
AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

# Opioids

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## Overview

This Opioids Treatment Guideline is designed to provide health care providers who are the primary target users of this guideline with evidence-based guidance on the use of opioids for treatment of working age adults who have acute, subacute, chronic, or post-operative 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 (FDA) has recognized that there does not appear to be evidence that cancer-related, non-terminal pain should be treated differently.[1] Pain has been defined as an "unpleasant sensory and emotional experience,"[2] 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 of this guideline include evaluations of: 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 chapters of the ACOEM Practice Guidelines. It is recognized that there are differences in workers' compensation systems.[3] There also are regional differences in treatment approaches.[4-6] [961, 962] 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 Reed Group, neither of which have influenced the guideline. The literature is routinely monitored and formally searched at least annually for evidence that would overturn this guidance. The guideline is planned to be updated at least every three years or more frequently should evidence require it.
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 sensitive 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?
- What is the prevalence of aberrant urine drug testing results among patients using opioids for treatment of chronic pain?
- What evidence supports the use of intrathecal drug delivery systems for treatment of chronic, non-malignant pain?
- What tapering regimens are effective for weaning off opioids?

A detailed methodology document used for guideline development including evidence selection, scoring, incorporation of cost considerations,[7] and formulation of recommendations is available on the web as a full-length document [8] and also summarized.[9, 10] [963] The only noteworthy additions regarding this guideline are inclusion of large epidemiological studies for evidence of harms used for guidance and a change in the databases searched. All evidence in the prior opioids guidelines [11-19] [964] [965] from 7 databases searched was included in this Guideline (Medline, EBM Online, Cochrane, TRIP, CINAHL, EMBASE, PEDro). Additionally, new comprehensive searches for evidence were performed with both Pubmed and Google Scholar up through October 2013 to help assure complete capture. 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 (https://www.acoem.org/guidelines_methodology.aspx).

Guidance is developed with sufficient detail to facilitate assessment of compliance [Institute of Medicine (IOM] and auditing/monitoring [Appraisal of Guidelines for Research and Evaluation (AGREE)]. [7, 20] 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 guidelines. [11-19] [964]

This guideline has undergone extensive external peer review. All AGREE, [22] IOM, [26] 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.[20]

## Summary of Recommendations and Evidence

The Evidence-based Practice Opioids Panel has 100% agreement on these recommendations. Recommendations are based on critically appraised higher quality research evidence and on expert consensus observing First Principles(9) [963] when higher quality evidence was unavailable or inconsistent. **The reader is cautioned to utilize the more detailed indications, specific appropriate diagnoses, temporal sequencing, prior testing or treatment, and contraindications that are elaborated in more detail in the body of this Guideline in 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: [8, 9][963]

- 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

## 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, and hoarding to overt diversion. [21, 22]

**Aberrant Drug Use:** Drug use including any of the behaviors listed above.
**Acute pain:** For purposes of these guidelines, this is defined as pain within the first month.

**Addiction:** Addiction is persistent, compulsive use of a substance known by the user to be harmful. [23] Less formally, addiction may be defined as a process whereby a behavior, that can function both to produce pleasure and to provide relief from internal discomfort, is employed in a pattern characterized by: 1) recurrent failure to control the behavior (powerlessness); and 2) continuation of the behavior despite significant negative consequences (unmanageability). [24] [966] Dose escalation may also occur that is related to opioid tolerance.

Addiction is a neurobiological, psychological, and behavioral syndrome characterized by:
An intense desire for the drug and overwhelming concern about its continued availability (psychological dependence).

1. Evidence of compulsive drug use, characterized, for example:
   a. Unsanctioned dose escalation,
   b. Continued dosing despite significant side effects,
   c. Use of drugs to treat symptoms not targeted by therapy, or
   d. Unapproved use during periods of no symptoms.

2. Evidence of one or more of a group of associated behaviors, including:
   a. Manipulation of the treating physician or medical system for the purpose of obtaining additional drug (e.g., altering prescriptions),
   b. Dose escalation,
   c. Acquisition of drugs from other medical sources or from a non-medical source,

d. Drug hoarding or sales, and/or
e. Unapproved use of other drugs (particular alcohol or other sedatives/hypnotics) during opioid therapy.

**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.[25] 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 in this document 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.[26]

**Iatrogenesis:** Inadvertent and preventable induction of disease or complications by the medical treatment or procedures of a physician, surgeon or other healthcare provider.(27) 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.[27, 28]

**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 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."[29, 30]

**Opioids:** Opioids are derived from the opium poppy and have long been used to treat pain. They are potent analgesics widely viewed as helpful in managing moderate to severe acute pain and cancer pain.[13] 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.[31]

**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. [133] Signs and symptoms may include: 1) Dysphoric mood, 2) nausea and/or vomiting,3) muscle aches, 4) lacrimation or rhinorrhea, 5) pupillary dilation, piloerection and/or sweating, 6) diarrhea, 7) yawning, 8) fever and 9) 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 addiction.

**Post-operative 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 approximately range from 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:** For purposes of these guidelines, this 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.

**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. 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." [133]
    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. [133, 134].

**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.

## History of Opioids

Opium is derived from the opium poppy and its use for the treatment of pain 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 addiction. International laws to restrict the sale of opioids were promulgated in the 1930s.[32]

In contrast with prior efforts to limit opioid use, Portenoy and Foley reported a case series of 38 short-term inpatients in the 1980s and opined that long acting opioids for chronic, non-cancer pain were safe, effective with less than 1% risk of addiction and with no upper dose limit. Pharmaceutical companies then marketed proprietary opioids to physicians and potential patients.[33-35]

Legislative and regulatory activities have also been important in driving the epidemic. The U.S. Department of Health and Human Services Agency for Health Care Policy and Research (now the Agency for Healthcare Research and Quality) was created in 1989 and first published institutional guidelines for acute pain management in 1992. Congress passed the Pain Relief Act in 1999 with the intent of removing the threat of inappropriate legal liability and disciplinary action against health care professionals who follow established guidelines in the management of chronic pain.[36]

Beginning in the 1990s, there were a series of legal actions alleging that providers were undertreating pain. In 1999, the Oregon Board of Medical Examiners disciplined a physician for not prescribing enough pain medication; similarly, other lawsuits for undertreatment of pain have been filed.[37-39] In 2001, a California jury convicted a doctor of elder abuse for undertreating a patient's pain.[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 and adverse effects.[41, 42] 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.[43]
Later, the JCAHO provided standards for the evaluation of pain and provisions for withholding accreditation, which would result in threatened/punitive financial consequences for health care institutions that do not meet them. These regulations require health care organizations to implement and give priority to pain management strategies across all departments. These strategies must include ongoing education of providers and patients, pain assessment throughout the hospitalization, discharge planning that includes pain management, and quality management programs that measure progress.[44]
Over the past 15 years, there are increasing numbers of guidelines and policies that have been developed to address this epidemic.[13, 45-71] The Federation of State Medical Boards has recently detailed its model policy for opioids used for chronic pain.[72] All states have now creaed "prescription monitoring programs" with controlled substances databases, although the impact of these actions remains somewhat unclear.

## Impact

Opioid use has been rising sharply in the U.S. over the past three decades. [967-976] Total paid schedule II[1] through IV prescription opioids increased and in 2012, it was estimated that there were 289 million opioid prescriptions in the US. An estimated 84.9% contained hydrocodone or oxycodone. [977, 978] In a nationally-representative telephone survey assessing prevalence and characteristics of opioid use among US adults aged 18 or older, 926 (4.9%) used opioids during the previous week, and 406 (2.0%) individuals used them regularly.[979, 980] An estimated 20.8% of Utah adults aged ≥18 years had been prescribed opioids during the prior year. Of those 20.8%, 3.2% used their prescription more frequently than directed by their doctor, while 72% had leftover medication and 71% retained the leftover medication.[981] [961]

Emergency department visits for non-medical use of opioids increased 111% from 2004 to 2008, and over 28% from 2007 to 2008 alone.[982] Data from the Nationwide Inpatient Sample (NIS) saw a 400% increase in methadone related poisoning hospitalizations in the U.S. from 1999 to 2006. [983]

Opioids are centrally acting drugs that produce not only analgesia but also adverse effects that have been consistently associated with increased risk of motor vehicle crashes (MVCs)[964, 984-990] [964, 984-991]; [992] and interfere with the performance of other safety-sensitive tasks. Workers using prescribed opioids may be unfit to perform their safety-sensitive tasks such as operating an aircraft, driving a truck, or operating heavy equipment [see Physical Qualifications for Drivers 49CFR 391.41; or/and Medical Review Board Recommendations for substances identified in 21 CFR 1308.11 (391.42(b)(12); and Guide for Aviation Medical Examiners].

Opioid use and deaths associated with opioids have risen closely together.[962, 993-999] [1000, 1001] Deaths related to opioid overdoses more than tripled from 1999 through 2006 in the U.S., increasing from 4,000 to 13,800 and further increasing to 33,091 deaths in 2015. [1002], Population-based studies have reported opioids have surpassed motor vehicle crashes as the cause of death in several states. [981, 1001, 1003-1006] There were a total of 52,404 prescription drug related overdoses in 2015, and 33,091 (63.1%) of these were opioid related.[961] More men die from drug overdoses than women, although the percentage increase in deaths has been greater among women since 1999 and more women have died from drug overdoses than from motor vehicle injuries each year since 2007.[1007] Deaths are not confined to urbanized areas, as drug overdose deaths in rural Virginia increased 300% from 1997 to 2003, most of

[1]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 pre-gabalin.

which (74.0%) were prescription opioids. [1008] Also, most opioid-related deaths in Connecticut occurred in suburban towns and rural areas.[1009]

# Recommendations

## Comprehensive History and Physical Evaluation (All Patients, Regardless of Acuity)

### Conducting Comprehensive History and Physical Evaluation

**A comprehensive history and physical is recommended for all patients being considered for opioid therapy regardless of acuity.**[1, 72]

*Indications* – All patients being considered for opioid therapy.
*Frequency/Duration* – All patients at baseline. May require only 1 evaluation for conditions of relatively short durations. Comprehensive evaluations recommended at least quarterly for patients with chronic pain who are treated with opioids (see below for recommended contents of this evaluation). Include screening tool(s), such as COMM, ORT, Patient Health Questionnaire, Ninth edition PMQ Patient Medication Questionnaire (PHQ-9), AID Cut down, Annoyed, Guilty, Eye-opener—Adapted to Include Drugs (CAGE-AID), although the performance data for one tool, SOAPP-R, include unhelpful likelihood ratios near 1 for that tool (CDC 16). There is no quality evidence or consensus that one tool is superior to the others.

*Harms* – Negligible.
*Benefits* – Identification of effective therapies not yet utilized, or for which compliance is needed to optimize treatment. Improved identification of more appropriate candidates for opioids. Identification of patients at increased risk of adverse effects.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**
*Level of Confidence* – High

*Rationale for Recommendation*
Appropriate pain management is a responsibility of those treating pain. It requires adequate knowledge about, and assessments of, a patient's pain and function. Pain management often requires multiple pharmacological and nonpharmacological methods to safely and appropriately control pain that should be evaluated.[1, 72, 114, 115] A comprehensive evaluation and documentation includes: a history, prior treatment, vocation, avocational activities, current functional level, past medical history, family history, social history including substance(s) use (tobacco, alcohol, and illicit substances), review of systems, laboratory testing, and imaging studies as appropriate.[71, 72, 114-117] This systematic approach should result in a clear diagnosis to treat as evidence allows. [72, 114, 116] 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.
When considering prescribing an opioid, the treating physician should have a clear, quantified treatment plan and functional goals.[49, 72, 115, 118, 119] 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 5As: **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),[120] **A**dverse effects (any side effects, especially constipation, dizziness, confusion and inability to function due to the opioids),[86] **A**berrant behaviors (self-dose escalation, poor compliance, continued 'pain behaviors' despite use of opioids) and **A**ffect (mood changes such as worsening of depression).[72, 115]
Documentation should also include informed consent,[71, 72, 121] including an agreed-on opioid treatment contract (for subacute or chronic pain patients), and monitoring results (see detailed sections below).[71, 72] Provider and organizational barriers to implement this recommendation are few.
*Evidence for Conducting Comprehensive History and Physical Evaluation*
There are no quality studies for this analysis.

## Workers in Safety-Critical Jobs

Many studies of drivers using opioids have been reported, including both epidemiological studies [81-88, 122-128] and experimental studies.[129-139] Driving simulator and experimental studies have suggested opioids are associated with driving-related impairments with acute exposures.[129, 133, 140] After initiation of an ongoing opioid prescription, self-reported adverse effects markedly decline over days to weeks.[141, 142] Most driving simulator and experimental studies of chronic opioid exposures have reported no indirect evidence of increased risk of crash.[130-132, 135-137, 139, 143-148] Yet, other evidence suggests cognitive compromise among those with chronic opioid use, especially decision-making.[149-151] Some theorize that chronic pain itself causes cognitive decline, thus, potentially confounding opioid use. However, the evidence does not appear to support this theory.[152-156] Some have reviewed the literature in the past, and concluded there was no increased risk of motor vehicle crash with chronic opioid use. [81, 130, 157-160]

### Use of Opioids by Workers in Safety-critical Jobs

**Acute or chronic opioid use is not recommended for patients who perform safety-critical jobs. These jobs include operating motor vehicles, other modes of transportation, forklift driving, overhead crane operation, heavy equipment operation, sharps work (e.g., knives), work with injuries risks (e.g., heights), and tasks involving high levels of cognitive function and judgment.**

*Harms* – May preclude someone from working who is theoretically not at increased risk, although there is no validated method to demonstrate an individual's safety while consuming opioids.

*Benefits* – Reduce accident and injury risks to worker, the public, and coworkers.

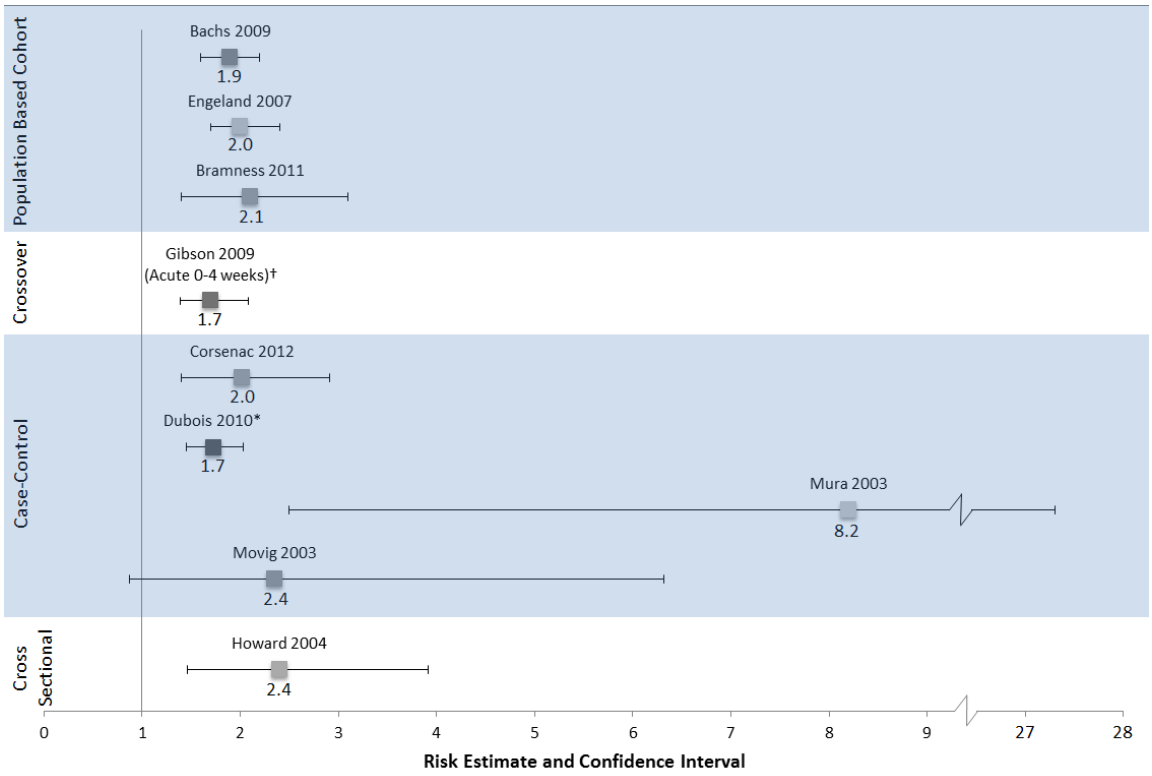
*Strength of Evidence* – **Not Recommended, Evidence (C)**

*Level of Confidence* – Moderate

*Rationale for Recommendation*

Opioids are centrally acting drugs that produce sedation and otherwise hinder or impair higher cognitive function. [85-87, 122, 126, 160-165] Both strong and weak opioids have been consistently associated with increased risk of motor vehicle collisions (MVCs) in all large epidemiological studies of working age adults sufficiently powered to detect MVC risk with the risk estimates ranging from 29 to more than 800% increased risk (see Figure 1. Risk Estimates and Confidence Intervals of Included Studies Assessing Relationships Between Opioid Use and Crashes). [82-84] One study, although likely underpowered with only 28 motorists being prescribed opiates (8 cases vs. 20 controls), still had a risk estimate of 2.3-fold (OR = 2.3, 95% C.I.0.87-6.32).[166] Another study additionally found an association with unsafe driving actions (especially failure to stay in the lane) that preceded fatal crashes.[85] There also is some evidence suggestive of a dose-response relationship. [82, 164] Some evidence suggests higher risk with acute opioid use, but risk remained elevated throughout treatment with an opioid and reversed on cessation.[83] Preclusion of safety-critical job functions while under treatment with opioids is recommended. Among those treated with opioids, sufficient time after the last dose is recommended to eliminate approximately 90% of the drug and active metabolites from their system. Considerable caution is also warranted for those consuming other depressant medications such as benzodiazepines and sedating antihistamines. 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.

*FIGURE 1. RISK ESTIMATES AND CONFIDENCE INTERVALS OF INCLUDED STUDIES ASSESSING RELATIONSHIPS BETWEEN OPIOID USE AND CRASHES*




† 99% Confidence Interval
* Cases are fatal crashes where unsafe driver action was reported as compared to crashes where there was not unsafe driver actions reported
Some articles were excluded (Gomes 2013, Mørland 2011, and Majdzadeh 2009) because the comparison group was low dose opioid use

*Evidence for Use of Opioids in Safety-Critical Jobs*
There are 12 studies incorporated into this analysis.
*Search Strategy: A total of 21,478 article abstracts (176 PubMed, 1552 EBSCO, 19,750 Google Scholar) of epidemiological studies were found. All were evaluated. A total of 12 articles were included in these analyses.*

# Acute Pain (up to 4 Weeks)

## Routine Use of Opioids for Treatment of Non-severe Acute Pain

**Routine opioid use is strongly not recommended for treatment of non-severe acute pain (e.g., low back pain, sprains, or minor injury without signs of tissue damage).**

*Harms* – May inadequately treat acute, severe pain.

*Benefits* – Faster recovery, less debility, reduced accidents risks and risks of dependency or addiction.

*Strength of Evidence* **– Strongly Not Recommended, Evidence (A)**
*Level of Confidence* – High

## Opioids for Treatment of Acute, Severe Pain

**Opioids are recommended for treatment of acute, severe pain (e.g., crush injuries, large burns, severe fractures, injury with significant tissue damage) uncontrolled by other agents and/or with functional deficits caused by pain. 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). Tramadol[2] may be indicated if there is true allergy to nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, other contraindication to an alternative medication, or insufficient pain relief with an alternative. A Schedule II opioid may be indicated for more severe pain. Recommend to taper off opioid use in 1 to 2 weeks.**

Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than 7 days will rarely be needed. (CDC, 2016)

*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).[3]
2) Other more efficacious treatments should have been instituted,[4] and either:
2a) documented to have failed and/or
2b) 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. Any of these are strong contraindications for a prescription, especially in the absence of severe objective injury. [5] When the PDMP indicates other opioids medications have been recently used, yet there is need for a second prescription of opioids, a few days of prescription at a low dose (e.g., 20mg morphine equivalent dose (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. 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:

i) benzodiazepines,
ii) anti-histamines ($H_1$-blockers), and/or
iii) illicit substances. [976, 1009, 1018, 1019] 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 or have:
i) older age (>65 yrs.),
ii) pregnant,
iii) sleep apnea,
iv) psychiatric/mental health disorders (anxiety, depression, personality disorder, suicidal),
v) drug-seeking behavior,
vi) current or past substance abuse,
vii) consuming alcohol in combination with opioids,
viii) renal insufficiency,
ix) hepatic insufficiency, and those who are
x) unemployed (10-fold risk of death).[976, 1003, 1018]

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, current tobacco use, attention

[2]USA classifies controlled substances that includes a classification system, ranging from Class 1 to Class V corresponding to lower risks of abuse and dependence. Class I includes substances with a high potential for abuse and without a recognized medical use (e.g., heroin, marijuana, LSD). Class II includes most opiates, amphetamines and cocaine. Class III includes buprenorphine, dihydrocodeiene, hydrocodone/codeiene when compounded with an NSAID, Marinol. Class IV includes tramadol, carisoprodol, benzodiazepines, and long-acting barbiturates. Class V includes small amounts of codeine (e.g, 30mg, 60mg).
[3]Other indications beyond the scope of this guideline include acute myocardial infarction or agitation interfering with acute trauma management.
[4]Treatments to have tried generally include NSAIDs [1010-1017] and acetaminophen. For LBP patients, additional considerations include muscle relaxants, progressive aerobic exercise, and directional exercise. For LBP patients, this may also include consideration of manipulation (see Low Back Disorders Guideline).
[5]Exceptions such as acute, severe trauma should be documented.

deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), impulse control problems, thought disorders, chronic obstructive pulmonary disease (COPD), or recurrent pneumonia. [976, 981, 1004, 1008, 1020-1038]

Additional risks and/or adverse effects are thought to be present from other comorbidities such as chronic hepatitis and/or cirrhosis, [1039] 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 Appendix 2: Drug Interactions between Methadone or Buprenorphine and other Medications and Appendix 3: Cytochrome P450 3A4 (2D6) Inhibitors and Inducers).

5) 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.

*Frequency/Duration* – Generally, opioids should be prescribed at night or while not working.[985] Lowest effective, short-acting opioid doses are preferable as they tend to have the better safety profiles, less risk of escalation, [1040] less risk of lost time from work, [1041] and faster return to work. [1042] 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. Short-acting opioids are recommended for treatment of acute pain and long-acting opioids are not recommended. Recommend opioid use as required by pain, rather than in regularly scheduled dosing (except severe pain such as extensive burns).

Dispensing quantities should be only what is needed to treat the pain. Generally, the first prescription should not exceed 3 days treatment, and rarely more that 7 days (Surgeon General August 2016; CDC 16; MMWR 2017). 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, other adjunctive treatments to consider.

If parenteral administration is required, ketorolac has demonstrated superior efficacy compared with opioids for acute severe pain, [1013, 1014] although ketorolac's risk profile may limit use for some patients. Parenteral opioid administration outside of obvious acute trauma or surgical emergency conditions is rarely required.

*Indications for Discontinuation* – Resolution of pain, 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.
*Harms* – Adverse effects are many (see section below on "Opioids Benefits and Harms").
*Benefits* – Improved short-term pain control.
*Strength of Evidence* **– Recommended, Evidence (C)**
*Level of Confidence* – High

## Initial Screening of Patients Prior to Initiation of Opioids

**Initial screening of patients is recommended with more detailed screening for: i) requiring continuation of opioids beyond 2 weeks for those with an acute severe injury; and ii) at consideration of initiation for severe pain but no objective evidence.** Screening should include history(ies) of depression, anxiety, personality disorder, other psychiatric disorder, substance abuse, sedating medication use (e.g., anti-histamine/anti-$H_1$ blocker [109], benzodiazepine use, opioid dependence, alcohol abuse, current tobacco use, other substance use history, COPD, sleep apnea, PTSD, other psychotropic medications, (severe) obesity, cognitive impairment, balance problems/fall risk, osteoporosis, and renal failure (see Appendix 1: Tools). Those who screen positive, especially to multiple criteria, are recommended to: i) undergo greater scrutiny for appropriateness of opioids (may include psychological evaluation); ii) consideration of consultation and examination(s) for complicating conditions and/or appropriateness of opioids; and iii) if opioids are prescribed, more frequent assessments for compliance, achievement of functional gains,[120, 167, 192]

adverse effects, and symptoms and signs of aberrancy.

*Harms* – Negligible. If a consultation is needed, there are additional costs that are incurred.

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

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**
*Level of Confidence* – High

## Maximum Daily Oral Opioid Doses for Patients in Acute Pain

**The maximum daily oral dose recommended for opioid-naïve, acute pain patients based on risk of overdose/death is 50mg MED** [193].† **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, 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, addiction, or other adverse effects. Monitoring is also recommended and consultation may be considered for those patients on higher doses.

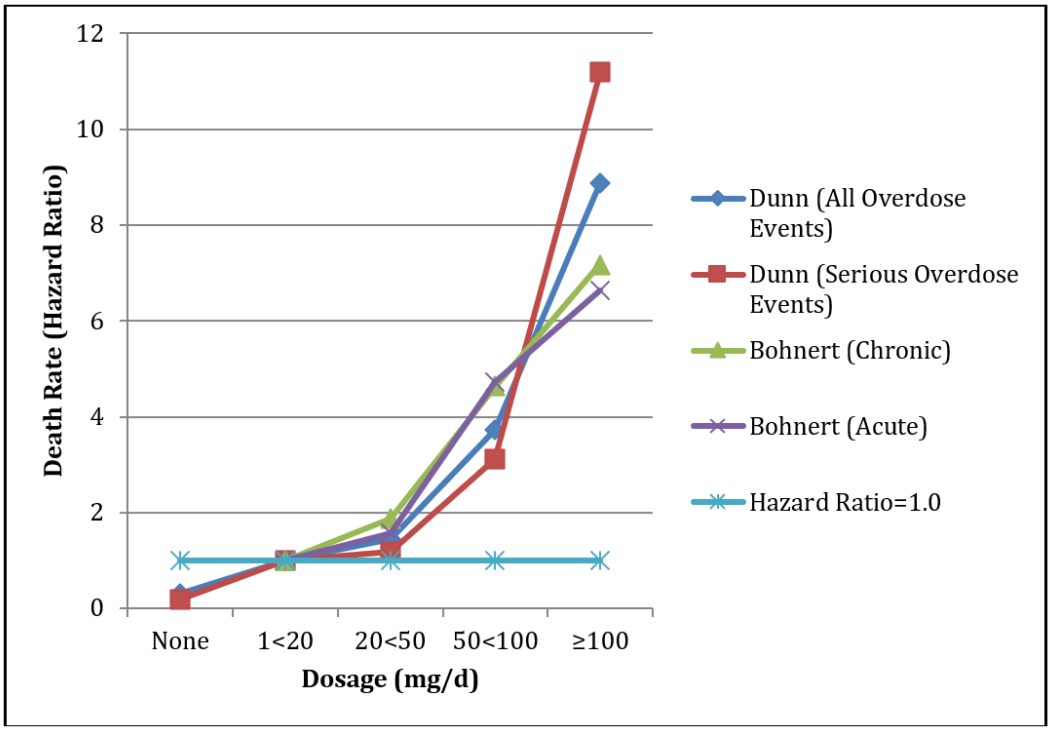
*Harms* – Theoretical potential to undertreat pain in some patients with increased pain sensitivity.

*Benefits* – Reduced risk for adverse physical and cognitive effects, dependency, addiction and opioid-related overdoses and deaths.

*Strength of Evidence* – **Recommended, Evidence (C)**
*Level of Confidence* – Moderate

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

*FIGURE 2. DEATH RATE (HAZARD RATIO) VS. MORPHINE EQUIVALENT DOSAGE (MG/D)**



Adapted from Dunn 2010 and Bohnert 2011.
*Statistical significance present for acute and chronic pain at and above 50 mg per day of oral morphine equivalent dose.

*TABLE 1. EXAMPLES OF DECISION LOGIC**

| INJURY CLASSIFICATION | OPIOIDS RECOMMENDATION | RECOMMENDATION DETAILS |
|---|---|---|
| **MILD INJURY** (e.g. strains, tendonitis, non-specific pain, mild to moderate low back pain) | Opioids NOT indicated | • Primary treatments generally not medication(s). Primary treatments usually are related to physical activity; reduction in exposure especially if high force; passive and active range of motion; heat/cold therapies. Consider physical therapy and/or manipulation for spine pain especially if mild 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.)<br>• NSAIDs or acetaminophen should be first medication(s) utilized first unless contraindicated. Consider gastric protection in those with high risks.<br>• Generally, muscle relaxants also not indicated for mild spine pain; may be indicated for persistent or pain unresponsive to above treatments. |
| **MODERATE (**e.g. severe sprains of moderate or large joints, moderate trauma, moderate to severe low back pain) | Opioids MAY BE indicated | • Other treatments are indicated as primary treatments (see above; see links).<br>• Muscle relaxant is preferable to opioid, and indicated especially for nocturnal use for treatment of moderately severe spine pain.<br>• A short-acting opioid may be indicated. Few days of treatment may be indicated. |
| **SEVERE (**e.g. fractures, major trauma, large burns) | Opioids ARE indicated | • Other treatments are indicated as primary treatments (see above). Definitive treatment (e.g., fracture treatment) are indicated.<br>• Muscle relaxant is preferable to opioid, and indicated especially for nocturnal use for treatment of spine pain.<br>• Prescribe weaker opioids and the lowest effective dose.<br>• Stronger opioids may be considered only if weaker ones are ineffective or not tolerated. |

*Adapted from California, Opioids Guideline.

## Post-Operative Pain (Up To 4 Weeks) (After 4 weeks, see Subacute Pain)

Oral opioids are commonly prescribed after sinus surgery,[194] major non-cardiac surgical procedures,[195] mastectomy and immediate breast reconstruction (IBR),[196, 197] coronary artery bypass graft surgery,[198] major

abdominal surgery (abdominal laparoscopic, abdominal hysterectomy, bowel resection or radical hysterectomy),[199-202] orthopedic surgery,[203] and molar extraction.[204]

## Limited Use of Opioids for Post-operative Pain

**Limited use of opioids is recommended for post-operative pain management as an adjunctive therapy to more effective treatments.**

*Indications* – For post-operative pain management, a brief prescription of short-acting opioids as an adjunct to more efficacious treatments (especially Cox-2 NSAIDs such as celecoxib, non-selective NSAIDs after risk of bleeding is no longer a concern). [More efficacious treatments also include therapeutic exercises, e.g., progressive ambulation especially for moderate to extensive procedures (e.g., arthroplasty, fusion).]
A brief course of opioids is often needed for minor surgical procedures. However, minor wound laceration repairs often require no opioids. Evidence suggests peri-operative pregabalin for 14 days and/or continuous femoral nerve catheter analgesia instead of solely using oral opioids results in superior knee arthroplasty functional outcomes with less venous thromboses.[205] Additional considerations include:

1) Non-opioid prescriptions (e.g., NSAIDs, acetaminophen) should nearly always be the primary treatment and accompany an opioid prescription. Computerized programs may also assist in optimal management.[206]
2) Planning for opioids use to treat post-operative pain should begin during the pre-operative assessment.
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:
    i) benzodiazepines,
    ii) anti-histamines ($H_1$-blockers), and/or
    iii) illicit substances.[105, 109, 167, 168] 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 (have):
    i) older (>65 yrs.),
    ii) pregnant,
    iii) sleep apnea,
    iv) psychiatric/mental health disorders (anxiety, depression, personality disorder, suicidal),
    v) drug-seeking behavior,
    vi) current or past substance abuse,
    vii) consuming alcohol in combination with opioids,
    viii) renal insufficiency,
    ix) hepatic insufficiency, and who are
    x) unemployed (10-fold risk of death).[109, 167]

    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.[78, 102, 104, 108, 109, 169-186]

    Additional risks and/or adverse effects are thought to be present from other comorbidities such as chronic hepatitis and/or cirrhosis,[187] 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 Appendix 2: Drug Interactions between Methadone or Buprenorphine and other Medications and Appendix 3: Cytochrome P450 3A4 (2D6) Inhibitors and Inducers).

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, consultations with anesthesiology and/or pain management are generally needed as post-operative dosing may be very high and management is often quite challenging.
6) Ongoing prescriptions of opioids after the immediate post-operative 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 the opioids. Patients who have not progressed should be carefully evaluated for physical complications or psychiatric comorbidity, adherence to active treatments, and pending development of addiction 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.

**Frequency/Duration** – For moderate and major surgeries, opioids are generally needed on a scheduled basis in the immediate post-operative period. Other post-operative 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.

The lowest effective dose of a short-acting opioid should be used,[188] as well as weaker opioids if possible.[112, 189] Short-acting opioids are recommended for treatment of acute pain. Long-acting opioids are not recommended. High dose use at night is not recommended due to respiratory depression and disruption of sleep architecture. 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. Dispensing should be only what is needed to treat the pain. (Generally, this should be sufficient to cover two weeks of treatment. Prescriptions of 90-day supplies in the post-operative setting are not recommended.) 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, non-compliance, 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.

*Harms* – Adverse effects are many (see section on "Opioids Benefits and Harms").
*Benefits* – Improved short-term, post-operative pain control. Some studies suggest this may modestly improve functional outcomes in the post-operative population.

*Strength of Evidence* **– Recommended, Evidence (C)**
*Level of Confidence* – High

## Screening Patients Prior to Continuation of Opioids

**Screening is recommended for patients requiring continuation of opioids beyond the second post-operative week.** Screening should include history(ies) of: depression, anxiety, personality disorder, pain disorder, other psychiatric disorder, substance abuse history, sedating medication use (e.g., anti-histamine/anti-$H_1$ blocker), benzodiazepine use, opioid dependence, alcohol abuse, current tobacco use, and other substance use history, COPD, sleep apnea, PTSD, other psychotropic medications, (severe) obesity, cognitive impairment, balance problems/fall risk, osteoporosis, and renal failure (see Appendix 1: Tools). Those who screen positive, especially to multiple criteria, are recommended to: i) undergo greater scrutiny for appropriateness of opioids (e.g., may include psychological and/or pain evaluation), ii) compliance with active therapies (e.g., ambulation and other exercise after arthroplasty), iii) consider consultation examination(s) for complicating conditions and/or appropriateness of opioids, and iv) if ongoing

opioids are prescribed, ensure more frequent (e.g., quarterly) assessments for treatment compliance, achievement of functional gains,[120, 167, 192] and symptoms and signs of aberrancy.

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

*Benefits* – Identification of patients at increased risk of adverse effects. Improved identification of more appropriate and safe candidates for opioids compared with attempting post-operative pain control with non-opioids. This should reduce adverse effects. In cases where someone has elevated, but potentially acceptable risk, this may alert the provider to improve surveillance for complications and aberrant behaviors.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**
*Level of Confidence* – High

### Maximum Daily Oral Opioid Dose for Post-operative Pain Patients

**The maximum daily oral dose recommended for opioid-naïve, acute pain patients based on risk of overdose/death is 50mg MED** [193]. Post-operative patients particularly require individualization due to factors such as the severity of the operative procedure, response to treatment(s) and variability in response. Higher doses beyond 50mg MED may be particularly needed for major surgeries in the first two post-operative weeks to achieve sufficient pain relief, however, greater caution and monitoring are warranted and reductions below 50mg MED at the earliest opportunity should be sought. Lower doses should be used for patients at higher risk of dependency, addiction and other adverse effects. In rare cases with documented functional improvement, ongoing use of higher doses may be considered, however, risks are substantially higher and greater monitoring is also recommended every 2 to 4 weeks (see Subacute/Chronic Opioid recommendations below).

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

*Harms* – Theoretical potential to undertreat pain, which could modestly delay functional recovery.

*Benefits* – Reduced risk for adverse effects, dependency, addiction, and opioid-related deaths.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**
*Level of Confidence* – Low

## Subacute (1-3 Months) and Chronic Pain (>3 Months)

### Routine Use of Opioids for Subacute and Chronic Non-malignant Pain

**Opioid use is moderately not recommended for treatment of subacute and chronic non-malignant 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).**

*Harms* – May inadequately treat severe subacute or chronic pain.

*Benefits* – Less debility, fewer adverse effects, reduced accident risks, lower risks of dependency, addiction, overdoses, and deaths.

*Strength of Evidence* – **Moderately Not Recommended, Evidence (B)**
*Level of Confidence* – High

### Opioids for Treatment of Subacute or Chronic Severe Pain

**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.**[72, 115] An opioids trial is then recommended for treatment of both function and pain impaired by subacute or chronic severe pain (e.g., 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 opioids treatment beyond the trial period would be dependent on the results of the opioids trial [120].

*Indications* – Patients should meet all of the following:

1) A complete history and physical should be done, if not previously accomplished.
2) Reduced function is attributable to the pain. Pain or pain scales alone are insufficient reasons. [1, 118, 120, 167, 208-217]
3) Both function and pain treatment goals should be established (CDC 16) 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 (CDC 16). Opioids should only be continued beyond the opioids trial period if both goals are met and these outweigh risks to patient safety (CDC 16). Assessment of function and pain at least monthly in the first 3 months of treatment and then quarterly should be documented. There should be at least 30% improvement in both pain and function to continue opioids treatment.
4) A severe disorder warranting potential opioid treatment is present [e.g., CRPS, severe radiculopathy, advanced degenerative joint disease (DJD)].[1]
5) Other more efficacious treatments have been documented to have failed.(1) 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[6] 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 16). 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.[188] Weaker opioids should be used whenever possible.[112, 189] 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.[7]
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 opioids 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.[1] As needed opioids should generally be avoided for treatment of chronic pain, although limited use for an acute painful event (e.g., fracture, sprain) 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:
    i) benzodiazepines,
    ii) anti-histamines ($H_1$-blockers), and/or

[6]A previous trial of a muscle relaxant is generally recommended. However, if an opioid trial is contemplated, cessation of all depressant medications including muscle relaxants is advisable.

[7]Generally, this should be sufficient to cover one week of treatment at a time during the trial phase. If a trial is successful at improving function, prescriptions for up to 90-day supplies are recommended.

iii) illicit substances.[105, 109, 167, 168]

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 substance abuse,
- consuming alcohol in combination with opioids,
- renal insufficiency,
- hepatic insufficiency, and who are
- unemployed (10-fold risk of death).[109, 167]

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.[78, 102, 104, 108, 109, 169-186]

Additional risks and/or adverse effects are thought to be present from other comorbidities such as chronic hepatitis and/or cirrhosis,[187] 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 Appendix 2: Drug Interactions between Methadone or Buprenorphine and other Medications and Appendix 3: Cytochrome P450 3A4 (2D6) Inhibitors and Inducers).

16) Attempt to wean twice a year to lower than 90mg MED if patients were previously prescribed those doses.

*Frequency/Duration* – Opioids 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,[218] [1043] at night or when not at work.[82] 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,[188] less work loss,(112) and faster return to work.[189] [1042] 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.[219]
*Indications for Discontinuation* – Opioids should be discontinued based on lack of functional benefit [115], 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 16; Dasgupta 15)
*Harms* – Adverse effects are many (see section on "Opioids Benefits and Harms"). May lead to opioid dependency.

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

*Strength of Evidence* **– Recommended, Insufficient Evidence (I)**
*Level of Confidence* – Low

## Screening Patients Prior to Initiation of Opioids

**Screening of patients is recommended prior to initiating a trial of opioids for treatment of subacute or chronic pain.** Screening should include history(ies) of depression, anxiety, personality disorder and personality profile,[189, 220, 221][1042, 1044, 1045] other psychiatric disorder, substance abuse history, sedating medication use (e.g., anti-histamine/anti-$H_1$ blocker), [170][1021] benzodiazepine use, opioid dependence, alcohol abuse, current tobacco use, and other substance use history, COPD, sleep apnea, PTSD, other psychotropic medications, (severe) obesity, cognitive impairment, balance problems/fall risk, osteoporosis, and renal failure (see Appendix 1: Tools). Those who screen positive, especially to multiple criteria, are recommended to: i) undergo greater scrutiny for appropriateness of opioids (may include psychological and/or psychiatric evaluation(s) to help assure opioids are not being used instead of appropriate mental health care); ii) consideration of consultation and examination(s) for complicating conditions and/or appropriateness of opioids including by a pain specialist; iii) consultation with an addiction specialist if there is a history of substance use disorder; and iv) if opioids are prescribed, 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.

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

*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.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**
*Level of Confidence* – High

## Maximum Daily Oral Opioid Dose for Patients with Subacute and Chronic Pain

**The maximum daily oral dose recommended for subacute or chronic pain patients based on risk of overdose/death is 50mg MED**.[171, 193, 1022, 1046] (See Opioid Dose Calculator at http://www.agencymeddirectors.wa.gov/Calculator/DoseCalculator.htm.) In rare cases with documented functional improvements occurring with use above 50 mg MED, subsequent doses up to 90 mg may be considered (CDC 16), however, risks of death are much greater and more intensive monitoring is then also recommended. Lower doses should be considered in high risk patients. Caution appears warranted in all patients as there is evidence the risk of dose escalation is present even among patients enrolled in a "hold the line (stable dose) prescribing strategy" treatment arm who experienced an approximately 17% increase in dose over 12 months compared with 79% in the liberal escalating dose arm.[222] [1047] Extrapolated linearly, the hold-the-line prescribing strategy would result in average doses over 50mg within approximately 3.5 years while the liberal policy exceeded 50mg in approximately 11 months.

For patients whose daily consumption is more than 50mg MED, greater monitoring is recommended to include: i) 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; ii) at least semiannual attempts to wean below 50mg MED if not off the opioid; iii) at least semiannual documentation of persistence of functional benefit; iv) at least quarterly urine drug testing (see drug testing section); and v) at least semiannual review of medications, particularly to assure no sedating medication use (e.g., benzodiazepine, sedating anti-histamines).

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

*Benefits* – Reduced risk for adverse effects, dependency, addiction, and opioid-related deaths.

*Strength of Evidence* – **Recommended, Evidence (C)**
*Level of Confidence* – High

## Use of an Opioid Treatment Agreement (Opioid Contract, Doctor/Patient Agreement, Informed Consent)

**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: Tools**).** [71, 72, 223-233] **If consent is obtained, it is recommended that appropriate family members be involved in this agreement.**

*Harms* – Negligible.

*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.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**
*Level of Confidence* – Moderate

## Urine Drug Testing

**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. In certain situations, other screenings (e.g., hair particularly for information regarding remote use** [234-239] [1048-1052] [1053] [1054] **or blood (for acute toxicity) may be appropriate.**

*Indications* – All patients on opioids for subacute or chronic pain.

*Frequency* – Screening is recommended at baseline, randomly at least twice and up to 4 times a year and at termination. Should be 4 times/yr if MED > 50mg. More intensive screening is recommended for those consuming more than 50mg MED (see above). Federal guidelines recommend at least 8 tests a year among those utilizing opioid treatment programs.[77] [1055] 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, hoarding of medications, and selling medications). Standard urine drug/toxicology screening processes should be followed (consult a qualified medical review officer).[240-242] 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 the opioid discontinued or weaned due to opioid contract violation and high risk of overdose. Those with a drug test that shows absence of the prescribed opioid (or metabolites) should have the opioid discontinued due to either not taking the opioid, having already detoxified from the opioid, and/or diverting the opioid. [115][1056]

*Harms* – No adverse clinical effects if properly interpreted.

*Benefits* – Identifies aberrant medication(s) and substance(s) use. Such uses are high-risk for opioid events including fatalities (see tables below). It provides objective evidence to cease an opioid trial or ongoing treatment. Identifies patients who may be diverting medication (those screening negative for prescribed medication).

*Strength of Evidence* – **Recommended, Evidence (C)**
*Level of Confidence* – High

## Opioids Rotation

**Rotation of Opioids is selectively recommended.**

*Indications* – Patients on opioids for subacute or chronic pain who appear to lose evidence of efficacy or experience intolerable adverse effect(s) [1057, 1058] [1059, 1060]. May be reasonable to also rotate from one opioid to a second opioid on a one-time basis when there was no opioids 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.

*Frequency/Dose* – 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 [1057]; [1060]. Rotation schedules are typically accomplished over 3 to 10 days Choquette 08; [1060]. Functional gains should be carefully tracked. If there are no functional gains, further taper and complete cessation of the opioid is generally indicated.

*Harms* – Negligible. Requirement to reduce dose during rotation, and thus likely report increased pain. If not cautious, may become another means for dose escalation.

*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.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**
*Level of Confidence* – Low

*Rationale for Recommendations: General Considerations and Study Design Issues*
Opioids are considered to be the most potent, short-term, pain-relieving medications. There are dozens of high- and moderate-quality trials documenting short-term efficacy compared with placebo for acute, post-operative, and chronic pain. Trials consistently report high rates of adverse effects (see evidence tables below).

Many of the studies have small sample sizes. The RCT methods used in the trials for treatment of chronic pain include features that may limit generalizability. For example, in RCTs that include all patients in the RCT, the overall dropout rates[8] and adverse effect profiles each frequently exceed 50% and several are over 75%. [86, 243-251] [989, 1061-1068] Studies that require prior chronic opioid use and/or have early washout and/or run-in phase(s) likely remove patients who: i) cannot tolerate the adverse effects, ii) are unwilling to endure the adverse effects for a duration of time, iii) recognize prior adverse impacts on function, and/or iv) have lower psychological and substances use profiles. Consequently, most opioids RCTs for chronic pain likely report artificially low adverse-effect profiles compared with treatment of the general population.[252] [1069] Consequently, fewer than 50% of chronic pain patients appear likely to tolerate opioids, even if they are potentially indicated. [243-246, 248-251] [1061-1063, 1065-1068]

*Rationale for Recommendations: Trial Sponsorship*
The vast majority of the trials of opioids are industry-sponsored. Sponsored studies have been frequently reported to have better results and lower complication rates than studies conducted by independent investigators.[253-256] [1020] A prior review of 546 pharmaceutical trials found 63% were primarily funded by industry, 14% by government and 23% by nonprofit or nonfederal organizations.[253] Industry sponsorship for this systematic review and guideline on opioids was greater still especially for chronic pain. For acute pain, 42.1% of 19 trials for acute pain patients,[9] 60.0% of

[8]Overall dropout rates in randomized trials are clinically meaningful and include wash-out phases, run-in phases, conversion phases, titration phases, trial "enrichment" phases, as well as those who dropout during the trial.

[9]For treatment of acute pain patients, there were 24 high- or moderate-quality trials; of those mentioning conflicts of interest and funding (n = 19), 8 (42.1%) were at least partially industry sponsored, 5 (26.3%) non-governmental organization, 3 (15.8%) hospital funded, 2 (10.5%) National Institutes of Health, and 1 (5.3%) identified no COI. However, when limiting the data to those with at least 24 hours of followup, there were only 10 studies remaining that identified COI: 8 (80.0%) were at least partially industry sponsored, 1 (10.0%) non-governmental organization, and 1 (10.0%) hospital funded.

20 perioperative and postoperative trials,[10] and 87.1% of 93 chronic pain patient trials[11] with sponsorship identified had partial or full industry sponsorship. When analyzing only the studies that had a minimum level of follow-up time (1, 7, and 30 days for acute, postoperative and chronic pain respectively), 80.0%, 80.0% and 93.9% had partial or full industry sponsorship, respectively.

The number of comparative trials with non-opioid treatment arms compared to an opioid is fairly limited. Altogether, there are 9 acute pain, 7 peri/post-operative and 12 chronic pain comparative trials that scored high- or moderate-quality. Industry sponsorship of these is similarly 73.9%.[12] Thus, the large majority of evidence regarding efficacy of opioids is at least partially industry-sponsored.

*Rationale for Recommendations: Health Outcomes*
Nearly all studies reported subjective pain ratings for outcomes. None primarily targeted and reported objective functional measures. Two studies of post-operative patients identified demonstrated objective functional measures, however, both found superiority when an adjunct treatment was prescribed that *reduced* opioid consumption and are addressed with postoperative pain (see below).[205, 257] [1070, 1071] A few suggested subjective functional outcomes were better with an opioid than placebo.[258-262] [1072-1075]

*Rationale for Recommendations: Adverse Effects Recommendations (see also separate section)*
Opioids have a wide therapeutic range. Adverse effects appear prominent, and include effects on the CNS (drowsiness, somnolence, fatigue, tolerance) and the gastrointestinal (GI) tract (constipation, nausea, dyspepsia), although there are other CNS and GI effects, as well as effects on the cardiovascular, respiratory, dermatologic, endocrine, and musculoskeletal systems. Adverse effects are worrisome, particularly for workers, with high rates of adverse CNS effects including somnolence, dizziness, executive function decrements and reduced reaction times.[263] [1076]

*Rationale for Recommendations: Adverse Effects (see also separate section)*
Very high risks of dose-related death have been associated with both acute and chronic use of opioids (see Figure 2. Death Rate (Hazard Ratio) vs. Morphine Equivalent Dosage (mg/d)*). Risk factors for opioid-associated deaths reportedly include: illicit drug use (e.g., cocaine, marijuana), unemployment, depression, anxiety, personality disorder, benzodiazepine use, histamine-1 antagonists, alcohol use, current smoking, lack of regular church attendance, unmarried status, younger age, white race, less than high school education, and legal problems.[79, 102, 105, 108, 109, 167-169, 171-173, 176-178, 180][976, 982, 1004, 1009, 1018-1020, 1022-1025, 1028-1030, 1032] The lifetime prevalence of substance use disorders among opioid users reportedly ranges from 36 to 56%. Current substance use disorders reportedly ranges from 3 to 43%, and aberrant medication-taking behaviors also ranges from 5 to 42% among opioid users.[264-268][1077-1081]

*Rationale for Recommendations: Acute Pain Treatment Recommendations*
For acute pain, there is quality evidence that other medications and treatments are at least equivalent if not superior and no quality published evidence an opioid is superior for treatment of acute pain (e.g., NSAIDs; [190, 191, 269-274] [1010-1017])carisoprodol;[275][1082] transcutaneous electrical nerve stimulation [TENS]).[13] [276] There are many emergency department trials of very short duration treatments, with follow-ups of up to a few hours, with minimal if any differences, and thus of unclear utility for guidance.[277-288][1083] Additionally see post-operative studies below, as some studies may have analogies to other acute pain situations and findings are somewhat similar. Quality evidence indicates safety profiles are considerably worse for opioids. Studies also demonstrate worse functional outcomes for

[10]For treatment of peri- and post-operative patients, there were 27 high- or moderate-quality trials; of those mentioning COI and funding (n = 20), 12 (60.0%) were at least partially industry sponsored, 1 (5.0%) non-governmental organization, and 7 (35.0%) had no industry sponsorship or remote industry-related COI. However, when limiting the data to those with at least 7 days of followup, there were only 5 studies, 4 (80.0%) of which had at least partial industry sponsorship and one did not mention COIs.
[11]For treatment of chronic pain, there were 101 high- or moderate-quality trials; of those mentioning conflicts of interest and funding (n = 93), 81 (87.1%) were at least partially industry sponsored, 5 (5.4%) government funded, 1 (1.1%) non-governmental organization funded, 5 (5.4%) hospital funded and 2 (2.2%) identified no conflict of interest. However, when limiting the data to those with at least 30 days of followup, there were only 66 studies remaining that identified COI: 62 (93.9%) were at least partially industry sponsored, 1 (1.5%) non-governmental organization, and 1 (1.5%) with no COI.
[12]Of those comparative trials mentioning sponsorship and COI, 4 of 6 (66.7%) of acute pain, 4 of 5 (80.0%) of peri/postoperative and 9 of 12 (75.0%) chronic pain had partial or full industry sponsorship.
[13]Flutirpine also has evidence of efficacy, although not currently approved in the U.S.

patients treated early with opioids.[289-291][1084] Among trials for treatment of acute pain, ibuprofen was reportedly superior to codeine or acetaminophen for acute injuries including fractures.[270][1011] Diflunisal was equivalent to codeine for sprains, strains and mild to moderate LBP.[273] Valdecoxib[14] was better tolerated and trended towards greater pain relief than tramadol for ankle sprains.[269] Valdecoxib was equivalent to oxycodone as assessed by pain ratings, but trended toward less rescue medication use and had fewer adverse effects among spine and extremity pain patients.[271] Global ratings for LBP showed carisoprodol is superior to propoxyphene and has fewer adverse effects,[1082]) although there are concerns about abuse of carisoprodol. Ketorolac was equivalent for pain relief, but superior to meperidine in terms of adverse effects for treating severe LBP. [1013] Ketorolac was also superior to codeine/acetaminophen for acute LBP treated in emergency departments.[1014] Ketorolac appeared superior as a primary pain treatment supplemented with opioids compared with opioids alone for spine and joint procedures.[1085] Diflunisal was superior to codeine/APAP for LBP. [1015] There are no quality trials to suggest superiority of opioids to other active treatments. Prolonged use of opioids after an acute event has been associated with worse functional outcomes.[289-291]

Thus, routine use of opioids 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.[1040] Lower potency opioids are recommended when sufficient for pain relief and dispensing only quantities sufficient for the pain are recommended. A morphine equivalent dose limit of 50mg is recommended [1046] (see Figure 2. Death Rate (Hazard Ratio) vs. Morphine Equivalent Dosage (mg/d)*). Exceeding that should be based on documented need and increased surveillance for adverse effects. PDMPs are recommended to be checked. 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.[79, 102, 104, 105, 108, 109, 167-186] Due to risk of impairments and lost time from work,[1041, 1042] opioids should be prescribed at night or while not working when possible.[985] It is recommended to taper off the opioid in 1-2 weeks.

*Rationale for Recommendations: Post-operative Pain Treatment Recommendations*
Similar to the literature for acute pain, findings are comparable that treated post-operative pain (see evidence table). However, studies also include at least one showing modestly improved long-term knee range of motion and less opioid use with pregabalin for 14 days plus epidural and opioid management after total knee arthroplasty.[1070] Another trial found superior range of motion and fewer venous thromboses after continuous femoral nerve catheters analgesia instead of solely using oral narcotics.[1071] Thus, quality evidence suggests opioids may have deleterious post-operative 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, [274, 293-297] although these studies would likely be underpowered for rare complications. It is also recommended to dispense only what is needed, and not 90-day or other lengthy treatment supplies to avoid either over-medication 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 it also limits complications is overwhelming and so oversedation remains a concern. For patients on chronic opioids pre-operatively, especially moderate to high doses, consultation with a physician experienced in managing these complex cases may be necessary.
*Rationale for Recommendations: Subacute and Chronic Pain Treatment Recommendations*
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 subacute or chronic pain [e.g., NSAIDs,[258, 298-300] nortriptyline,[1086] clonidine,[1087] and flupirtine. [1088] 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. One trial suggests morphine is superior to benztropine for pain, but not function.[1089] 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. [1086] Another found neither morphine nor mexiletine superior to placebo. [1090] Another found celecoxib superior to tramadol for chronic LBP.[298] Diclofenac was superior to dextropropoxyphene/ APAP for treatment of hip or knee osteoarthritis.[1091] Diclofenac was approximately equivalent to tramadol in another trial.[1072] Naproxen was equivalent to oxycodone for treatment of chronic LBP. [1092] 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.

[14]Valdecoxib is currently withdrawn from the market.

[1088] There are no trials documenting improved objective functional outcomes, with more than 100 studies documenting many adverse effects (see evidence table below). [989] There is quality evidence that opioids are associated with *reduced* pain thresholds. [1093] 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 [119] (see evidence table).

*Rationale for Recommendations: Tramadol Issues*

Tramadol is a synthetic opioid that is schedule IV in the US. Tramadol is associated with potential abuse, [1094] and has a similar adverse effect profile as other opioids (see evidence table). However, death risks appear somewhat lower than other opioids. Tramadol appears to be a better initial option than more potent opioids. However, with chronic use, especially higher dose, it may be considered equivalent to other opioids for purposes of this guideline.

*Rationale for Recommendations: Tolerance, Addiction and Drug Screening Considerations*

Tolerance is a common occurrence, although generally not significantly problematic. Addiction and drug-seeking behaviors are less common.[245, 304, 307-310] Yet, approximately 80% of patients experience some adverse effects from opioids and approximately 33 to 80% do not finish a clinical trial with opioids due primarily 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).[1061, 1095, 1096] Drug screening may also determine that the person is not actually taking the prescribed opioid(s).

*Rationale for Recommendations: Opioid Agreement Recommendations*

There is evidence that many patients do not adhere to prescribed treatment (even with an opioid agreement)[1097] however, these agreements are felt to be needed and are recommended to be coupled with a drug-screening program.[71, 72, 224, 313] Drug screening may identify both aberrant use as well as other substance use.[1097, 1098]

*Rationale for Recommendations: Opioid Rotation*

There are no quality studies showing efficacy of opioids rotations [1059] [1057] [1099] [1060] [1100] [1057, 1101]. 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.

*Rationale for Recommendations: Overall Literature Assessment and Conclusions*

Opioids are not invasive, but have numerous adverse effects. Some patients have insufficient pain relief with NSAIDs, analgesics or other medications, thus judicious use of opioids may be helpful. Low-dose nocturnal opioids for treatment of acute pain may be helpful for achieving sleep, although caution is warranted as nocturnal overdosing also occurs. Opioids are recommended for brief, acute, select use in post-operative patients with primary use at night to achieve sleep post-operatively. Caution in those settings is warranted as well as opioids are the second leading cause of in-hospital adverse drug reactions,[1102] which also contribute to adverse economic impacts.[1103] Data suggest patient-controlled analgesia (PCA) may not be superior to intramuscular opioids. [1104, 1105] Opioids are recommended for highly selective treatment of other severe pain conditions (see criteria above).

While there are a few trials (2 high and 2 moderate) of acute pain patients treated with opioids compared with placebo, the overall magnitude of benefit is small while the adverse effects profile is sufficiently high that this resulted in the recommendation being downgraded from "A" to "C." While there are trials among chronic pain patients that last up to 4 months, there are no long-term trials of opioids. There also is no quality literature to identify which patients can safely be prescribed opioids without escalation of dose or other adverse risks. This caused a downgrading of the level of evidence from "C" to "I" especially when combined with evidence of major adverse effects reviewed elsewhere in addition to concerns regarding the inability to control escalating doses.[1047]

Opioids are moderate to high cost depending on duration of treatment. Provider and organizational barriers to implement recommendations to prescribe non-opioid medications and therapies are low, consisting primarily of altering practice habits. Barriers regarding dose limit recommendations are similarly low for new patients. Screening for new patients is provided. An algorithm is provided. Barriers are greater for established patients, especially on higher doses. Tools are identified to assess functional progress, assessing opioid risk, and guidance to assist with tapering. Urine drug testing guidance has been developed. A comprehensive Opioid Contract/ Doctor-Patient Agreement/Informed Consent document has been developed to assist with managing patients.

*Evidence for the Use of Opioids for Acute, Post-operative, Subacute, and Chronic Pain*

There are 4 high- or moderate-quality placebo-controlled clinical trials addressing opioid use for acute pain patients. There are 67 high- or moderate-quality placebo-controlled clinical trials addressing opioid use for chronic pain

patients. Of these, 52% lasted up to 1 month, 12% were 1 to 2 months, and 34% were 3 months in duration. There was one trial of longer than 3 months which lasted 16 weeks. [1106]
Altogether, there are 25 high-[257, 269-271, 274, 275, 277, 284, 287, 301, 319-333] and 132 moderate-quality RCTs incorporated into this analysis.[190, 191, 205, 222, 245-250, 258, 260, 261, 272, 273, 276, 278-283, 285, 286, 288, 293-300, 302-305, 318, 334-426]
There are 21 low-quality RCTs [335, 339, 427-445] and 2 other studies [1069, 1107] in Appendix 4. There are additional trials beyond the scope of these guidelines. [447-455]

# Discontinuation and Tapering of Opioids

## Discontinuation and Tapering of Opioids

Discontinuation of opioids is recommended for acute pain and post-operative patients who have reached meaningful functional recovery. 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 three to seven days.
Discontinuation is also recommended for subacute and chronic pain patients who: i) used opioids on a chronic basis, and ii) [any one of] no demonstrated functional gain, non-compliance, aberrant drug screening results and/or diversion, adverse effects (e.g., cognitive impairment, falls, poor judgment, untreated sleep apnea, psychological disorders, and concurrent use of depressant medications such as benzodiazepines and diphenhydramine)].[64, 115]
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 the opioid is thought to be taken as prescribed (e.g., rather than partially diverted) and the dose is over 50 mg MED.
Tapering is recommended if the opioid was used at a moderate or high level (e.g., above 50-90mg[15] MED) on a chronic basis. Consultation with an addiction specialist or psychiatrist is recommended for complex patients (e.g., high-dose patients, prior withdrawal problems, complex psychosocial confounders, complicating medical conditions).
Transitioning to only an NSAID or acetaminophen or complete cessation of analgesics is/are generally indicated.
*Frequency/Duration* – Duration of a taper is empirical, dependent on dose, prior opioid use duration, and informed patient decision-making. Rates of the taper vary. The following are options:

- 10% per day [456]
- 20% every 3-5 days [456]
- 10% per week [65, 457]
- 25% per week [456]
- 20-50% per day until lower doses reached (e.g., oxycodone CR 30mg, then decrease dose by 10mg/day every 2-5 days [64]
- Faster tapers over a few days have been safely accomplished.

The speed of the taper should generally be an informed choice involving the patient, as some will prefer a faster or slower taper.

- The slowest taper in common use is 10% per week, thus lasting 10 weeks.
- A faster taper is 25% per week for 4 weeks.
- Some will opt for tapering over, e.g., 10 days.

A pilot study found a 22-week taper support intervention was effective (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 2016).
Other agents are used when weaning is challenging, and/or dependence and addiction 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. Those patients with unstable cardiovascular disease and polypharmacy dependence should be considered for in-patient detoxification under the supervision of an addiction specialist. For those using chronically

[15] Quality evidence supports a ceiling dose of 50mg as overdoses and fatalities rise rapidly above that dose. A maximum dose of 90mg is supportable by consensus.

high doses with difficulty tapering and/or undue anxiety, referral to a psychologist may also be helpful to address anxiety and behavioral issues.

A process is recommended:

1. Develop a taper plan. Elements of the plan include: 1) agreement to taper, 2) education on expected symptoms during the taper, 3) return visits for intolerable symptoms with consideration of a pause in the taper, and 4) other treatments to be changed or substituted.
2. The provider should be supportive and engaged in the patient's care, management and concerns. Do not 'abandon' the patient. Consider engaging the patient in other active therapies during taper (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.
3. Rate of tapering is not critical, rather the direction of the dose is. A typical rate is 10%/week to 10%/month in chronic pain patients in outpatient settings. Tapers may be faster in inpatient and more controlled settings, or when use has been for a shorter period of time. Brief negotiated pauses in the rate of a taper is acceptable.
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. The taper should be stopped if there is objective worsening of function, excessive withdrawal, and/or intolerance. After stabilization, resumption of the taper should 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 years.

*Harms* – None for nearly all patients. Theoretical potential to worsen functional gain through cessation of opioid treatment.

*Benefits* – Reduce risk of adverse events and opioid-related deaths.
*Strength of Evidence* – **Recommended, Evidence (C)**
*Level of Confidence* – High

*Opioid Conversion/Transition*
Conversion of opioids to a MED is helpful to transfer from one opioid to another. (See Opioid Dose Calculator at http://www.agencymeddirectors.wa.gov/Calculator/DoseCalculator.htm.) This is most commonly performed to attempt to achieve a better functional outcome and/or to reduce adverse effects. Quality evidence to support this practice has not been published. Several resources are available [458, 459] that include a spreadsheet-based calculator [460] and online converting tool. [461] To avoid drug overdoses, when transferring from one opioid to another, the MED prescribed should be approximately 50% of the prior dose.[462-465]
*Rationale for Recommendation*
There is one moderate quality pilot trial of a supportive group compared with usual care for tapering suggesting some efficacy (Sullivan 16). There are many studies that have described various methods of tapering opioids. However, there are no high or moderate quality studies among the desired target population to define the best methods. The clinical approach is therefore largely empirical. US Federal Guidelines for those with opioid dependency recommended a taper at 2.5-10mg/week as an outpatient.[77] The rate of long term success of tapers and discontinuation is also unclear, with a database study suggesting high dose opioid use predicts long term opioid use.[1108]

Some tapers are relatively unspecified.[1109, 1110] Tapers with buprenorphine also vary widely. [1111-1115] Naltrexone or naloxone are also sometimes used as adjunct agents.(207, 386, 388, 473-481) [1113, 1116-1125]

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.[467, 479-570] There are a few studies on detoxifying opioid using, non-abusing

inpatients that are also beyond the scope of this guideline.[571-573] There are few barriers to implementing this recommendation. Those complex patients may need referral to a program for treatment of addiction, which may be geographically limited.

## Opioids Medications for Tapering: Treatment of Dependency and Addiction

Most tapering is most often 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 opioids dependency and addiction. Often, the same medications are used for both of these purposes, and include buprenorphine, clonidine, methadone, and naltrexone.

### Buprenorphine for Opioid Tapering

**Buprenorphine is selectively recommended for adjunctive treatment in opioid tapering.**

*Indications* – Most patients are weaned without use of a 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 (CDC 16; Addiction guidelines), as well as for the treatment of addiction. As treatment of these conditions is behaviorally and medically challenging, most are treated by addiction specialists (e.g., high-dose patients, prior withdrawal problems, complex psychosocial confounders, complicating medical conditions). Special licensing may be required for treatment with buprenorphine. When there are complex medical issues (e.g., significant cardiovascular disease), inpatient treatment may be indicated. Buprenorphine is not indicated for those with safety critical jobs (JOEM 2014).
Buprenorphine is generally not recommended for those with no demonstrated functional gain; 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).

*Frequency/Dose* – For treatment of opioid addiction, buprenorphine is generally thought to be better prescribed as combined with naloxone to reduce abuse and diversion potentials (SAMHSA). Monotherapy with buprenorphine is recommended for treatment during pregnancy and conversion 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.

*Benefits* – May help reduce opioids withdrawal symptoms. Reduced risk for abuse and diversion when using combined buprenorphine/naloxone.
*Harms* – Buprenorphine/naloxone may precipitate opioids withdrawal. Sedation, daytime fatigue, overdose, fatalities, however the risk of fatalities is considerably lower than with methadone. Potential for abuse (Cassidy 14). Risk for safety including motor vehicle crash and other injuries. (JOEM 2014; Rudisill 16)

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**
*Level of Confidence* – Moderate

### Methadone for Opioid Tapering

**Methadone is selectively recommended for adjunctive treatment in opioids tapering.**

*Indications* – Most patients are weaned without use of a controlled substance medication. Methadone is sometimes used for tapering 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 (CDC 16; Addiction guidelines), as well as for the treatment of addiction. 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 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 indicated for those with safety sensitive jobs (JOEM 2014).
Buprenorphine is generally not recommended for those with no demonstrated functional gain; 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). Instead of methadone, transitioning to only an NSAID or acetaminophen or complete cessation of analgesics is/are generally indicated.

Methadone is not indicated 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).

*Frequency/Dose* – Per manufacturer's and addiction specialist's recommendations.

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

*Benefits* – May help reduce opioid withdrawal symptoms.
*Harms* – Methadone has a particularly high risk of overdose and fatalities. [104, 170, 647] There is no safe dose of methadone when converting from other opioids. Also, sedation, daytime fatigue. Potential for abuse, diversion. Risk for safety including motor vehicle crash and other injuries. (JOEM 2014)

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**
*Level of Confidence* – Moderate

*Rationale*
Methadone and buprenorphine increase adherence to treatment and reduce risk of illicit opioid use among patients with opioid use disorder. [151–155]. Methadone and buprenorphine may be used for opioid addiction, although they should be prescribed by experienced and licensed providers. These medications 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 (only methadone), and dysrhythmias (FDA; Washington State Guidelines). Both of these medications are also not indicated in workers with safety sensitive jobs [985-988, 990, 1126-1129] [1130]. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder. (CDC 2016)

Methadone reportedly accounts for more overdose deaths when compared to hydrocodone or oxycodone. [1008, 1131, 1132] Because methadone is also used to treat substance abuse, overdose decedents tend to have used other prescription and/or illicit medications as well. [1006, 1133] Still, some methadone deaths appear to be related to the medication's tight therapeutic window. [1133-1135] 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.[1131] Methadone should not be used to treat breakthrough pain (BTP) or as an as needed medication.[1136] Switching to methadone requires careful conversion. Supervised administration of methadone is reportedly associated with lower fatality rates than unsupervised administration,[746-749] yet numerous studies have shown elevated mortality rates associated with methadone.[997, 1023, 1137]

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 [616, 627, 751] and has been associated with some risk of fatalities in most [669, 752-758] but not all studies especially with sedative abuse.[759] It requires training of the prescriber and is expensive.[1135] 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.[1138]

## 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."[574, 575] It is also defined as "the transient exacerbation of pain occurring in a patient with otherwise stable, persistent pain."[576] BTP is typical among cancer/terminal illness patients,[576-592] but is also reported in patients with chronic noncancer pain. It occurs in 33-65% of patients with chronic cancer pain and in ~70% of patients with chronic noncancer pain.[1139] Patients admitted to hospice have a prevalence of BTP between 40 and 86%.[1140] BTP is a transitory pain (reaching maximum severity in ~15 minutes and lasting ~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. [1141] BTP also has a self-limiting average duration around 30 minutes.[1142] Non-cancer related BTP has been treated with opioids.[251, 574, 575, 592, 594]

### Opioids for Breakthrough Nonmalignant Pain

**Opioids are not recommended for routine treatment of breakthrough superimposed on chronic pain in the absence of overt trauma or acute nociceptive pathology (e.g., fracture, myocardial infarction, tooth abscess).**

*Harms* – May inadequately treat severe chronic pain.
*Benefits* – Reduced dose escalation, accident risks, risks of dependency, addiction and death.
*Strength of Evidence* – **Not Recommended, Insufficient Evidence (I)**
*Level of Confidence* – Moderate

*Rationale for Recommendation*
Non-cancer related BTP has been treated with opioids.[251, 574, 575, 592, 594] There are cases where BTP may indicate hyperalgesia, or potentially, insufficient treatment of pain. However, in treating BTP, functional gain must be documented; otherwise the dose should revert to the prior dose level. BTP treatment with opioids is likely an accelerator for problems with dose escalation. [1047] Thus, treatment of non-malignant BTP in the absence of overt trauma is not recommended. There are few barriers to implementing this recommendation for new or existing patients.

*Evidence for Breakthrough Pain*
There is 1 moderate-quality RCT and 3 other studies incorporated into this analysis.

*Search Strategy: We searched PubMed, EBSCO, and Google Scholar. The following terms were used: breakthrough pain, incidence, prevalence, cohort population, population-based observational studies, and population death estimates. A total of 7,366 articles were found. We reviewed 21 articles. The timeframe was not limited.*

## Intrathecal Drugs ("Pain Pumps")

The primary use of intrathecal drug delivery systems (aka, "pain pumps") has been for chronic pain and terminal care [321, 599-601]. Multiple agents have been utilized, including morphine, fentanyl and other agents.

### Intrathecal Drug Delivery Systems for Chronic Non-malignant Pain Conditions

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

*Harms* – Device complications, fatalities, potential for dose escalation. [1143]
*Benefits* – Reduced pain ratings, reduced oral opioid use.
*Strength of Evidence* – **Not Recommended, Insufficient Evidence (I)**
*Level of Confidence* – High

*Rationale for Recommendation*
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. [1144, 1145] Deaths have been associated with intrathecal opioid use, including a one-year mortality rate estimated at 3.9%.[1143] Granulomas appear to frequently develop; the expected "permanency"

of neurologic abnormalities associated with their formation has not been established.[1146]

Ziconotide has been used in intrathecal delivery systems.[1147] 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. Since 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 potential long-term sequelae from both implantation/ retention of the devices, granulomas, and those associated with the concurrent use of intrathecal opioids. [1148] As 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 for the Use of Intrathecal Drug Delivery Systems*
There are 2 high-quality RCTs incorporated into this analysis.

*Search Strategy: Articles from this section were included from a previous Chronic Pain Chapter.*

## Naloxone (Narcan) for Prevention of Overdose Fatalities

Naloxone has been used for the prevention of overdose fatalities. It is also used in pharmaceutical combinations with opioids primarily as an attempted, but potentially insufficient abuse deterrent.

### Naloxone (Narcan) for Opioid Overdose

**Recommended.**

Naloxone has long been used as an antidote for opioid overdose. It has more recently been prescribed for treatment of opioid overdose among those on chronic opioids at home, particularly at higher doses. Legislation has been passed in many 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* – **Not Recommended, Insufficient Evidence (I)**
*Level of Confidence* – **Moderate**

| | |
|---|---|
| *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. It is indicated for those who have had serious overdoses but have not (yet) been tapered. Recommendations to have encountered and/or considered prior to a naloxone prescription is(are) adherence to evidence-based opioid guidelines which would prevent vast majority of overdoses and deaths. Earlier treatment options include: 1) prescribing active exercises for most chronic pain conditions, 2) prescribing non-opioids for pain relief first, 3) avoiding opioids in those with risk factors, 4) only prescribing chronic opioids if a trial is successful to improve objective measures of function and pain, 5) not exceeding 50mg MED, and 6) performing monitoring and discontinuation of opioids with aberrant drug screen results. Yet, for those who are already taking more than 50mg MED, a prescription for naloxone is recommended, including while instituting other treatment based guidance to reduce risks of overdose and death |
| *Benefits:* | Rescue some individuals who overdose |
| *Harms:* | Theoretical potential for the patient to learn that there is a rescue medication, which then may promote more risky behavior and overdoses in susceptible individuals. |
| *Frequency/Dose/Duration:* | Administer the medication when there is lack of responsiveness or substantially reduced sensorium. For those known to have overdosed, yet 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. Generally requires approximately one hour observation after resuscitation, although the length is dependent on the specific drug, dose and route (Willman 16).

*Indications for Discontinuation:* Normalization of consciousness

*Rationale:* There are no randomized controlled trials. There are studies of lay-dispensed naloxone that all suggest efficacy (Strang 08; Lankenau 13; McAuley 10; Galea 06; Strang 16); however, most event and recovery data are self-reported. Lay-dispensed naloxone recoveries were approximately 8-fold more likely with naloxone administration compared with those where naloxone was not administered. Also, there are extensive case series experiences with naloxone reversing reduced consciousness or comatose states. Naloxone has negligible adverse effects other than increasing experience of pain, is low cost, has extensive empirical evidence of efficacy and is recommended to have available for treatment of overdoses and near-fatalities.

# Opioids Benefits and Harms

## Benefits

### Pain Relief

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. Other comparative efficacy trials have largely failed to find superiority of opioids compared with other active treatments including NSAIDs (see evidence tables below).[13] Magnitudes of those pain reductions are modest compared with placebo (i.e., generally 1/10 VAS pain scale reduction) and few of those trials lasted more than one month while none were over 6 months in duration. [13] These trials and details of the results are reviewed below.

## Harms

### Adverse Events

Opioids have been associated with numerous adverse effects (see **Table 2. Adverse Opioid Effects by Organ System** (171, 653, 659, 682, 684, 688, 691-725)), which differ somewhat based on the specific drug and route of administration. In aggregate, these effects include: opioid-induced lower pain thresholds (hyperalgesia), [1149, 1150] nausea, vomiting, delayed gastric emptying, constipation, pruritus, drowsiness, sedation, respiratory depression,[62, 607-645] clouding of consciousness or "mental fog," dysphoria, decreased concentration, lack of coordination, myoclonus, muscle rigidity, dizziness, euphoria, sexual dysfunction, bladder dysfunction, immune system effects, hair loss, anaphylaxis, sleep disturbance,[71, 599, 646-659] motor vehicle crashes,[82-85, 87], physical or psychological dependence (virtually all patuents, addiction, feminization, muscle wasting, balance problems, altered color vison, slowed reaction time, problems with decision making, lack of impulsecontrol, osteopenia/porosis, falls, fractures, increased incidence of coronary events [1151-1153], birth defects (Ailes 15; [1154]; Kellogg 11; Yazdy 15), immune suppression (Budd 06; Gach 11), erectile dysfunction, infertility, lower return to work status, [1155] injuries and other accidents, [1037] disability, [1155, 1156] and drug tolerance.[1157] Deaths from unintentional and intentional overdoses, misuse and therapeutic misadventures occur, although they are infrequent relative to the adverse events listed above.

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. [1158] Osteoarthritis patients receiving opioids compared to those receiving NSAIDs had increased risk of cardiovascular events, hospitalization, and overall mortality.[664]

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.[1159, 1160]

Adverse events may be related to the specific drug and route of administration. For instance, the adverse effects of oral morphine include constipation, nausea, pruritus, and drowsiness. Transdermal fentanyl may result in rapid drug tolerance and is absorbed through subcutaneous fat, making it reportedly less effective in those with little subcutaneous fat; regardless, mortality risks are considerable with fentanyl. [1161] On the other hand, methadone is particularly reported to prolong the QT interval [646, 668-670] and has been widely associated with cardiac dysrhythmias, polymorphic ventricular tachycardia, and sudden cardiac death. Respiratory depression, sedation, [1131] somnolence, mental fog, decreased concentration, and lack of coordination constitute negative effects of opioids.[71, 648, 649] Other adverse effects include euphoria, dysphoria, and itching. Long-term adverse effects also include hormonal and immune system effects. [1162] [650] reported delayed gastric emptying, sexual dysfunction, muscle rigidity, myoclonus, sleep disturbances, pyrexia, and dizziness. The adverse effects of long term use were sleep disturbances and bladder dysfunction. [1163] The use of prescription opioids can alter sleep patterns by increasing time spent in light sleep and decreasing time spent in deep sleep.[1164] Intrathecal opioid drug delivery system-associated deaths have been reported in patients receiving new implants, after pump replacement, or after catheter revision and attributed some deaths to opioid overdose. [1143] Adverse effects of intrathecal and epidural opioids include pruritus, nausea and vomiting, urine retention, respiratory depression, mental status changes, central nervous system excitation, hyperalgesia, herpes simplex labialis virus reactivation, neonatal morbidity, sexual dysfunction, ocular dysfunction, gastrointestinal dysfunction, thermoregulatory dysfunction, water retention, cardiac dysrhythmia, hair loss, neurotoxicity, and anaphylaxis.[652-654]

Opioid-using patients undergoing surgery have been associated with greater resource utilization. [1165] They are widely thought to be associated with greater peri-operative management challenges.[49] Coronary artery bypass graft patients who use pre-operative opioids are more likely to be readmitted within 6 months. [1166] Opioid use is associated with elevated risk of 1-year mortality after hip fracture whereas osteoporosis medications were associated with reduced risk.[1167]

Opioid-induced hyperalgesia is a paradoxical state where opioids are associated with increased pain sensitization that may manifest in as little as 2 weeks of treatment.[655, 656, 675] This phenomenon is either becoming more prevalent and/or increasingly recognized as more patients receive opioids. [1168] Opioid-induced hyperalgesia should be suspected when there is: i) waning opioid treatment efficacy; ii) unexplained pain and/or; iii) diffuse allodynia unassociated with the original painful condition; iv) paradoxically reduced pain after opioid reduction or withdrawal; v) dose escalation; or vi) excessive post-operative pain.[655, 658, 659, 676-683]

Opioid-associated endocrine effects include 48-57% lower estrogens,(684) (Daniell 08) disturbed or cessation of menses, [1169] 74% subnormal testosterone levels among men [685-687] and women, [1169] lack of libido, [1170] infertility, [1170] and low luteinizing hormone. [1171-1173]

***TABLE 2. ADVERSE OPIOID EFFECTS BY ORGAN SYSTEM (171, 653, 659, 682, 684, 688, 691-725)***

| 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, tachyrhythmias, 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 |
| Endocrine | Suppression of testosterone | 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 |

| System | Effect | Clinical Effect |
|---|---|---|
| Immune | Allergic reactions to medication | Rash, shortness of breath, itchy skin, edema |
| 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 opioids/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 on opioids 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 |

*Evidence for Adverse Events*
There are many studies incorporated into this analysis.[109, 167, 726-729] See adverse events evidence table below.

## Myocardial Infarction

Chronic Opioid Therapy has been associated with an increased risk of cardiovascular outcomes. [1151, 1152] Opioid use also exhibits an increased relative risk of many safety events compared with NSAIDs. [1153]

## Immunosuppression

Opioid use has been linked to suppression of the immune system. (Budd 2006) Morphine has been postulated to affect tumor growth, [1174], although the overall quality of the data preclude a conclusion regarding whether opioids increase risk of tumor spread [1174-1176].

## Birth Defects

An association between early pregnancy maternal opioid analgesic treatment and certain birth defects has been shown [1154] These birth defects include conoventricular septal defects, atrioventricular septal defects, hypoplastic left heart syndrome, spina bifida and gastroschisis. The literature does document the potential harms associated with

prescription opioid use during pregnancy, including poor fetal growth, preterm birth, birth defects, and neonatal abstinence syndrome (Yazdy M 2015)

## Addiction (Abuse/Misuse)

Chronic opioid utilization for treatment of chronic non-cancer pain has increased greatly in the past two decades. The reasons for this are likely complex, with possible etiologies that include socioeconomic considerations, pharmaceutical marketing, inaccurate information provided to physicians, psychosocial determinants, and differences in clinical practice and interindividual variation in biological pathways. However, there remains a lack of knowledge about underlying mechanisms for the development of opioid abuse and misuse. Also, the tools used to stratify risk and monitor therapy may not be effective addressing the core issues underlying opioid abuse and misuse.[220, 730, 731] Prescribing opioids carries a risk of addiction, along with the associated adverse effects of addiction, and that these risks appear to receive insufficient consideration and weighting of the risk/benefit analysis when prescribing opioids. The magnitude of risk of addiction is uncertain and has been estimated from 0-50%.[264, 310, 732-734]

Patients who have aberrant drug-related behaviors, psychosocial comorbidities, and a history of substance abuse are more likely to misuse and abuse prescription opioids and become addicted to them.[1099] Of the prescribed opioids, caution is particularly advised in prescribing long-lasting oxycodone for chronic pain due to higher risk of abuse, high cost and high street value, [1135] although some data also suggest and oxymorphone is problematic as well. (Coplan 17; Cassidy 14)

*Evidence for Addiction*
There is 1 study incorporated into this analysis. [1177] See adverse events evidence table below.

## Depression/Anxiety

Opioids are beneficial when prescribed in lower amounts and under specific conditions (see evidence tables below), helping to decrease the perception of pain. On the other hand, when opioids are used in medium and high doses, they may acutely or chronically contribute to clinical depression, and increase perceived pain intensity.
A prospective cohort study found 7% of 768 consecutive chronic pain program patients produced a normal MMPI, 15% conversion V, 9% neurotic and 69% had a disability profile. [1045] Aberrant psychological findings were also opioid dose-dependent, although that may be confounded by the apparent colinearity between psychological findings and opioid treatment. One large case series of 500 consecutive pain patients reported depression, anxiety and somatization disorder in 59%, 64% and 30% of the cases. [1178] Another longitudinal study found that those who reported some opioid use at time of admission into the study, "uniformly demonstrated higher pre-rehabilitation ratings of pain, disability, and depression." [1155] Other studies suggest associations between opioid use and depression [173, 182, 185, 738-740] and anxiety.[185, 739, 740]
*Evidence for Depression/Anxiety*
There are 11 studies incorporated into this analysis.[173, 221, 226, 660, 737-739, 741-743] See evidence table for adverse events below. There is 1 low-quality study in Appendix 4.[1179]

## Post-Traumatic Stress Disorder

Patients with PTSD are reportedly more likely to be prescribed opioids and show less improvement than those without PTSD. [1037, 1038]
*Evidence for Post Traumatic Stress Disorder*
There are 2 studies incorporated into this analysis. [1037, 1038] See adverse events evidence table below.

## Suicide

Opioids are among the most common substances found in decedents from suicide. [1180]

## Respiratory Depression

Opioids are associated with respiratory depression in most studies and are also associated with obstructive and central sleep apnea.[618, 620-623, 627-631, 635, 636, 751, 761] Some experimental evidence suggests this is present regardless of opioid-naïvete.[1181, 1182] Some data suggest that peak respiratory depression may occur hours after administration. [1181, 1183] Buprenorphine also produces this effect.[1181, 1184]

In overdose situations, some manifestation of anoxic brain injury is found on imaging studies with leukoencephalopathy most commonly reported.[762-769]
*Evidence for Respiratory Depression*
There are 13 studies incorporated into this analysis.[618-623, 627-632, 751] See adverse events evidence table below.

## Post-operative Sleep Disturbances

Opioids are associated with post-operative sleep disturbances that include suppression of rapid eye movement sleep, [1185] as well as appear apparent associated association with sleep apnea.[1186] There was no association between sleep disturbance and level of pain.[1187]
*Evidence for Post-operative Sleep Disturbances*
There are 2 studies incorporated into this analysis. [1186, 1187] See adverse events evidence table below. There is 1 low-quality RCT in Appendix 4.[1185]

## Prescription Opioid-associated Deaths

Deaths have been reported among both those prescribed opioids and those obtaining opioids through diversion.[89, 105, 109, 169, 171, 193, 772-778] The most common medications associated with opioid-related deaths are methadone, hydrocodone, oxycodone and fentanyl, although there are regional variations based on practice patterns and diversion.[6, 89-91, 93, 95, 97, 102, 779] Long-acting oxycodone has been linked to increased mortality.[1000] Tramadol has been represented as a safer alternative, yet overdose deaths have been associated with tramadol.[752, 780-788] In a cohort study by Dunn, et al., 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 2. Death Rate (Hazard Ratio) vs. Morphine Equivalent Dosage (mg/d)*). 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. [1022]

In a similar case cohort study by Bohnert, et al., 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. [1046]

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 numbers of opioid-related deaths. [1188] However, the magnitude of that state's reduction has not been large.

In a matched case control comparison, Paulozzi, et al., found 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. [1024]

At least one study has suggested no difference in risk of respiratory depression in those opioid-naïve patients compared to those on strong opioids. Clemens [1182] suggested some corroborative evidence for the nearly identical dose-response curves in Figure 2.

A 2010 study by Fitzgibbon found that those who died were more likely to be on long-acting opioids, more likely to be taking opioids with nonopioid psychoactive medications, more likely to display medication misuse behaviors, and more likely to be taking additional opioids and psychoactive medications without a physician's knowledge. [1189]

A study assessing means to decrease prescription opioid deaths used physician targeted presentations about the opioid epidemic and how to reduce deaths with the state subsequently experiencing a 14.0% drop in prescription opioid unintentional deaths in 2008 compared to 2007. [1190]

Deaths from unintentional drug overdoses in the U.S. have become the second leading cause of accidental death with 27,658 deaths in 2007. Opioids specifically caused 11,499 of those 27,658 deaths. From 2004 to 2008, visits to emergency departments more than doubled and from 1998 to 2008, admissions to substance abuse treatment programs increased by 400%. Prescription pain killers were the second most abused drugs during these 10 years. [1191] There appears to be a need for additional training, management, and policies for those who prescribe opioids due to the magnitude of the epidemic of drug abuse and overdose deaths.

*Evidence for Prescription Opioid Deaths/Causes of Death in Those Taking Opioids*
There are 28 studies incorporated into this analysis.[104, 112, 171, 182, 185, 188, 189, 221, 289, 535, 660, 661, 663, 669, 726, 738, 757, 772, 792-801] See adverse events evidence table below.
*Search Strategy:*
For adverse events, we searched PubMed, EBSCO and Google Scholar without limits on publication dates. We used the following terms: incidence, prevalence, cohort, population, population-based, observational studies, population death estimates, high risk opioids, low risk opioids and hazards to find 29,107 articles. Of the 29,107 articles found, we reviewed 16 and used six. For addiction, we searched PubMed and Google Scholar without limits on publication dates. We used the following terms: incidence, prevalence, cohort, population, population-based, observational studies, population death estimates to find 7,004 articles. Of the 7,004 articles found, we reviewed 3 and used one. For Depression/Anxiety, we searched PubMed and Google Scholar without limits on publication dates. We used the following terms: opioids, risk factors, abuse to find 36,088 articles. Of the 36,088 articles, we reviewed 14 and used 11. For post-traumatic stress disorder, we searched PubMed and Google Scholar without limits on publication dates. We used the following terms: opioids, post-traumatic stress disorder to find 6,844 articles. Of the 6.844 articles, we reviewed two, and both were used. For Respiratory Depression, we used the following search terms: respiratory depression, respiratory insufficiency, respiratory failure and ventilator depression. The search terms were used in Google Scholar, PubMed and EBSCO databases. Most of the articles were found using the PubMed database; with a total of 52 articles. However, only 13 were used in the draft. There was no limit on dates for these searches. For Post-operative sleep disturbances, we used the following search terms: sleep disturbance, sleep disorder, and dyssomnia. The search terms were used in Google Scholar, PubMed, and EBSCO databases. Most of the articles were found using the PubMed database with eight. However, only three were used in the draft. There was no limit on dates for these searches. For Prescription opioids deaths, we used the following search terms: Chronic Pain, Complex Regional Pain Syndrome (CRPS), Neuropathic Pain, Radicular Pain, Peripheral Neuropathic Pain, and Chronic Persistent Pain (CPP). The search terms were used in Google Scholar, PubMed, and EBSCO databases. Most of the articles were found in PubMed with 94 articles and in EBSCO with 4 articles. However, only eight were used in the draft. Other searches were done to look at the harms and benefits of opioid use. For causes of death in those taking opioids, we used the following search terms: death, opioids, incidence, prevalence, cohort, population, population-based, observational studies, and population death estimates. The search terms were used is Google Scholar, PubMed, and EBSCO databases. Google Scholar found eight and PubMed only found one article. However, only for of the articles were used in the draft. There was no limit on dates for these searches.

## Financial Costs Associated with Opioid Usage

Opioids are associated with a higher rate of in-hospital adverse drug reactions, greater lengths of stay, [1103] and consequently higher hospitalization costs, although they are reportedly effective treatments. A randomized trial found that use of ketorolac resulted in fewer complications and less cost than an opioid. (Gora-Harper 01) There also is evidence that patient controlled analgesia is most costly but not more effective for post-operative management. Opioids have been associated with greater workers' compensation claim costs and risk of catastrophic claims, although this relationship may be partially confounded by injury severity and psychopathology.

*Evidence for Financial Costs of Opioid Usage*
There is 1 moderate-quality RCT and 7 other studies incorporated into this analysis. (Choiniere 98; Davies 09; Gora-Harper 01; Kwong 10; Masson 02; Obradovic 12; Oderda 07; Vogt 05)

*Search Strategy: The following search terms were used: incidence, prevalence, cohort, population, population-based, observational studies, population deaths estimates, opioid use and adverse events. Most of the articles were found in PubMed and Google Scholar, with a total of six articles in each database. However, only seven articles were used in the draft. There was no limit on dates for these searches.*

## Comorbidities

The contribution that comorbidities have with respect to the treatment of pain, especially chronic pain, is complex and varies. Much of chronic pain is spine pain, and most chronic spine pain has no clearly defined etiology. 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 thosse 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.

Detailed screening for comorbidities is recommended when considering prescribing opioids for treatment of chronic pain. This includes a review of systems, medication review, physical examination and screening. Abbreviated screening substance use disorder and psychiatric illnesses and other sedating medications is recommended for consideration of prescribing opioids for treatment of acute pain.

*Evidence for Comorbidities*
There are 10 studies incorporated into this analysis. (Deyo 11; Dominick 12; Gerhardt 11; Gerrits 12; Ho 11; Knaster 12; Ohayon 12; Reme 11; Tang 12; Wong 12)

*Search Strategy: The following search terms were used: psychiatric illness, psychopathology, chronic pain, psychiatric profile, and psychological profile. Most of the articles were found in the PubMed database, with a total of 10 articles saved. However, nine were used in the draft, and one was an additional search found in the background section.*

## Effectiveness of Risk Evaluation and Mitigation Strategies (REMS) Training and Training Facilities

FDA has suggested risk evaluation and mitigation strategies (REMS) with three components: a medication guide, elements to assure safe use, and timetable for submission of assessments for extended release and long acting opioids. 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.[820]

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 (16,651)," illustrating the importance of appropriate prescribing and patient monitoring. (CDC 13) 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 in to 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*.

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 abuse of prescription drugs. While REMS has targeted long-acting opioids; there is little evidence they are more hazardous than short-acting opioids.

REMS are organized plans of action designed to monitor and manage drug risks, such as potential for addiction and abuse, 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/abuse and inappropriate or uniformed prescribing. In an attempt to address this issue, a key element of the opioids 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 2008-2011. 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." (Office Insp General 13) The Inspector General's Office made the following seven recommendations to address these findings, and 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 stopping prescribing opioids, and thus preventing patients from receiving pain medication. (Slevin 11) 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. (Dal Pan 12) REMS remains a work in progress and may be but one relatively weak tool to address the multi-factorial issue of opioid abuse/misuse and inappropriate prescribing.

## Diagnostics and Monitoring

Opioid treatment agreements are used to monitor patients on opioids. Commonly, these include provision for urine drug testing for assessing compliance for use of that particular opioid, as well as ascertaining other illicit substance use. Finding either type of urine drug testing discrepancy is normally considered grounds for 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, although it cannot be used for acute toxicity and its interpretation is frequently, considerably more difficult[16]. 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. For those with no scalp hair, if body hair is submitted for testing 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 three 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). (DOT 10) Many commercial labs do this 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 most current prescription opioids. To be useful, one must choose a test that the laboratory states 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/abused surreptitiously, and that increase the risk of accidental overdose mortality (e.g., benzodiazepines, barbiturates, etc.).

If the state has a controlled substance database, the prescribing physician is able to verify whether other physicians are prescribing (other) controlled substances. 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 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;[17] these employees generally should not be taking opioids if in a "full duty" 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 are effectively a heroin detection system pioneered by the US Army for testing American

[16] 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 addiction treatment, with subsequent termination that may be interpretable as a violation of the ADA.

[17] An employer may require a wider battery beyond the NIDA panel at the employer's discretion.

soldiers serving in the Vietnam War. The new synthetic and semi-synthetic pharmaceutical opiates are not detected by this panel.

Multiple laboratories conduct urine drug testing. Each lab offers testing for the basic 5 categories, but each lab typically also offers "expanded panel" testing capable of detecting many more classes of drugs. 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 abuse. 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 abusable drugs the person might be surreptitiously taking.

Urine drug testing should be done in federally certified labs. The certified labs use a 2-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 labs do step 2, which is gas chromatography-mass spectroscopy (GC-MS). This test is more expensive, but detects the unique chemical "finger print" 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.[832] Hydrocodone is metabolized to hydromorphone (Dilaudid) before excretion, and the USD 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 this seems 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 labs for testing that includes both screening immunoassay and confirmatory gas chromatography-mass stectroscopy 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.

*Evidence for Diagnostics and Monitoring*
There are 14 studies incorporated into this analysis. (Michna 07; Katz 02; Hariharan 07; Compton 08; Ives 06; Wiedemer 07; Vaglienti 03; Chelminski 05; Manchikanti 06a, 06b, 06c; Manchikanti 07; Manchikanti 01; Fishbain 99)

*Search Strategy: For Diagnostics, we searched PubMed, EBSCO, and Google Scholar. The following terms were used: Urine Drug Screens, Opioid Drug Tests, Aberrant Opioid Rate, and Chronic Opioid Users. A total of 19,456 articles were found. We reviewed three articles and included one. The timeframe was not limited. For Monitoring Diagnostics, we searched PubMed, EBSCO, and Google Scholar without limits on publication dates. We used the following search terms: opioid, urine screening, urine text, urine toxicology, and urine drug test to find 42,690 articles. Of the 42,690 articles, we reviewed 17 articles and included 14 articles.*

## Screening Tools

While the clinical interview remains an important method to identify risk for aberrant drug-related behaviors, it is neither systematic nor efficient. Thus, there are many screening methods that have been developed. The three tools

with the largest volume of research are the Screener and Opioid Assessment for Patients with Pain (SOAPP) and its revised version (SOAPP-R), the Pain Medication Questionnaire (PMQ), and the Current Opioid Misuse Measure (COMM). All three of these tools have undergone partial validations, although none of these has been fully validated to document prevention of opioid misuse/abuse. The Pain Disability Index is also widely used, it is also wholly subjective and has somewhat fewer supportive data.
The SOAPP was designed to reflect the consensus of experts and determine the circumstances, and characteristics, related to aberrant drug use by a self-administered screening tool for chronic pain patients. The patient-self report items for the SOAPP were generated based on the concept mapping results, literature, and clinical experience of the patients. (Butler 04) However, a SOAPP-R was created later to place limitations, and improve the original assessment. (Butler 08) The SOAPP-R has been reportedly reliable and valid as a screening tool for those chronic pain patients with risk of aberrant drug-behavior, having undergone partial validations, yet the likelihood ratios are unhelpfully near 1 (CDC 16). (see Appendix 1: Tools).
The second assessment tool is the COMM. The COMM, also a self report instrument, was developed to complement other screening assessments tools for opioid misuse. It also helped physicians to evaluate patients risk for aberrant use of opioids. The COMM appears to be a reliable screening tool to identify chronic pain patients with aberrant drug related behaviors (see Appendix 1: Tools).
The third tool is the Pain Medication Questionnaire (PMQ). It has also undergone partial validation.
Other tools including the Prescription Drug Use Questionnaire, DIRE score, Opioid Risk Tool (ORT) (see Appendix 1: Tools), 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

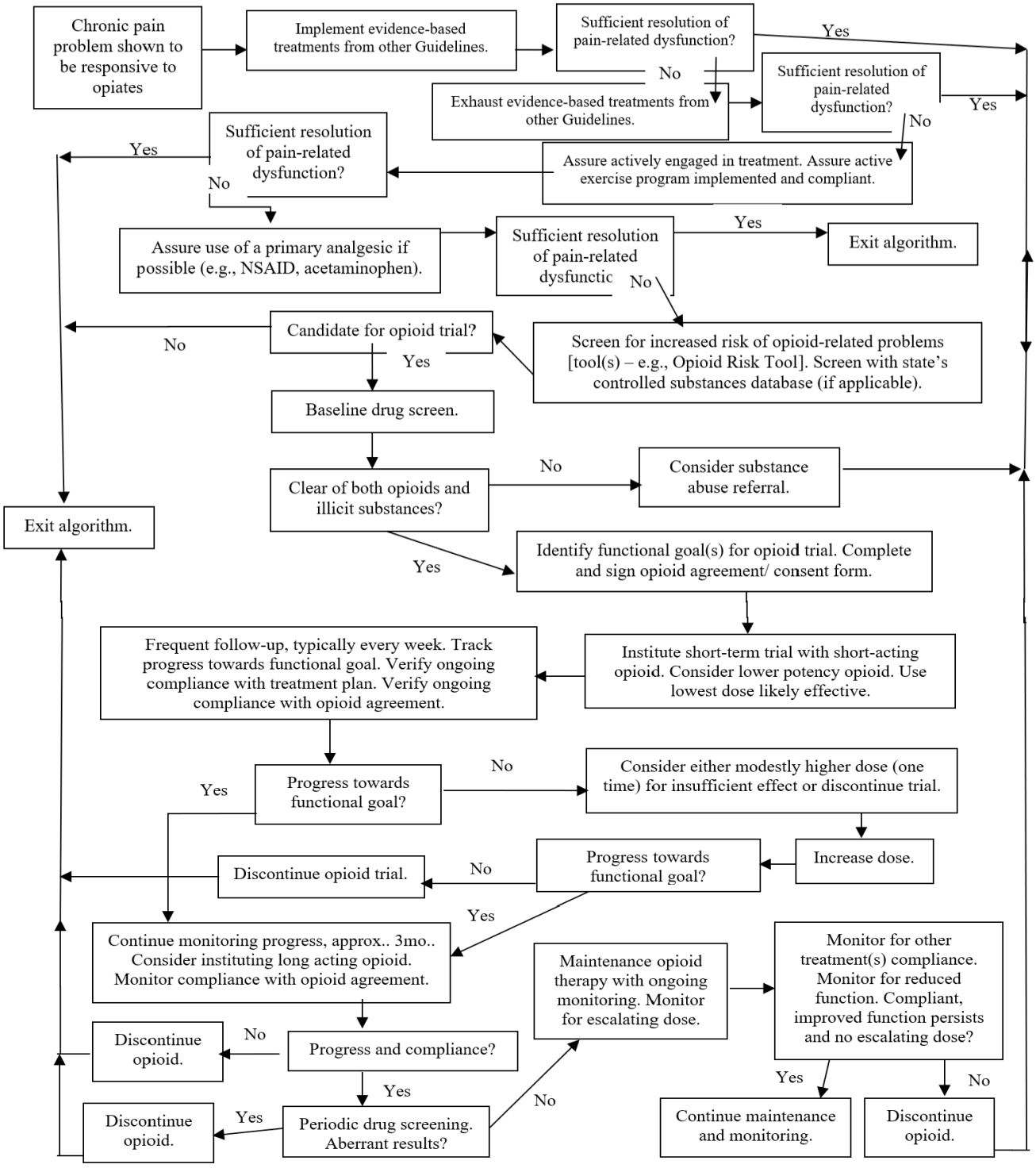
Opioid deaths have been associated with CYP2D6 and OPRMI gene variations, with the CYP cytochromes (CYP 3A4/3A5, CYP 2D6, CYP 2C9, CYP2D9) responsible for metabolism through the cytochrome P450 system, and genetic variations impairing opioid metabolism (see Appendix 3: Cytochrome P450 3A4 (2D6) Inhibitors and Inducers). As one example of potential clinical impacts, there is a strong tendency for those of Chinese ancestry, as well as some Caucasians to not metabolize codeine to morphine. Currently, screening for genetic risks prior to opioid treatment is not in widespread use. Cytochrome blocking drugs and cytochrome inducing pharmaceuticals also influence efficacy and toxicity.
*Evidence for Screening Tools*
There is 1 moderate-quality RCT and 28 other studies incorporated into this analysis. (Jamison 10; Butler 04; Moore 09; Akbik 06; Butler 08; Butler 09; Edwards 11; Martel 13; Jones 12; Adams 04; Holmes 06; Dowling 07; Buelow 09; Hojsted 11; Morasco 13; Jones 13; Webster 05; Witkin 13; Meltzer 11; Parhami 12; Butler 10; Wasan 07; Butler 07; Moore 09; Belgrade 06; Atluri 04; Michna 04; Compton 98; Manchikanti 04)
*Search Strategy:* For Screening Tools, we searched PubMed, EBSCO, and Google Scholar without limits on publication dates. We used the following search terms: preferred, questionnaires, aberrant drug behavior, and validated to find 17,639 articles. Of the 17, 639 articles, we reviewed 19 articles and included nine articles. For SOAPP-R, we searched PubMed, EBSCO, and Google Scholar. The following terms were used: Screening Tools, Screener and Opioid Assessment for Patients with Pain-Revised, and SOAPP-R. A total of 550 articles were found. We reviewed eight articles and included six. The timeframe was not limited. For PMQ, we searched PubMed, EBSCO, and Google Scholar. The following terms were used: Pain Medication Questionnaire, PMQ, Opioids, Medication, and Misuse. A total of 388 articles were found. We reviewed thirteen articles and included seven. The timeframe was not limited. For ORT, we searched PubMed, EBSCO, and Google Scholar. The following terms were used: Screening Tool, Opioid Risk Tool, and ORT. A total of 23,959 articles were found. We reviewed twelve articles and included five. The timeframe was not limited. For DIRE, we searched PubMed, EBSCO, and Google Scholar without limits on publication dates. We used the following search terms: DIRE, Diagnostic Intractability Risk Efficacy tool, and screening tool to find 16,902 articles. Of the 16,902 articles found, we reviewed two articles and included both articles. For Current Opioid Misuse Measure, we searched PubMed, EBSCO, and Google Scholar. The following terms were used: Current Opioid Misuse Measure, COMM, Validity, Reliability, Outcome Measure, and Screening. A total of 25,831 articles were found. We reviewed ten articles and included six. The timeframe was not limited.

# Auditing/Monitoring Criteria

The provider is recommended to assure:

1. Patients prescribed opioids for acute pain are prescribed no more than 50mg MED. Target 90%
2. Patients prescribed opioids for acute pain are prescribed not more than 5 days for the initial prescription. Target 90%.
3. Patients prescribed a trial of opioids for chronic pain should have documentation of at least 3 prior non-opioid medications that have been prescribed previously and failed. Target 100%
4. Patients who are prescribed opioids for chronic pain over 3 months should have a signed informed consent form and pain contract. Target 100%
5. Patients should be screened for aberrant and illicit drug use prior to initiating, or continuing, prior opioids at the first visit. Target 100%
6. Patients on opioids should be prescribed at a morphine equivalent dose (MED) less than 90mg. Target >98%
7. Patients on opioids at MED over 100mg are not taking benzodiazepine(s). Target 100%
8. Patients who are in violation of his/her opioid contract (e.g., illicit drugs, >1 prescriber, diverting drugs) should have the opioid weaned or stopped.. Target 100%
9. Patients performing safety sensitive jobs are not taking opioids. Target 100%

## Algorithm. Opioid Use for Subacute/Chronic Pain



# Appendix 1: Tools

## Opioid Risk Tool©

Date _____

Patient Name _____

| | | Mark each box that applies | Item Score if Female | Item Score if Male |
|---|---|---|---|---|
| 1. Family History of Substance Abuse | Alcohol | [ ] | 1 | 3 |
| | Illegal Drugs | [ ] | 2 | 3 |
| | Rx Drugs | [ ] | 4 | 4 |
| 2. Personal History of Substance Abuse | Alcohol | [ ] | 3 | 3 |
| | Illegal Drugs | [ ] | 4 | 4 |
| | Rx Drugs | [ ] | 5 | 5 |
| 3. Age (Mark box if 16 – 45) | | [ ] | 1 | 1 |
| 4. History of Preadolescent Sexual Abuse | | [ ] | 3 | 0 |
| 5. Psychological Disease | Attention Deficit Disorder | [ ] | 2 | 2 |
| | Obsessive Compulsive Disorder | | | |
| | Bipolar | | | |
| | Schizophrenia | | | |
| | Depression | [ ] | 1 | 1 |
| **TOTAL** | | **[ ]** | | |

**Total Score Risk Category** Low Risk 0 – 3 Moderate Risk 4 – 7 High Risk ≥8

Webster LR, Webster R. Predicting aberrant behaviors in Opioid-treated patients: preliminary validation of the Opioid risk tool. *Pain Med*. 2005;6(6):432. Reproduced with permission from Dr. Lynn Webster, Lifesource Foundation, Salt Lake City, Utah; lynnw@lifetreepain.com.

## Opioid Treatment Functional Goal(s)

Name:_____ Date:_____

| Activity | Goal | Baseline | Recheck #1 Date: | Recheck #2 Date: | Recheck #3 Date: | Recheck #4 Date: | Recheck #5 Date: | Recheck #6 Date: |
|---|---|---|---|---|---|---|---|---|
| **Return to work, modified** | | | | | | | | |
| **Return to work, full** | | | | | | | | |
| **Household chores, Specify_____** | | | | | | | | |
| **Sport/Activity, Specify: _____** | | | | | | | | |
| **Activity (ies) of Daily Living, Specify_____ _____** | | | | | | | | |
| **Other: _____** | | | | | | | | |
| **Other: _____** | | | | | | | | |
| **Other: _____** | | | | | | | | |

## Opioid Treatment Agreement

Patient Name (Print): _____
Prescriber Name (Print): _____
Medical Condition requiring Opioid: _____
Planned Opioid Medication: _____

**I (patient) understand the following (initial each):**

_____ I understand this agreement applies to opioid medications. Some of the common examples include but are not limited to oxycodone (e.g., Percocet), hydrocodone (e.g., Vicodin, Lortab), Hydromorphone (Dilaudid), morphine, fentanyl (e.g., Actiq), codeine (e.g., Tylenol with codeine), methadone, tramadol (e.g., Ultram), and buprenorphine (Suboxone or Subutex).

_____ I understand that opioids are prescribed to see if they increase my function including my ability to work, perform household chores, or otherwise regain activities.

_____ I understand that opioids are only one part of my treatment program.

_____ I understand that opioids may slightly reduce pain levels. Most studies report this as approximately 1/10, or in other words, from a pain level of "6 out of 10" to "5 out of 10." Opioids will **NOT** eliminate chronic pain and are unlikely to produce major improvements in pain.

_____ I understand that opioid medications have all of the following reported adverse effects (see Table 1a). Many, but not all of these risks increase with higher doses.

_____ I have had an opportunity to discuss these risks with my prescriber. I accept these risks.

**Table 1a. Adverse Opioid Effects by Organ System**

| System | Effect | Secondary Effect |
|---|---|---|
| Cardiovascular | Myocardial infarction | Heart attack |
| | Orthostatic hypotension (dizziness on standing up) | Fainting on standing up |
| | Abnormal heart rhythm (QT prolongation) (methadone) | Sudden death |
| Gastrointestinal | Gastroparesis (slow gut movement) | Nausea, weight loss |
| | Reduced colon motility; spasm | Constipation, bowel obstruction |
| | Biliary spasm | Stomach pain |
| Genitourinary | Exacerbation of prostate problems | Urinary retention |
| Endocrine | Suppression of testosterone | Impotence or reduced sex drive and erectile dysfunction, osteoporosis, feminization, reduced muscle mass, reduced strength |
| | Suppression of LH, FSH | Abnormal menstrual periods |
| | Adrenal suppression | Fatigue, low blood pressure, electrolyte changes |
| Immune | | |
| | Allergic reactions to medication | Rash, shortness of breath, itchy skin, edema |
| Neurological/ Psychiatric | Impairment of thinking or executive function | Outbursts, inappropriate behavior, limit testing, violence, reduced impulse control |
| | 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 |
| | Increased CNS pressure | Headache |
| | Hyperalgesia | Increased pain sensitivity, increasing doses of opioids/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 |

| System | Effect | Secondary Effect |
|---|---|---|
| | 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 on opioids 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 |

_____ Opioids will be initially prescribed to me on a trial basis. The primary goal of this treatment is to improve my ability to perform various functions, including return to work, household chores or other physical or mental activities. If significant demonstrable improvement in my functional capabilities does not result from this trial, my prescriber will likely end the trial.

Goal for improved function: _____

_____ Opioids may also be prescribed to make my pain more tolerable, but these medications will not cause the pain to disappear entirely.

_____ Drowsiness and slowed reflexes may be temporary or ongoing adverse effects of opioids, especially during dosage adjustments. If I am experiencing drowsiness while taking opioids, I agree not to drive a vehicle or perform other tasks that could involve danger to myself, family members, coworkers, or others.

_____ Increased motor vehicle crashes have been reported in many studies among those taking opioids on a chronic basis. Especially for this reason, workers performing safety sensitive jobs (e.g., driving, operating heavy machinery, transporting goods or people, using overhead cranes, working at elevated heights, making complex judgments) are recommended to be precluded from performing safety sensitive jobs while taking opioids. If I am employed in a safety sensitive job, I will check with my employer to make sure this medication does not prevent me from working.

_____ Due to evidence of crashes and accidents among those taking opioids, I also agree to discuss whether I can drive my personal car and/or operate machinery at home with my provider.

_____ Using opioids to treat chronic pain will result in the development of a physical dependence on this medication, and sudden decreases or discontinuation of the medication will lead to symptoms of opioid withdrawal. These symptoms may include: nervousness, anxiety, difficulty sleeping, runny nose, yawning, large pupils, goose bumps, abdominal pain and cramping, diarrhea, vomiting, irritability, aches, and flu-like symptoms. I understand that opioid withdrawal is uncomfortable but not physically life threatening.

_____ There is a risk that opioid addiction may occur. This most commonly occurs in, but is not limited to, patients with a personal or family history of other drug or alcohol abuse. If my prescriber of opioids believes I may be developing addiction, I should expect that I will be taken off opioids.

**I agree to the following (initial each):**

_____ I agree to take the medication, _____(name) as prescribed. If problems arise, including adverse effects, I agree to promptly notify my prescriber.

_____ I agree to obtain opioids from **ONE** designated licensed prescriber.

_____ I agree to obtain opioids from **ONE** designated licensed pharmacist or pharmacy. By signing this agreement, I give consent to this provider to talk with the pharmacist.

_____ I agree to take the following non-opioid medication(s) as prescribed:

_____

_____

_____ I agree to attend and fully participate in all appointments, treatments, examinations and consultations of my pain treatment which may be requested by my prescriber at any time.

_____ I agree to attend and fully participate in a regular exercise program if required. My specific exercise program is:
_____

_____ I agree to participate in fear avoidance belief training and/or cognitive behavior therapy if prescribed.

_____ I will participate fully in any psychiatric or psychological assessments if necessary.

_____ I agree to keep my scheduled appointments and/or cancel my appointment a minimum of 24 hours prior to the appointment. I agree to provide a reason for canceling any appointment.

_____ I understand that lack of improvements in function or a later loss of those functional benefit(s) are reasons that my prescriber may discontinue the opioid.

_____ I agree to **NOT** take more opioid medication than prescribed. I agree to **NOT** take doses of opioids more frequently than prescribed.

_____ I agree that in the event of an emergency potentially requiring pain medication, I will notify the emergency department or other treatment facility of this agreement. I will ask that this prescriber be contacted and the problem should be discussed with the emergency department or other treating provider. I agree that no more than 3 days of medications may be prescribed by the emergency department or other provider without this provider's approval. If a situation arises in which I have no alternative but to obtain my necessary prescription from another prescriber (e.g., out of the country), I will then immediately advise my prescriber that I obtained a prescription from another prescriber.

_____ I agree to keep the opioid medication in a safe and secure place. I will keep all medications away from children.

_____ I understand that lost, damaged, or stolen medication will **NOT** be replaced.

_____ I agree to immediately report stolen opioid medication(s) to the police. My provider will also produce a police report if requested to do so.

_____ I agree not to share, sell, or in any way provide my medication to **ANY** other person.

_____ I agree to not use **ANY** other mood-modifying drugs, including alcohol (and marijuana if legal in my state), unless agreed to by my prescriber. Use of nicotine and caffeine are exceptions to this restriction.

_____ I agree to not use sedating over-the-counter medications, including diphenhydramine (e.g., Bendaryl).

_____ I agree to discuss any medication with a warning label that states it causes drowsiness or sleepiness with my prescriber prior to taking it.

_____ I agree to submit to unscheduled urine, blood, saliva, or hair drug testing at my prescriber's request, to verify my compliance.

_____ I agree that an abnormal urine, blood, saliva, or hair test will likely result in an end to the treatment with opioids. This includes a finding of a substance not expected (e.g., marijuana and/or illicit drugs).

_____ I understand that, if applicable, my prescriber may check my state's controlled substances database and/or Prescription Monitoring Database at any time to check my compliance.

_____ I agree to be seen by an addiction specialist if requested.

_____ I hereby agree that my provider has the authority to discuss my pain and opioid management with other health care professionals and my family members and/or significant others when it is deemed medically necessary in the provider's judgment. I agree to involve family and/or significant others in periodic assessments of my progress.

**I have read this document. I understand it and have had all my questions answered satisfactorily. I consent to the use of opioids to improve my functioning through hopefully controlling my pain. I understand that my treatment with opioids will be carried out as described above. I understand that ANY deviation(s) from the above agreement are grounds for my prescriber to stop prescribing opioids at any time.**

_____ _____

Patient Signature Date

_____ _____

Prescriber Signature Date

*Adapted from the Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain, Utah Department of Health, 2009; U.S. Veterans Affairs Administration, Clinical Practice Guideline: Management of Opioid Therapy for Chronic Pain, 2010; and Washington State Department of Labor & Industries, Washington Agency Medical Directors' Group, Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain: An educational aid to improve care and safety with opioid therapy, 2010 Update.*

## Appendix 2: Drug Interactions between Methadone or Buprenorphine and other Medications

| HIV Medications | Methadone | Buprenorphine |
|---|---|---|
| AZT (Zidovudine)[1] | Increase in AZT concentrations; possible AZT toxicity[918] (McCance-Katz 98) | No clinically significant interaction[919] (McCance-Katz 01) |
| Didanosine[2] (in tablet form) | Significant decrease in Didanosine concentrations[920] (Rainey 00) | |
| Stavudine[2] | Significant decrease in Stavudine concentrations[920] (Rainey 00) | |
| Delavirdine[2] | Increased methadone (and LAAM) concentrations; no cognitive impairment[921] (McCance-Katz 06) | Increased buprenorphine concentrations; no cognitive impairment |
| Atazanavir[2] | Not associated with increased levels of methadone[922] (Atazanavir Product Label) | Significant increases in buprenorphine and report of cognitive dysfunction[923] (Freimuth 96) |
| Darunavir[2] | Opiate withdrawal may occur[924] (Darunavir Product Label) | |
| Efavirenz[2] | Opiate withdrawal may occur[925-929] (Back 03; McCance-Katz 02; Boffito 02; McCance-Katz 03; McCance-Katz 05) | No clinically significant interaction[930-932] (McCance-Katz 06; McCance-Katz 06b; McCance-Katz in press) |
| Fosamprenavir[1] | Data suggest that the PK interaction is not clinically relevant; however, patients should be monitored for opiate withdrawal symptoms[933] (Fosamprenavir Product Label) | |
| Nelfinavir[1] | Methadone levels are decreased. Opiate withdrawal may occur.[934] (Nelfinavir Product Label) | No clinically significant interaction[930-932] (McCance-Katz 06; McCance-Katz 06b; McCance-Katz in press) |
| Nevirapine[2] | Opiate withdrawal may occur[925-929] (Back 03; McCance-Katz 02; Boffito 02; McCance-Katz 03; McCance-Katz 05) | No clinically significant interaction[930-932](McCance-Katz 06; McCance-Katz 06b; McCance-Katz in press) |
| **Tuberculosis Medications** | | |
| Rifampin[2] | Opiate withdrawal may occur[935] (McCance-Katz 09) | Opiate withdrawal may occur[935] (McCance-Katz 09) |
| Rifabutin[2] | Not clinically significant interaction[936] (Brown 96) | Not studied |
| **Hepatitis C** | | |
| Interferon | Not clinically significant interaction[937, 938] (Berk 07; Gupta 07) | |
| Ribavirin[2] | Not studied | |
| **Other Infections** | | |
| Fluconazole[2] | Increased methadone plasma concentrations[939] (Physician's Desk Reference 05) | |
| Voriconazole[2] | Increased methadone plasma concentrations[939] (Physician's Desk Reference 05) | |
| Ciprofloxacin[2] | Increased methadone plasma concentrations[940] (Karin 00) | |
| Biaxin, Clarithromycin[2] | Increased methadone plasma concentrations[939] (Physician's Desk Reference 09) | |
| **Antidepressants** | | |
| Fluoxetine[2] | Not associated with increased levels of methadone[941] (Bertschy 96) | |
| Fluvoxamine[2] | May cause increased methadone plasma levels and discontinuation has been associated with onset of opioid withdrawal[942] (Bertschy 94) | |

| HIV Medications | Methadone | Buprenorphine |
|---|---|---|
| Sertraline[2] | No associated adverse drug interaction[943] (Hamilton 00) | No clinically significant interaction[943] (Hamilton 00) |
| Citalopram[2] | No clinically significant interaction[944] (Dvir 08) | No clinically significant interaction[944] (Dvir 08) |
| Mirtazepine[2] | No clinically significant interaction | |
| Duloxetine[2] | Potentially lead to increased duloxetine exposure[945] (Gore 08) | |
| Amitriptyline[2] | Could be associated with increases in plasma methadone concentrations[946] (Bomsien 07) | |
| St. John's Wort[3] | Increased metabolism and elimination of methadone[947] (Di 08) | Increased metabolism and elimination of buprenorphine[947] (Di 08) |
| Desipramine[1] | Associated with increased Desipramine levels[948] (Maany 89) | |
| Dextromethorphan[2] | Associated with delirium[949] (Lotrich 05) | |
| **Antipsychotics** | | |
| Quetiapine[2] | Increased plasma methadone concentrations[950] (Uehlinger 07) | |
| Risperidone[2] | No clinically significant interaction | No clinically significant interaction |
| Clozapine[2] | No clinically significant interaction | No clinically significant interaction |
| Aripiprazole[2] | No clinically significant interaction | No clinically significant interaction |
| Olanzapine[2] | No clinically significant interaction | No clinically significant interaction |
| Ziprasidone[2] | No clinically significant interaction | No clinically significant interaction |
| **Anticonvulsants** | | |
| Carbamazepine[2] | Associated with opiate withdrawal[951] (Perucca 06) | Not studied |
| Phenytoin[2] | Associated with opiate withdrawal[951] (Perucca 06) | Not studied |
| Phenobarbital[2] | Associated with opiate withdrawal[951] (Perucca 06) | Not studied |
| Oxcarbazepine[2] | No clinically significant interaction | No clinically significant interaction |
| Lamotrigine[2] | No clinically significant interaction | No clinically significant interaction |
| Topiramate[2] | No clinically significant interaction | |
| **Psychostimulant Medications** | | |
| Methylphenidate[2] | No clinically significant interaction | No clinically significant interaction |
| Pemoline[2] | No clinically significant interaction | No clinically significant interaction |
| Modafinil[2] | No c clinically significant interaction | No clinically significant interaction |
| **Antihistamines** | | |
| Promethazine[2] | May have synergistic depressant effect[952] (Sharma 03) | |
| Diphenhydramine[2] | May have synergistic depressant effect[952] (Sharma 03) | |
| **Cardiac and Pulmonary Disease Medications** | | |
| Digoxin[2] | Not studied | Not studied |
| Quinidine[2] | Not studied | Not studied |
| Verapamil | Not studied | Not studied |
| Heparin[1] | Not studied | Not studied |
| Theophylline[2] | Not studied | Not studied |
| Aspirin[2] | No clinically significant interaction | |
| **Psychostimulants** | | |
| Cocaine[2] | Decrease in trough methadone concentrations[953] (McCance-Katz 10) | Increased metabolism and diminished plasma concentrations[954-957] (McCance-Katz 10; Pellinen 96; Lopez 05; Madden 95) |
| Methamphetamine[2] | No clinically significant interaction | |

| HIV Medications | Methadone | Buprenorphine |
|---|---|---|
| **Alcohol**[2] | Severe adverse events including death,[958] (Kreek 84) alcohol appears to be eliminated more frequently.[959] (Kreek 81) | Not studied |

*Adapted from: McCance-Katz EF, Sullivan LE, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. Am J Addict. 2010;19(1):4-16.*

# 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
- Troleandomycin
- Zafirlukast
- Itraconazole
- Ketoconazole
- Metronidazole
- Mibefradil
- Miconazole
- Nefazodone

## CCBs

- Amlodipine
- Diltiazem
- Felodipine
- Nicardipine
- Nifedipine
- Verapamil

## Statin

- Simvastatin

## Antiarrhythmic Agents

- Amiodarone
- Quinidine

## Phosphodiesterase Inhibitor

- Tadalafil

## Psychiatric Drugs

- Bromocriptine
- Clonazepam
- Desipramine
- Fluoxetine
- Fluvoxamine
- Haloperidol
- Nefazodone
- Norclomipramine
- Nortriptyline
- Sertraline

## Chemotherapeutic agents

- 4-Ipomeanol
- Imatinib
- Irinotecan
- Tamoxifen

## Hormonal therapies

- Ethinyl estradiol
- Levonorgestrel
- Raloxifene

### Other drugs

- Cimetidine
- Disulfiram
- Methylprednisolone
- Phenelzine

### Foods

- Bergamottin
- (grapefruit juice)
- Star fruit

### Antibiotics

- Ciprofloxacin
- Clarithromycin
- Erythromycin
- Josamycin
- Norfloxacin
- Oleandomycin
- Roxithromycin
- Telithromycin

### Azole Antifungal Agents

- Clotrimazole
- Fluconazole
- Itraconazole
- Ketoconazole
- Miconazole
- Voriconazole

### Antiretroviral Agents

- Amprenavir
- Atazanavir
- Delavirdine
- Efavirenz
- Indinavir
- Lopinavir
- Ritonavir
- Nelfinavir
- Nevirapine
- Saquinavir
- Tipranavir

## 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

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

*Adapted from: Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement Protocol (TIP) Series 43. HHS Publication No. (SMA) 12-4214.Rockville, MD: Substance Abuse and Mental Health Services Administration, 2005 and Smith HS. Opioid metabolism. Mayo Clin Proc. 2009;84(7):613-24.*

## Appendix 4: Low-quality Randomized Controlled Trials and Non-randomized Studies

The following low-quality randomized controlled studies (RCTs) and other non-randomized studies were reviewed by the Evidence-based Practice Opioids Panel to be all inclusive, but were not relied upon for purpose of developing this document's guidance because they were not of high quality due to one or more errors (e.g., lack of defined methodology, incomplete database searches, selective use of the studies and inadequate or incorrect interpretation of the studies' results, etc.), which may render the conclusions invalid. ACOEM's Methodology requires that only moderate- to high-quality literature be used in making recommendations.[9]

## Appendix 5: Randomized Controlled Trials with Malignant Pain

The following randomized controlled studies (RCTs)[451-455, 960] (Ahmedzai 11; Mercadante 00; Arai 10; Slatkin 07; Rodriguez 08; Stambaugh 87) were reviewed by the Evidence-based Practice Opioids Panel to be inclusive, but were not relied upon for purpose of developing this document's guidance because this document addresses non-malignant pain. These are provided for interested readers.

## Appendix 6: PICO Questions

1. What evidence supports the need for a comprehensive history and physical examination prior to prescribing opioids?
2. What evidence supports the use of opioids in workers performing safety-sensitive jobs?
3. Should opioids be recommended for the treatment of non-severe acute pain, and if so, under what circumstances?
4. Should opioids be recommended for the treatment of acute severe pain, and if so, under what circumstances?
5. What evidence supports initial screening of patients prior to initiation of opioid treatment?
6. What is the evidence for maximum daily oral opioid dosing for patients with acute pain?
7. Are opioids superior to other medications or treatments for acute, subacute, chronic or post-operative pain relief and functional improvement?
8. Does evidence support the use of opioids for post-operative (up to 4 weeks) pain?
9. Should patients be screened prior to continuation of opioids 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 opioids 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 addresses the balance of risks and benefits of opioid use for acute, subacute, chronic and post-operative pain?
15. What evidence supports the use of an opioid treatment agreement (opioid contract, doctor/ patient agreement, informed consent)?
16. Is there evidence to support efficacy for opioid treatment agreements?
17. What evidence supports urine drug testing for opioid use?
18. What is the prevalence of aberrant urine drug testing results among patients on opioids for treatment of chronic pain?
19. Is there evidence to support opioid rotation?
20. What evidence supports discontinuation and/or tapering of opioids?
21. Does evidence support the use of buprenorphine for opioids tapering?
22. What is the evidence for the use of methadone as a tapering agent?
23. Is there evidence for using opioids for breakthrough non-malignant pain?
24. What evidence supports the use of intrathecal drug delivery systems for chronic non-malignant pain conditions?
25. What evidence supports the use of naloxone (narcan) for opioid overdose?
26. Is there evidence that screening for risk factors is effective for reducing the adverse effects of opioids?
27. What evidence exists for a dose-response relationship between morphine equivalent dose and overdoses, fatalities and other adverse effects?

## Appendix 7: List of Abbreviations

BTP Break-Through Pain

CAGE-AID Cut down, Annoyed, Guilty, Eye-opener—Adapted to Include Drugs

CLIA Clinical Laboratory Improvement Amendments

CNS Central Nervous System

COMM Current Opioid Misuse Measure

COPD Chronic Obstructive Pulmonary Disease

DSM-V Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

ECG Electro-Cardiogram (same as EKG, electrokardiogram)

GC/MS Gas Chromatography Mass Spectrometry

GCPS Graded Chronic Pain Scale

LC/MS Liquid Chromatography Mass Spectrometry

MED Morphine Equivalent Dose (equivalent to MME)

MME Morphine Milligram Equivalents (equivalent to MED)

NSAID Nonsteroidal Anti-Inflammatory Drug

ORT Opioid Risk Tool

PCA Patient-Controlled Analgesia

PDMP Prescription Drug Monitoring Program

PEG Average Pain Intensity (P), Interference with Enjoyment of Life (E), and Interference with General Activity (G).

PHQ-9 Patient Health Questionnaire, Ninth edition PMQ Patient Medication Questionnaire

PNS  Periphernal Nervous System

POC Point of Care

POMI Prescription Opioid Misuse Index

PTSD Post-Traumatic Stress Disorder

RCT Randomized Controlled Trial

SIMP Structured Intensive Multidisciplinary Program

SOAPP-R Screener and Opioid Assessment for Patients with Pain–Revised TICS Two-Item Conjoint Screen

UDS Urine Drug Screen (same as UDT)

UDT Urine Drug Test (same as UDS)

WHYMPI West Haven-Yale Multidimensional Pain Inventory

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