, 2017).

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: Buprenorphine; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 777 articles in PubMed, 466 in CINAHL, 164 in Cochrane Library, 25,300 in Google Scholar, and 0 from other sources†. We considered for inclusion 29 from PubMed, 10 from CINAHL, 0 from Cochrane Library, 8 from Google Scholar, and 0 from other sources. Of the 47 articles considered for inclusion, 26 randomized trials and 13 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

METHADONE FOR OPIOID TAPERING

Sometimes Recommended

Methadone is almost exclusively used as a maintenance medication for opioid use disorder (Schwartz, 2011, Schwartz, 2012, Schwartz, 2014, Schwartz, 2017, Zhou et al., 2017). It is selectively recommended for adjunctive treatment in opioid tapering, but should be done by an expert in treatment of opioid use disorder.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Indications

Most patients are weaned without use of a controlled substance medication. Methadone is primarily used for opioid use disorder treatment (Schwartz, 2011, Schwartz, 2014, Schwartz, 2017, Schwartz, 2012) although it is sometimes used for tapering from high-dose opioids. Methadone is recommended for select cases with opioid use at over 50-90 mg MED for at least 3 months duration (Chou et al., 2014), as well as for the treatment of opioid use disorder. As treatment of these conditions is behaviorally and medically challenging, bioaccumulation is problematic, and special licensure is required for methadone, most are treated by trained and qualified addiction/opioid use disorder specialists. When there are complex medical issues (e.g., significant cardiovascular disease, high-dose patients, prior withdrawal problems, complex psychosocial confounders, complicating medical conditions), inpatient treatment may be indicated. Methadone is not recommended for those with safety-sensitive jobs (Hegmann et al., 2014).

Methadone is not recommended for tapering from opioid use for acute pain or post-operative use, other than potentially with highly selective use among those post-operative with use that became high dose and chronic (>3 months).

Benefits

May help reduce opioid withdrawal symptoms.

Harms

Methadone has a particularly high risk of overdose and fatalities (Wunsch et al., 2009) (Webster et al., 2011) (Burgess, 2009). There is no safe dose of methadone when converting from other opioids. Due to its long half-life, respiratory depression may occur days later, thus initiation must be particularly cautiously and carefully monitored. There is potential for misuse and diversion. Methadone is associated with sedation and daytime fatigue. Other risks include motor vehicle crash and other injuries (Hegmann et al., 2014).

Frequency/Dose/Duration

Per manufacturer's and addiction/opioid use disorder specialist's recommendations. Initial dosing is typically 2.5-10mg every 8 to 12 hours and estimated from daily morphine dose usage, with subsequent adjustments cautiously made based most importantly on risk of respiratory depression.

Indications for discontinuation

Resolution of pain, non-tolerance, significant sedating effects that carry over into the daytime, or other adverse effects.

Rationale

Methadone increases adherence to treatment and reduce risk of illicit opioid use among patients with opioid use disorder (Xu et al., 2021) (Iezzi et al., 2004) (Berryman et al., 2013) (Hart et al., 2000) (Moriarty et al., 2011). Methadone may be used for opioid use disorder, although they should be prescribed by experienced and licensed providers. Methadone should be taken exactly as directed, not started/stopped or used with other medications or dietary supplements without advice of the provider. Providers should be aware of the adverse effects including overdose, fatalities, respiratory depression, prolonged QT interval, and dysrhythmias (FDA, 2019). Methadone is also not recommended for workers with safety-sensitive jobs (Gomes et al., 2013) (Gibson et al., 2009) (Engeland et al., 2007) (Dubois et al., 2010) (Majdzadeh et al., 2009) (Bachs et al., 2009) (Corsenac et al., 2012) (Bramness et al., 2012) (Movig et al., 2004). Clinicians should offer or arrange evidence-based treatment (usually treatment with methadone in combination with behavioral therapies) for patients with opioid use disorder (Dowell D, 2016). Methadone reportedly accounts for more overdose deaths when compared to hydrocodone or oxycodone (Park et al., 2020) (Toblin et al., 2010) (CDC, 2005). Because methadone is also used to treat substances use, overdose decedents tend to have used other prescription and/or illicit medications as well (Kuehn, 2012) (Modesto-Lowe et al., 2010). Still, some methadone deaths appear to be related to the medication's tight therapeutic window (Modesto-Lowe et al., 2010) (Chugh et al., 2008) (Berland et al., 2012). Prescribers of methadone should be experienced; physicians and patients may both be unfamiliar with methadone and its potential for inappropriate dosing and long and unpredictable half life. Conversion ratios vary with dose. The 40mg diskette form of methadone may contribute to drug overdose because of the large amount of drug in each diskette. The liquid form of methadone can be subject to errors during preparation. Some medications induce the metabolism of methadone, such as anticonvulsants and rifampin, while other medications lead to increases in methadone blood levels contributing to toxicity (Burgess, 2009). Methadone should not be used to treat breakthrough pain (BTP) or as an as needed medication (Chou et al., 2009). Switching to methadone requires careful conversion. Supervised

administration of methadone is reportedly associated with lower fatality rates than unsupervised administration (Caplehorn et al., 1996) (Marsch, 1998) (Sporer, 2003) (Strang et al., 2010), yet numerous studies have shown elevated mortality rates associated with methadone (Piercefield et al., 2010) (Paulozzi et al., 2009) (Seal et al., 2012).

One comparative trial of buprenorphine/naloxone vs. methadone for treatment of opioid use disorder found indirect evidence of non-inferiority of buprenorphine/naloxone for opioid use (Jutras-Aswad et al., 2022) and also reported that cravings were reduced more by buprenorphine/naloxone than for methadone (McAnulty et al., 2022). The same trial also reported indirect evidence of the effects on depression and found comparable results with reductions in illicit opioids explaining the reductions in depressive symptoms (Bastien G, 2022). However, this trial is of limited use for assessment of tapering as it is for treatment of OUD.

Buprenorphine appears to be considerably safer than methadone due to its partial agonist effects. Yet, while appearing safer, it may cause respiratory depression with high doses (Yassen et al., 2007) (Dahan et al., 2006) (van Dorp et al., 2006) and has been associated with some risk of fatalities in most (Anchersen et al., 2009) (Hakkinen et al., 2012) (Pelissier-Alicot et al., 2010) (Lai et al., 2006) (Kintz, 2002) (Romelsjo et al., 2010) (Soyka et al., 2006) (Ho et al., 2009) but not all studies especially with use of sedatives (Bauer et al., 2008). It requires training of the prescriber and is expensive (Berland et al., 2012). Naltrexone has been used in both oral and implantable forms, as a means of treating problematic opioid use, but only after tapering has been completed. However, while it has been associated with reduced risk, it also does not eliminate risk (Kelty et al., 2012). Evidence of the need for supervised compared with at-home administration is poor (Saulle R, 2017).

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar from April 2017 to July 2022 using the following terms: methadone, taper, analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 1337 articles in PubMed, 0 in CINAHL, 0 in Cochrane Library, 1850 in Google Scholar, and 0 from other sources†. We considered for inclusion 9 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 9 articles considered for inclusion, 0 randomized trials and 8 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

LOFEXIDINE FOR TREATMENT OF OPIOID WITHDRAWAL SYMPTOMS

Recommended

Lofexidine is moderately recommended for the treatment of opioid withdrawal symptoms.

Strength of evidence Moderately Recommended, Evidence (B)

Level of confidence Moderate

Indications

Opioid-dependent patients with withdrawal symptoms and/or individuals beginning withdrawal who are estimated to be likely to experience withdrawal symptoms.

Benefits

Reduced withdrawal symptoms and improved retention in treatment, yet while not being an opioid medication.

Harms

Chest pain, irregular heart rate, bradycardia, prolonged QT interval, hypotension, confusion, fatigue, drowsiness, dizziness, lightheadedness, dry mouth, tinnitus, hearing loss (Doughty et al., 2019, Renfro et al., 2020, Darpö et al., 2019).

Frequency/Dose/Duration

Lofexidine 0.54mg QID (2.16mg/day) or 0.72mg QID (2.88mg/day) were used for 7 days in one trial, although the higher dose did not result in greater efficacy for withdrawal symptoms (Alam et al., 2020). Another trial initiated treatment with 0.8mg/day in 3 divided doses, increased by 0.4-0.8 mg/day up to 2.2mg/day (Guo et al., 2018). Another regimen initiated treatment at 0.4mg BID, increased to 0.8mg BID in week 1, and 1.2mg BID in week 2 for up to 11 weeks (Hermes et al., 2019).

Indications for discontinuation

Completion of withdrawal, intolerance, adverse effects or non-compliance.

Rationale

Three trials found lofexidine to be superior to placebo for reduction in withdrawal symptoms and retention (Fishman et al., 2019, Gorodetzky et al., 2017, Alam et al., 2020), the first two of which were also reported in a pooled analysis (Alam et al., 2020). One trial found lofexidine was at least as effective as diazepam for withdrawal symptoms, yet without the risks of addiction (Guo et al., 2018). Another trial found a combination of lofexidine plus naltrexone superior to placebo for reducing cravings (Hermes et al., 2019). One study of combination therapy found equivalency between buprenorphine/naloxone and methadone/lofexidine (Law et al., 2017). There are multiple moderate-quality trials suggesting efficacy of lofexidine, it is not invasive, has some adverse effects, is high cost, and is selectively recommended.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: lofexidine; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 27 articles in PubMed, 14 in CINAHL, 11 in Cochrane Library, 569 in Google Scholar, and 0

from other sources†. We considered for inclusion 2 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 0 from other sources. Of the 6 articles considered for inclusion, 6 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

CLONIDINE FOR TREATMENT OF OPIOID WITHDRAWAL SYMPTOMS

Recommended

Clonidine is selectively recommended for the treatment of opioid withdrawal symptoms.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Opioid-dependent patients with withdrawal symptoms and/or individuals beginning withdrawal who are estimated to be likely to experience withdrawal symptoms. The highest quality trial compared placebo with clonidine during buprenorphine induction therapy after 2 weeks of abstinence from illicit use among heroin users (Kowalczyk et al., 2017).

Benefits

Reduction in withdrawal symptoms and increased engagement in usual or unstructured activities (Kowalczyk et al., 2017).

Harms

Hypotensive symptoms, bradycardia, allergic reactions, constipation, drowsiness, dry mouth, and fatigue.

Frequency/Dose/Duration

One trial used clonidine 0.1mg for 7 days, then 0.2 mg for 7 days, and then 0.3 mg for 7 days (Kowalczyk et al., 2017).

Indications for discontinuation

Adverse effects, intolerance, completion of withdrawal and/or non-compliance.

Rationale

There are few trials assessing the efficacy of clonidine for the treatment of opioid withdrawal symptoms, although there are many studies that used clonidine during tapering, withdrawal, and/or buprenorphine/methadone induction (Oreskovich et al., 2005, Umbricht et al., 2003, Janiri et al., 1994, Collins et al., 2005, Lintzeris et al., 2002, O'Connor et al., 1997). One trial found clonidine superior to

placebo during buprenorphine induction therapy for reducing cravings and increasing unstructured activities (Kowalczyk et al., 2017). One trial found clonidine inferior to olanzapine as measured by need of rescue medication and improved symptoms (Klein et al., 2019). Two trials found buprenorphine superior to clonidine for symptoms and other outcomes measures such as engagement in addiction treatment 1 month later (Srivastava et al., 2019, Lintzeris et al., 2002). Another trial found equivalency between buprenorphine, clonidine and methadone (Umbricht et al., 2003). Thus, there is some quality evidence that clonidine is superior to placebo, is not invasive, has relatively low adverse effects, and is low cost; thus, it is selectively recommended for treatment of withdrawal symptoms. There are some other options that may be preferable for initial and/or preemptive treatment of withdrawal symptoms.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: clonidine; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 155 articles in PubMed, 59 in CINAHL, 49 in Cochrane Library, 9,890 in Google Scholar, and 1 from other sources†. We considered for inclusion 3 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 7 from Google Scholar, and 1 from other sources. Of the 11 articles considered for inclusion, 11 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

NALTREXONE FOR TREATMENT OF OPIOID USE DISORDER

Recommended

Naltrexone is recommended for use as a treatment for opioid use disorder.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Moderate

Indications

Opioid-dependent patients at risk of recidivism after withdrawal. To avoid withdrawal symptoms, naltrexone should not be used until short-term opioids have been stopped for 7 days and long-acting opioids for 10-14 days (SAMHSA, 2023).

Benefits

Modestly reduced risk of recidivism.

Harms

Abdominal pain, nausea, vomiting, diarrhea, constipation, dyspnea, blurred vision, dysuria, headache, dizziness, tinnitus, hallucinations, fatigue, depression, anxiety, nervousness, irritability, palpitations, joint pain, muscle pain

Frequency/Dose/Duration

Naltrexone 50-100 mg PO QD, which is usually initiated with a 25-mg dose, followed by a second 25-mg dose. Also administered as an injectable, extended-release form of 380 mg IM Q4 weeks.

Indications for discontinuation

Intolerance, adverse effects, or non-compliance.

Rationale

There are multiple randomized controlled trials that involved naltrexone. A placebo-controlled trial found XR naltrexone superior to placebo for opioid-free weeks (Krupitsky et al., 2011). One trial found XR naltrexone superior to buprenorphine/naltrexone (Nunes Jr et al., 2021), although other studies found equivalence between those treatments (Tanum, 2017) or that buprenorphine/naltrexone was superior to the XR Naltrexone (Lee et al., 2018). Another trial found equivalency between naltrexone, buprenorphine, and placebo. One trial found buprenorphine superior to naltrexone for heroin relapse time and abstinence (Schottenfeld et al., 2008). Some randomized trials have used naltrexone as part of a treatment protocol (Sigmon et al., 2013), including equivalence between naltrexone/clonidine and buprenorphine. Naltrexone is either non-invasive or minimally invasive (IM) and ranges to high cost for the XR intramuscular preparation. As there is evidence of some efficacy, naltrexone is selectively recommended for maintenance treatment of opioid use disorder.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: naltrexone, tapering, discontinuation; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 64 articles in PubMed, 13 in CINAHL, 17 in Cochrane Library, 3,000 in Google Scholar, and 0 from other sources†. We considered for inclusion 7 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 9 from Google Scholar, and 0 from other sources. Of the 9 articles considered for inclusion, 9 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

COGNITIVE BEHAVIORAL THERAPY (CBT) FOR ABERRANT DRUG-RELATED BEHAVIOR

Recommended

Cognitive behavioral therapy (CBT) is recommended to reduce the risks associated with aberrant drug-related behavior (Guarino et al., 2018).

Strength of evidence Recommended, Evidence (C)
Level of confidence Moderate

Indications

Opioid-treated chronic pain patients who have aberrant drug-related behavior(s) and/or screen positive for same.

Benefits

Reduction in drug aberrancy, catastrophization and emergency department visits (Guarino et al., 2018).

Harms

Negligible

Frequency/Dose/Duration

The largest quality trial used a web-based self-management program with 27 modules (Guarino et al., 2018).

Indications for discontinuation

N/A

Rationale

One moderate-quality RCT used a web-based self-management program consisting of 27 modules and found it to be effective compared with treatment as usual for reductions in aberrancy, catastrophization and emergency department visits (Guarino et al., 2018). Another trial found lack of efficacy of a single, brief behavioral intervention in the emergency department (Banta-Green et al., 2019). There is evidence of efficacy in the one large trial of a web-based CBT program, it is not costly, and thus it is recommended.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: risk factor screening, risk factor testing; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 1063 articles in PubMed, 22 in CINAHL, 25 in Cochrane Library, 35400 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0

from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 0 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.9. PREVENTION OF OVERDOSE FATALITIES

Naloxone has been used for the prevention of opioid overdose fatalities (12) and is now available over-the-counter. It is also used in pharmaceutical combinations with opioids primarily as an attempted, but potentially insufficient, misuse deterrent.

Nalmefene nasal spray is also available by prescription only for reversal of opioid overdoses. Nalmefene has a longer duration of action which may be advantageous to reduce numbers of administrations needed to counteract an overdose, while also being potentially disadvantageous by prolonging withdrawal symptoms which can be serious. Thus, naloxone may be a safer option in most situations (13).

NALOXONE (NARCAN) FOR OPIOID OVERDOSE

Recommended

Naloxone has long been used as an antidote for opioid overdose, and the FDA has approved its use over-the-counter (U.S. Food and Drug Administration, 2023, Parmar, 2016, Mundin et al., 2017, Skulberg et al., 2019, Eggleston et al., 2020, McDonald et al., 2017, Meade et al., 2018, Samuels et al., 2018, Samuels et al., 2021, Tylleskar, 2020, Wong, 2019, Weiner, 2017, Ray et al., 2018, Purssell et al., 2021, Parkin et al., 2021, Morgenstern et al., 2019, McCann et al., 2021, Marco et al., 2018, Maloney et al., 2020, Kummer et al., 2022, Klebacher et al., 2017, Kilaru et al., 2021, Katzman et al., 2018, Katzman et al., 2020, Gruver et al., 2020, Fidacaro Jr et al., 2020, Farkas et al., 2020, Farkas et al., 2021, Dudley et al., 2018, Clemency et al., , Carpenter et al., 2020, Ashburn et al., 2020) (Weaver et al., 2018, Thompson et al., 2022, Weiner et al., 2022).

Naloxone is prescribed for subsequent treatment of opioid overdose among those on chronic opioids at home, particularly those on higher opioid doses (Coffin et al., 2016). Legislation has been passed in most jurisdictions to allow emergency personnel, police, firefighters, and others to provide naloxone to resuscitate unresponsive individuals. Naloxone is also used for treatment of pain in combination with an opioid.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence High

Indications

Naloxone (e.g., naloxone kits) is particularly indicated to be available for family and others for those patients who are prescribed more than 50mg MED (Katzman et al., 2018, Katzman et al., 2020, Kilaru et al., 2021, Marco et al., 2018), as well as among those at higher risk for adverse effects, (e.g. COPD,

sleep apnea), psychologic co-morbidities (including SUD/OUD, alcohol use or prior OD), and/or co-prescribed medications (e.g. benzos, anxiolytics, hypnotics). Education of patients and family members is recommended when naloxone is prescribed.

Others who should have access include police, paramedics and health professionals (Dudley et al., 2018, Farkas et al., 2021, Parkin et al., 2021, Samuels et al., 2021, Samuels et al., 2018, McCann et al., 2021, Weiner, 2017) (Weiner et al., 2022). Naloxone prescriptions in advance are indicated for those who have had serious overdoses but have not (yet) been tapered. Adherence to evidence-based opioid guidelines should be considered prior to a naloxone prescription, as they would prevent the vast majority of overdoses and deaths. Earlier treatment options include:

- prescribing active exercises for most chronic pain conditions,
- prescribing non-opioid medications for pain relief first,
- avoiding opioids in those with risk factors,
- only prescribing chronic opioids if a trial is successful to improve objective measures of function and pain,
- not exceeding 50mg MED, and
- performing monitoring and tapering of opioids with aberrant drug screen results.

Yet, for those who are already taking more than 50mg MED, a prescription for naloxone is recommended (Gruver et al., 2020, Katzman et al., 2020), including while instituting other treatment based guidance to reduce risks of overdose and death. There should be low thresholds for provision of prescriptions for all prescribed opioids, especially those who also treated with other CNS-depressing medications.

Benefits

Rescue some individuals who overdose

Harms

There are reports of respiratory complications including pulmonary edema and aspiration pneumonia associated with naloxone (Kummer et al., 2022, Farkas et al., 2020, Fidacaro Jr et al., 2020); however, it is unclear if this is a direct association with naloxone or an indirect association with overdose (Maloney et al., 2020).

Frequency/Dose/Duration

Naloxone is available in intranasal, intramuscular, and intravenous formulations. Intranasal formulations are available over-the-counter. Dosage is 0.4 mg IV/IM or 2 mg IN, with repeated administration up to 10 mg (Purssell et al., 2021, Tylleskar, 2020, Wong, 2019) (Thompson et al., 2022, Weaver et al., 2018, Weiner et al., 2022). There is conflicting evidence regarding whether the nasal spray is superior because it is easier for non-trained community member use (Eggleston et al., 2020); however, recovery was faster with intramuscular in another two studies (Dietze et al., 2019, Skullberg, 2022). The medication should be administered when there is a lack of responsiveness or substantially reduced sensorium. For those known to have overdosed but have not yet experienced the adverse effects, administration of naloxone at the earliest sign of impairment while on the way to the emergency room for definitive treatment is indicated. Naloxone generally requires approximately 1 hour of observation after resuscitation, although the length is dependent on the specific drug, dose, and route (Willman, 2017). Some epidemiological evidence has suggested the dosing approach is not

different in the era of illicit fentanyl (Carpenter et al., 2020, Klebacher et al., 2017). However, there is evidence that when higher doses of naloxone are required, there is an increased risk of pulmonary complications, including aspiration and pulmonary edema (Farkas et al., 2020, Fidacaro Jr et al., 2020). Post-rescue individuals may be combative or agitated and require additional support.

Indications for discontinuation

Sustained normalization of consciousness, mobilization, oxygen saturation, respiratory rate, temperature, heart rate, and Glasgow Coma Scale score (Clemency et al., 2018).

Rationale

There are no randomized controlled trials (RCTs) to determine efficacy. There are comparative RCTs of intranasal vs. intramuscular administrations (Dietze et al., 2019, Skulberg et al., 2019, Skulberg et al., 2022, McDonald et al., 2017, Eggleston et al., 2020, Mundin et al., 2017, Parmar, 2016, Meade et al., 2018), the highest quality of which suggest that intramuscular is more effective and/or efficient (Dietze et al., 2019, Skulberg et al., 2022). There are studies of lay-dispensed naloxone that all suggest efficacy (Strang et al., 2008) (Lankenau, 2013) (McAuley et al., 2010) (Galea et al., 2006) (Strang et al., 2016); however, most event and recovery data are self-reported. An RCT of naloxone administration by untrained community members found that nasal spray was the easiest to administer (Eggleston et al., 2020). A review also found similar outcomes with nasal compared with intramuscular administration (Chou et al., 2017). Also, there are extensive case series experiences with naloxone reversing reduced consciousness or comatose states. Naloxone has negligible adverse effects other than increasing the experience of pain. It is low cost and has extensive empirical evidence of efficacy. Therefore, it is recommended to have naloxone available for the treatment of overdoses and near-fatalities, including co-prescriptions with opioid prescriptions.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: naloxone, narcan; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 654 articles in PubMed, 281 in CINAHL, 21 in Cochrane Library, 14,000 in Google Scholar, and 0 from other sources†. We considered for inclusion 35 from PubMed, 12 from CINAHL, 0 from Cochrane Library, 7 from Google Scholar, and 0 from other sources. Of the 54 articles considered for inclusion, 4 randomized trials and 11 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.10. BREAKTHROUGH PAIN

Breakthrough pain (BTP) is “a transient increase in pain to greater than moderate intensity, which occurred on baseline pain of moderate intensity or less” (410, 411). It is also defined as “the transient exacerbation of pain occurring in a patient with otherwise stable, persistent pain" (412).

BTP is typical among patients with cancer or terminal illnesses (64, 412-427). However, it has also been reported in patients with chronic noncancer pain. BTP occurs in 33-65% of patients with chronic cancer pain and in approximately 70% of patients with chronic noncancer pain (428). Patients admitted to hospice have a prevalence of BTP between 40 and 86% (421).

BTP is a transitory pain (reaching maximum severity in approximately 15 minutes and lasting approximately 60 minutes in patients with cancer) that occurs despite the management of chronic pain with long-term around-the-clock analgesia. BTP can be unpredictable and can be severe. The range of BTP occurs between 1 and 240 minutes. BTP often has a peaking intensity around 3 minutes (412). BTP also has a self-limiting average duration around 30 minutes (423).

Non-cancer related BTP has been treated with opioids (41, 411, 427, 429, 430).

OPIOIDS FOR BREAKTHROUGH NONMALIGNANT PAIN

Not Recommended

Opioids are not recommended for routine treatment of breakthrough pain superimposed on chronic pain in the absence of overt trauma or acute nociceptive pathology (e.g., myocardial infarction, tooth abscess). Instead, specific exercises, non-pharmacological treatments, and other medications (e.g., gabapentinoids, duloxetine, topicals) are recommended. (See other ACOEM guidelines for specific indications.)

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Benefits

Reduced dose escalation, accident risks, risks of dependency, opioid use disorder and death.

Harms

May inadequately treat severe chronic pain.

Rationale

Non-cancer related BTP has been treated with opioids (Simpson et al., 2007) (Fine et al., 2010) (Hojsted et al., 2006) (Pavis et al., 2002) (Portenoy et al., 2006); however, there is no quality evidence supporting this approach. Instead, BTP may indicate hyperalgesia, or potentially insufficient treatment of pain with other more effective approaches. BTP treatment with opioids is also an important accelerator for problems with dose escalation (Naliboff et al., 2011). Regardless, in treating BTP, functional gain must be documented; otherwise, the dose should revert to the prior dose level. Thus, treatment of non-malignant BTP with opioids in the absence of overt trauma is not recommended. Instead, there are many other evidence-based treatment approaches, including specific exercises, non-pharmacological treatments, and other medications (e.g., gabapentinoids, duloxetine, topicals), which may be successfully used (see other Disorders guidelines for specific indications). There are few barriers to implementing this recommendation for new or existing patients.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: Non-malignant Breakthrough Pain; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 0 articles in PubMed, 98 in CINAHL, 4 in Cochrane Library, 696 in Google Scholar, and 0 from other sources.† We considered for inclusion 0 from PubMed, 2 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.11. INTRATHECAL DRUGS

The primary use of intrathecal drug delivery systems ("pain pumps") has been for treatment of severe chronic pain and terminal care among those with severe pain (14-20). Multiple agents have been utilized, including morphine, fentanyl, ziconotide, and other agents.

INTRATHECAL DRUG DELIVERY SYSTEMS FOR CHRONIC NON-MALIGNANT PAIN CONDITIONS

Not Recommended

Intrathecal drug delivery systems are not recommended for treatment of chronic nonmalignant pain conditions.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence High

Benefits

Reduced pain ratings, reduced oral opioid use.

Harms

Complications include device-related complications, urinary retention, wound infection, meningitis, and the potential for dose escalation (Von Korff et al., 2011). The mortality rate based on large registry and databases is reportedly 0.39% at 1 month and 3.89% at 1 year (Coffey et al., 2009, Delhaas et al., 2020).

Rationale

Intrathecal drug delivery systems have not been evaluated in quality studies to determine whether treatment with these systems is superior to standard treatment options (e.g., quality functional restoration program), oral medication(s) or other treatment options for chronic nonmalignant pain patients. The medications used are potent and some are not intended for chronic use (Hartrick et al., 2012) (Kidner et al., 2010). A registry-based analysis of 4,646 patients treated for chronic non-malignant pain (61.0% for back-related pain) found discontinuations (n=2,835) included: 23.1% patient deaths, 23.1% site closure, 19% transferred to another physician, and 10.2% adverse or device events (Schultz et al., 2021).

Complications include device-related complications, urinary retention, wound infection, meningitis, and the potential for dose escalation (Von Korff et al., 2011). The mortality rate based on large registry and databases is reportedly 0.39% at 1 month and 3.89% at 1 year (Coffey et al., 2009, Delhaas et al., 2020)(Von Korff et al., 2011). Granulomas frequently develop; the expected "permanency" of neurologic abnormalities associated with their formation has not been established (Bohnert et al., 2011).

Ziconotide has been used in intrathecal delivery systems (Naliboff et al., 2011). It is not known whether there is a reduced incidence of intrathecal granuloma formation with this drug since its use has not been widely applied over the long term. Ziconotide has a narrow therapeutic margin and has been associated with severe neuropsychiatric adverse effects. Because it does not share pharmacologic actions with narcotics, there is no known method to determine prospectively whether a patient will respond favorably to this drug.

Intrathecal opioid delivery systems are invasive and costly, have significant adverse effects including fatalities, and potential long-term sequelae from both implantation/retention of the devices, granulomas, and those associated with the concurrent use of intrathecal opioids (Lees et al., 2012). Because there is also a lack of documented efficacy, these devices are not recommended. For new patients, there are few barriers for implementing this guideline. For existing patients, this guideline should not be interpreted as requiring device removal.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: "injections, spinal" and "chronic pain"; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 19 articles in PubMed, 251 in CINAHL, 102 in Cochrane Library, 35,300 in Google Scholar, and 0 from other sources†. We considered for inclusion 5 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 0 randomized trials and 2 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this

pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.12. EFFICACY OF OPIOID GUIDELINES

ADHERENCE TO OPIOIDS GUIDELINES

Recommended

Opioid guidelines are recommended to improve the care of patients.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence High

Rationale

A pre/post evaluation of a guideline implemented in a Newark, NJ emergency department found a 60.9% reduction in numbers of opioid doses and a 33.9% increase in non-opioid prescriptions (Ramdin et al., 2021). A pre-post intervention study in Michigan found that opioid prescriptions were reduced at one large institution after a post-surgical opioid guideline adoption, including a 51.4% reduction in total MME prescribed (Ivanics et al., 2021). Another pre/post intervention study found a 48.3% reduction MME prescribed among patients with hip and knee arthroplasty (Wyles et al., 2019). A cluster-randomized trial of clinician practices with guidelines, comparison emails, and opioid justification found a significant reduction in proportions of acute pain patients provided opioid prescriptions, durations, conversion to long-term opioid use, and combinations of opioids and benzodiazepines (Kraemer et al., 2022). Post-operative studies of opioids are also informative, and some studies may have analogies to other acute pain situations and those findings suggest superior outcomes from low- or no- opioid approaches (see the recommendations for postoperative pain). A 3-year pre-post intervention study in Utah found that implementation of the ACOEM Opioids guideline was associated with a 50% reduction in the proportion of claims with an opioid prescription, a 15.8% (3.16 to 2.66) reduction in total prescriptions per claim, and 65,502 mg reductions in MEDs; this was associated with a state-wide reduction in opioid-related fatalities of 19.8%, although the reduction may likely have been contributed to by other factors (Phillips et al., 2019). An epidemiological study found 70% of carpal tunnel release surgeries were prescribed an opioid and 29% were incongruous with the ACOEM Opioids guideline, with non-compliance associated with disability durations that were 1.9 days longer and $422 higher medical costs per claim (Gaspar et al., 2017). An ecological database study of 625 cases in Illinois found that the proportion of patients with spine-related worker's compensation cases who were prescribed opioids declined after publication of the 2016 CDC guideline, from 54% in 2011-2016 to 37% in 2017-2021 (Alvarado et al., 2023), although other data noted above in this guideline found a strong down-trend in opioid prescription rates during that interval.

Feasibility of guideline adoption was felt to be improved with audit, feedback, academic detailing, and external facilitation (Quanbeck et al., 2018). A cluster randomized trial found a team-based intervention strategy successful at improving compliance with opioid treatment guidelines, including measures of mental health screening, urine drug screening, treatment agreements, avoiding co-prescribed benzodiazepines, average MED and maximum opioid dose (Quanbeck et al., 2018); however, it did not measure reduced adverse effects of non-compliance. A cluster-randomized trial of a multicomponent intervention reported improved guideline concordant care but failed to reduce early refills (Liebschutz et al., 2017). A tool has been developed to assess adherence to the CDC's 2016 opioid guideline (Navis et al., 2020). A multidisciplinary expert panel "largely supported" the CDC guideline but found issues with it, including: (1) application of dosage ceilings and prescription

duration guidance, (2) failure to appreciate the importance of patient involvement in decisions to taper or discontinue opioids, (3) barriers to diagnosis and treatment of opioid use disorder, and (4) impeded access to recommended comprehensive, multimodal pain care (Kroenke et al., 2019).

Thus, many large studies in multiple geographic locations have all found efficacy of the implementation of opioid guidelines, producing a strong evidence of efficacy of adherence to opioid guidelines.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from April 2017 to March 2022 using the following terms: guideline adherence; analgesics, opioid, narcotics, opiate, opiate alkaloids, narcotic; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 183 articles in PubMed, 70 in CINAHL, 59 in Cochrane Library, 35,400 in Google Scholar, and 0 from other sources†. We considered for inclusion 15 from PubMed, 2 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 0 from other sources. Of the 21 articles considered for inclusion, 5 randomized trials and 8 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

4.13. NON-OPIOID ALTERNATIVES

Numerous non-opioid alternative treatments exist for specific acute, post-operative, and subacute/chronic disorders. Importantly, the treatments that are effective have modest to major differences between the disorders. Thus, diagnostic precision is essential to effect better and faster outcomes with no or minimal use of opioids.

See disorder-specific guidelines for evidence of treatment efficacy:

- Low Back Disorders
- Cervical and Thoracic Spine Disorders
- Chronic Pain
- Hand, Wrist, and Forearm Disorders
- Elbow Disorders
- Shoulder Disorders
- Knee Disorders
- Hip and Groin Disorders
- Ankle and Foot Disorders

5. TABLES

5.1. TABLE 1. EXAMPLES OF DECISION LOGIC

INJURY CLASSIFICATION	OPIOID RECOMMENDATION	RECOMMENDATION DETAILS
MILD (e.g. strains, tendonitis, non-specific pain, mild to moderate low back pain)	Opioid NOT indicated	• Primary treatments generally not medication(s). Primary treatments usually are related to physical activity and disorder-specific exercises; reduction in exposure especially if high force; passive and active range of motion; heat/cold therapies. Consider physical therapy to teach disorder-specific exercises for spine pain especially if mild-moderate pain problem persists. (see Low Back Disorders Guideline; See Low Back Disorders Algorithm. See Cervical and Thoracic Spine Disorders Guideline. See Cervical and Thoracic Spine Disorders Algorithm. See Shoulder Disorders Guideline. See Shoulder Disorders Guideline Algorithm.) • NSAIDs or acetaminophen should be the first medication(s) utilized, unless contraindicated. Consider gastric protection in those with high risks. • Generally, muscle relaxants also not indicated for mild spine pain; may be indicated for especially with sleep disturbance.
MODERATE (e.g. severe sprains of moderate or large joints, moderate trauma, severe low back pain)	Opioid MAY BE rarely indicated	• Other treatments are indicated as primary treatments (see above; see links). • Scheduled NSAIDs, especially non-COX2-inhibiting NSAIDs (431), should nearly always be the primary medication, to which a muscle relaxant or opioid may be adjunctive (consider gastric protection as indicated).* • Muscle relaxant is preferable to opioid, and indicated especially for nocturnal use for treatment of moderately severe spine pain. • A short-acting weak opioid may be indicated. Few days of treatment may be indicated. • Opioid prescription duration of 3-7 days • Use beyond 7 days should be quite rare, and based on objective tissue damage (e.g., delayed wound healing) and prolonged recovery during which the effective treatments are continuing to be implemented, complied with, and utilized.
SEVERE (e.g. fractures, major trauma, large burns)	Opioid MAY BE indicated	• Other treatments are indicated as primary treatments (see above and other evidence-based treatment guidelines. • Scheduled NSAIDs should nearly always be the primary medication to which an opioid may be adjunctive (consider gastric protection as indicated). Please note separate issues regarding fractures and nonunions. † • Risk of nonunion associated with NSAID use has been reported. However, a systematic review found a higher risk of nonunion among the opioid users than the NSAID users. At least partial if not complete

		confounding is naturally likely whereby those with pain due to non healing are using these medications, thus whether there is an overall increased risk of nonunion is unclear (432). • Definitive treatments (e.g., fracture treatment) are indicated. • Muscle relaxant is preferable to opioid, and indicated especially for nocturnal use for treatment of spine pain. • Prescribe weaker opioid and the lowest effective dose. • Duration of opioid prescription of 3-7 days • Stronger opioid may be considered only if weaker ones are ineffective or not tolerated. If a trial of higher doses fails to improve function, then opioid discontinuation is recommended. • Use beyond 7 days should be quite rare, and based on objective tissue damage (e.g., delayed wound healing) and prolonged recovery, during which the effective treatments are continuing to be implemented, complied with, and utilized.

**There is evidence among those with a fracture of an association between NSAID use and non-union. There also is evidence of an association between opioid use and non-union. Whether these have causal associations, or rather are merely natural confounding whereby those with non-union are more likely to take any pain medication is unknown. At least some confounding appears highly likely, and physicians must make determinations of the risk-benefit assessments for these patients (433,431,434,435,436,437).*

†The evidence supporting a risk of NSAIDs as causing nonunions is low quality (i.e., not RCTs). It is also concerning that the OR for nonunion for opioids use is higher than for NSAIDs (432). Thus, there is a strong reason to believe these relationships are either partially or totally confounded (e.g., see also (438).

5.2. TABLE 2. ADVERSE OPIOID EFFECTS BY ORGAN SYSTEM

System	Effect	Clinical Effect
Cardiovascular	Myocardial infarction	Heart attack or sudden death
	Orthostatic hypotension (dizziness on standing up)	Fainting on standing up
	Abnormal heart rhythm (QT prolongation, tachyarrhythmias, cardiac arrest)	Sudden death, palpitations, syncope
Gastrointestinal	Gastroparesis (slow gut movement)	Nausea, abdominal pain, early satiety
	Reduced colon motility; spasm	Constipation, bowel obstruction
	Biliary spasm	Abdominal pain
Genitourinary	Exacerbation of urinary problems	Urinary retention, Incontinence
Endocrine	Suppression of testosterone, estradiol	Impotence or reduced sex drive and erectile dysfunction, osteoporosis, feminization, reduction of muscle mass, reduced strength

	Suppression of LH, FSH	Reduced or abnormal menstrual periods
	Adrenal suppression	Fatigue, low blood pressure, electrolyte changes
Immune	Allergic reactions to medication	Rash, shortness of breath, itchy skin, edema
		Angiogenesis and metastasis
	Immunosuppression	
	Infections	Pneumonia and invasive pneumococcal disease
Neurological/ Psychiatric	Impairment of thinking or executive function	Outbursts, inappropriate behavior, limit testing, violence, reduced impulse control, impaired mental function
	Frontal lobe atrophy	Alterations in executive function, emotional response
	Brain damage from overdose or apnea induced hypoxia	Slight to severe impairments if an overdose occurs
	Cognitive impairment	Problems thinking clearly
	Vision	Color vision impairment
	Increased CNS pressure	Headache
	Hyperalgesia	Increased pain sensitivity, increasing doses of opioid/dose escalation
	Altered sense of taste	Reduced pleasure in eating, weight loss
	Reduced seizure threshold	Seizures
	Confusion, Impaired concentration	Increased accident risks and unclear thoughts
	Drowsiness, somnolence	Crash risk and reduced functioning
	Increased reaction time	Unsafe operation of machinery, motor vehicles, motor vehicle crashes
	Impaired coordination	Unsafe operation of machinery, falls
	Non-medical use	Overdose, death
	Mood elevation, euphoria	Mistaken judgment, changed interactions with other people
	Reduction in anxiety; tranquility	Mistaken judgment, changed interactions with other people
	Depression	Altered mood, depressed feelings, suicidal
Reproductive	Birth defects	Birth defects, miscarriage

	Neonatal withdrawal	Newborn babies of mothers taking an opioid go through opioid withdrawal
Respiratory	Respiratory depression	Death
	Central sleep apnea	Reduced ability to breath during sleep; daytime sleepiness; death
	Obstructive sleep apnea	New or increased problems with obstructive sleep apnea; daytime sleepiness; death
	Pneumonia	Pneumonia
	Hypoventilation	Worsening asthma and chronic obstructive pulmonary disease (COPD)
Vestibular	Reduced balance	Falls, fractures

5.3. TABLE 3. MEDICATIONS CAUSING FALSE-POSITIVE URINE DRUG TEST RESULTS

Drugs identified on urine drug test	**Possible medications responsible for false-positive result**
Amphetamines	Selegiline, Menthol
Barbiturates	NSAIDs
Benzodiazepine	Oxaprozin
Opiate	Fluoroquinolones
Phencyclidine	Venlafaxine, Dextromethorphan

5.4. TABLE 4. DOSING ADJUSTMENTS FOR COMORBIDITIES

Comorbidity	**Dosing adjustment for Opioids**
Renal disease	*CrCl 30-60 ml/min:* 50-75% of usual dose *CrCl <30 ml/min:* 50% of usual dose
Liver disease	*Oxycodone:* 33-50% of usual dose for Oxycodone *Morphine:* No change
Obesity	Individualize dosing based on clinical assessment
Diabetes	Individualize dosing based on clinical assessment

Abbreviation: CrCl, creatinine clearance.

Based on (21,22,23).

6. APPENDIXES

6.1. APPENDIX 1: TOOLS

Opioid Risk Tool [opens as a PDF]

Opioid Treatment Functional Goal(s) [opens as a PDF]

Opioid Treatment Agreement [opens as a PDF]

6.2. APPENDIX 2: DRUG INTERACTIONS BETWEEN METHADONE OR BUPRENORPHINE AND OTHER MEDICATIONS

Medication	Methadone	Buprenorphine
HIV Medications		
Atazanavir (ATV)	No dose adjustment needed (439)	• Buprenorphine AUC increased 93% • Norbuprenorphine (active metabolite) increased 76% • Possible reduction in ATV, cognitive dysfunction (440) • Advised to "not co-administer" (439)
Atazanavir/ritonavir	N/A	• Buprenorphine AUC increased 66% • Norbuprenorphine AUC increased 105% • Monitoring for adverse effects and dose reductions may be needed
Darunavir	N/A	• Buprenorphine not significantly affected • Norbuprenorphine AUC increased 46% • No dose adjustment needed. • Monitor for adverse effects • When transferring from transmucosal to implantation, monitoring to ensure buprenorphine effect is adequate and not excessive.
Lopinavir/ritonavir	N/A	• Buprenorphine not significantly affected • Norbuprenorphine AUC increased 46% • No dose adjustment needed • Monitor for adverse effects • When transferring from transmucosal to implantation, monitoring to ensure buprenorphine effect is adequate and not excessive.
Protease inhibitors	• Titrate methadone dose using the lowest feasible initial dose. • Dose adjustment of methadone may be needed. • Monitor for methadone-related adverse events.	• Titrate buprenorphine dose using the lowest initial dose. • Dose adjustment of buprenorphine may be needed. • It may be necessary to remove implant and treat with a formulation that permits dose adjustments. • Monitor for buprenorphine-related adverse events.

Medication	Methadone	Buprenorphine
Efavirenz	• Opiate withdrawal may occur (441,442,443,444,445).	• No clinically significant interaction (446,447,448)
Nevirapine	• Opiate withdrawal may occur (441,442,443,444,445).	• No clinically significant interaction (446,447,448)
Tuberculosis Medications		
Rifampin	• Opiate withdrawal may occur (449)	• Opiate withdrawal may occur (449)
Rifabutin	• No clinically significant interaction (450)	• Not studied
Hepatitis C Medications		
Glecaprevir/pibrentasvir	• No interaction expected.	• No interaction expected.
Sofosbuvir/velpatasvir	• No interaction expected.	• No interaction expected.
Medications for Other Infections		
Fluconazole	• Increased methadone plasma concentrations (451)	N/A
Voriconazole	• Increased methadone plasma concentrations (451)	N/A
Ciprofloxacin	• Increased methadone plasma concentrations (452)	N/A
Biaxin, Clarithromycin	• Increased methadone plasma concentrations (451)	N/A
Antidepressants		
Fluoxetine	• Not associated with increased levels of methadone (453)	N/A
Fluvoxamine	• May cause increased methadone plasma levels and discontinuation has been associated with onset of opioid withdrawal (454)	N/A
Sertraline	• No associated adverse drug interaction (455)	• No clinically significant interaction (455)
Citalopram	• No clinically significant interaction (456)	• No clinically significant interaction (456)
Mirtazepine	• No clinically significant interaction	N/A
Duloxetine	• Potentially lead to increased duloxetine exposure (457)	N/A
Amitriptyline	• Could be associated with increases in plasma methadone concentrations (458)	N/A
St. John's Wort	• Increased metabolism and elimination of methadone (459)	Increased metabolism and elimination of buprenorphine (459)

Medication	Methadone	Buprenorphine
Desipramine	• Associated with increased desipramine levels (460)	
Dextromethorphan	• Associated with delirium (461)	
Antipsychotics		
Quetiapine	• Increased plasma methadone concentrations (462)	
Risperidone	• No clinically significant interaction	• No clinically significant interaction
Clozapine	• No clinically significant interaction	• No clinically significant interaction
Aripiprazole	• No clinically significant interaction	• No clinically significant interaction
Olanzapine	• No clinically significant interaction	• No clinically significant interaction
Ziprasidone	• No clinically significant interaction	• No clinically significant interaction
Anticonvulsants		
Carbamazepine	• Associated with opiate withdrawal (463)	• Not studied
Phenytoin	• Associated with opiate withdrawal (463)	• Not studied
Phenobarbital	• Associated with opiate withdrawal (463)	• Not studied
Oxcarbazepine	• No clinically significant interaction	• No clinically significant interaction
Lamotrigine	• No clinically significant interaction	• No clinically significant interaction
Topiramate	• No clinically significant interaction	
Psychostimulant Medications		
Methylphenidate	• No clinically significant interaction	• No clinically significant interaction
Pemoline	• No clinically significant interaction	• No clinically significant interaction
Modafinil	• No clinically significant interaction	• No clinically significant interaction
Antihistamines		
Promethazine	• May have synergistic depressant effect (464)	
Diphenhydramine	• May have synergistic depressant effect (464)	
Cardiac and Pulmonary Disease Medications		
Digoxin	• Not studied	• Not studied
Quinidine	• Not studied	• Not studied

Medication	Methadone	Buprenorphine
Verapamil	• Not studied	• Not studied
Heparin	• Not studied	• Not studied
Theophylline	• Not studied	• Not studied
Aspirin	• Not studied	
Psychostimulants		
Cocaine	• Decrease in trough methadone concentrations (448)	• Increased metabolism and diminished plasma concentrations (448,465,466,467)
Methamphetamine	• No clinically significant interaction	
Alcohol	• Severe adverse events including death (468) • Alcohol appears to be eliminated more frequently (469)	• Not studied

Adapted from: (439,448).

6.3. APPENDIX 3: CYTOCHROME P450 3A4 (2D6) INHIBITORS AND INDUCERS

CYP3A4 Inducers Expected to Reduce Opioid Medication Levels				
Carbamazepine Dexamethasone Ethosuximide Primidone Rifabutin Troglitazone	*Statins* • Atorvastatin • Fluvastatin • Lovastatin • Simvastatin *Antiretroviral Agents* • Efavirenz • Lopinavir • Nevirapine	*Anticonvulsant Agents* • Carbamazepine • Oxcarbazepine • Phenobarbital • Phenytoin • Primidone • Valproic acid	*Food* • Cafestol (caffeine)	*Hypnotic agent* • Pentobarbital
CYP3A4 Inhibitors Expected To Increase Opioid Medication Levels				
Amiodarone Cannabinoids Clarithromycin Erythromycin Grapefruit juice Indinavir Norfloxacin Omeprazole (slight) Quinine Saquinavir	*CCBs* • Amlodipine • Diltiazem • Felodipine • Nicardipine • Nifedipine • Verapamil *Statin* • Simvastatin	*Chemotherapeutic agents* • 4-Ipomeanol • Imatinib • Irinotecan • Tamoxifen *Hormonal therapies* • Ethinyl estradiol • Levonorgestrel	*Antibiotics* • Ciprofloxacin • Clarithromycin • Erythromycin • Josamycin • Norfloxacin • Oleandomycin • Roxithromycin • Telithromycin *Azole Antifungal Agents* • Clotrimazole • Fluconazole	*Antiretroviral Agents* • Amprenavir • Atazanavir • Delavirdine • Efavirenz • Indinavir • Lopinavir • Ritonavir • Nelfinavir • Nevirapine • Saquinavir • Tipranavir

Troleandomycin Zafirlukast Itraconazole Ketoconazole Metronidazole Mibefradil Miconazole Nefazodone	*Antiarrhythmic Agents* • Amiodarone • Quinidine *Phosphodiesterose Inhibitor* • Tadalafil *Psychiatric Drugs* • Bromocriptine • Clonazepam • Desipramine • Fluoxetine • Fluvoxamine • Haloperidol • Nefazodone • Norclomipramine • Nortriptyline • Sertraline	• Raloxifene *Other drugs* • Cimetidine • Disulfiram • Methylprednisolone • Phenelzine *Foods* • Bergamottin • (grapefruit juice) • Star fruit	• Itraconazole • Ketoconazole • Miconazole • Voriconazole	
Cytochrome P450 2D6 Inducers Expected To Reduce Opioid Medication Levels				
Antibiotic • Rifampin	*Glucocorticoid* • Dexamethasone			
Cytochrome P450 2D6 Inhibitors Expected To Reduce Opioid Medication Levels				
Antiarrhythmic agents • Amiodarone • Quinidine *Antipsychotic agents* • Chlorpromazine • Reduced haloperidol • Levomepromazine *SNRI* • Duloxetine	*Tricyclic* • Clomipramine *Other antidepressant/ antianxiolytic agents* • Bupropion • Moclobemide *Antihistamine* • Chlorpheniramine	*Other drugs* • Celecoxib • Doxorubicin • Ritonavir • Terbinafine	*Histamine H2 receptor antagonists* • Cimetidine • Ranitidine	*SSRIs* • Citalopram • Escitalopram • Fluoxetine • Paroxetine • Sertraline

Adapted from (24)

SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; CCB = calcium channel blocker.

6.4. APPENDIX 4: PICO QUESTIONS

1. What evidence supports the need for a comprehensive history and physical examination prior to prescribing an opioid?
2. Are opioids superior to other medications or treatments for acute, subacute, chronic or post-operative pain relief and functional improvement?
3. What evidence supports the use of opioids in workers performing safety-sensitive jobs?
4. Should an opioid be recommended for the treatment of non-severe acute pain, and if so, under what circumstances?
5. Should an opioid be recommended for the treatment of acute severe pain, and if so, under what circumstances?
6. What evidence supports initial screening of patients prior to initiation of opioid treatment?
7. What is the evidence for maximum daily oral opioid dosing for patients with acute pain?
8. Does evidence support the use of an opioid for postoperative (up to 4 weeks) pain?
9. Should patients be screened prior to continuation of an opioid for post-operative (up to 4 weeks) pain?
10. What is the evidence for maximum daily oral opioid dose for post-operative (up to 4 weeks) pain management?
11. Does evidence support the use of an opioid for subacute (1-3 months) and chronic (>3 months) non-malignant pain, and if so, under what circumstances?
12. What is the evidence regarding screening for patients prior to opioid initiation in subacute (1-3 months) and chronic (>3 months) pain patients?
13. Is there evidence regarding the maximum daily opioid dose for patients with subacute (1-3 months) and chronic (>3 months) pain?
14. What evidence supports the use of an opioid treatment agreement (opioid contract, doctor/ patient agreement, informed consent)?
15. What evidence supports urine drug testing for opioid use?
16. Is there evidence to support opioid rotation?
17. What evidence supports discontinuation and/or tapering of an opioid?
18. Does evidence support the use of medications for the treatment of opioid use disorder?
19. Does evidence support the use of buprenorphine for opioid tapering?
20. What is the evidence for the use of methadone as a tapering agent?
21. What is the evidence for the use of lofexidine for the treatment of opioid withdrawal?
22. What is the evidence for the use of clonidine for the treatment of opioid withdrawal?
23. What is the evidence for the use of naltrexone for the treatment of opioid use disorder?
24. What is the evidence for the use of cognitive behavioral therapy for aberrant drug-related behavior?
25. What evidence supports the use of naloxone (narcan) for opioid overdose?
26. Is there evidence for using an opioid for breakthrough non-malignant pain?
27. What evidence supports the use of intrathecal drug delivery systems for chronic non-malignant pain conditions?
28. What evidence addresses the adverse events related to opioid use?
29. What evidence addresses the balance of risks and benefits of opioid use for acute, subacute, chronic and post-operative pain?
30. What evidence exists on the financial costs associated with opioid use?

7. CONTRIBUTORS

7.1. CONTRIBUTORS

Editor-in-Chief:

Kurt T. Hegmann, MD, MPH, FACOEM, FACP

Evidence-based Practice Opioids Panel Chair:

Thomas Winters, MD, FACOEM, FACPM

Evidence-based Practice Opioids Panel Members:

Gerald M. Aronoff, MD

Fernando Branco, MD

Charl Els, MBChB, FCPsych, MMed Psych, ABAM, MROCC

Michael Erdil, MD, FACOEM

Steven D. Feinberg, MD, MPH

Steven Mandel, MD, FACOEM, FAAN, FAADEP

Kathryn L. Mueller, MD, MPH, FACOEM

Robert J. Nadig, MD, MPH, FACOEM

Michael I. Schaffer, PhD, MS, DABFT, NRCC-TC

Larry Studt, MD

Michael S. Weiss, MD, MPH, FACOEM, FAAPMR, FAANEM

These panel members represent expertise in occupational medicine, internal medicine, family medicine, pain medicine, psychiatry, physical medicine and rehabilitation, addiction medicine, neurology, emergency medicine, preventive medicine, medical toxicology, pharmacology, clinical infectious disease, and exercise physiology. As required for quality guidelines (Institute of Medicine's (IOM) Standards for Developing Trustworthy Clinical Practice Guidelines and Appraisal of Guidelines for Research and Evaluation (AGREE)), a detailed application process captured conflicts of interest. The above panel has none to declare relevant to this guideline.

Methodology Committee Consultant:

Jeffrey S. Harris, MD, MPH, FACOEM

Research Conducted By:

Kurt T. Hegmann, MD, MPH, FACOEM, FACP

Matthew S. Thiese, PhD, MSPH

Kristine Hegmann, MSPH

Emilee Eden, MPH

Adriele Fugal, MPH

Abril Lopez

Derrick Wong, BS

Madison Tallman, BS

Mubo Olufemi, BS

McKaylee Smith, BS

Jacob Overfelt, BS

Ian Penner, BS

Specialty Society and Society Representative Listing:

ACOEM acknowledges the following organizations and their representatives who served as reviewers of the Opioids Guideline. Their contributions are greatly appreciated. By listing the following individuals or organizations, it does not infer that these individuals or organizations support or endorse the Opioids Guideline developed by ACOEM. One reviewer wished to remain anonymous.

American Association of Hip and Knee Surgeons

American College of Medical Toxicology

American Occupational Therapy Association

American Podiatric Medical Association

Brandon Brooks, DPM, MPH, FACPM, FASPS

Colin Mizuo, DPM, FACFAS

Robert Smith, DPM

American Psychological Association

California Orthopaedic Association

Federation of State Physician Health Programs

Michael Baron, MD

Other Reviewers:

John Kuhn, MD

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