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INTERAGENCY GUIDELINE ON PRESCRIBING OPIOIDS FOR PAIN

Developed by the Washington State Agency Medical Directors' Group (AMDG)*
in collaboration with Senior State Officials, an Expert Advisory Panel, Actively
Practicing Providers, and Public Stakeholders

*The AMDG is a collaboration of state agencies working together to improve
health care quality for Washington State Citizens.

www.agencymeddirectors.wa.gov

*Written for Clinicians
who Care for Patients
with Pain
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Table of Contents

COMPARISON OF 2010-2015 GUIDELINES	4
INTRODUCTION	5
Correct Diagnosis and Realistic Expectations	5
Uncertain Long-term Efficacy, Clear Evidence of Harm.....	6
Opioids and Chronic Disability	7
PART I. RECOMMENDATIONS FOR ALL PAIN PHASES	8
Clinically Meaningful Improvement in Function (CMIF)	8
Dosing Threshold	11
Non-opioid Options for Pain Management	13
PART II. PRESCRIBING OPIOIDS IN THE ACUTE AND SUBACUTE PHASE	21
Opioids in the Acute Phase	21
(0-6 weeks post episode of pain or surgery).....	21
Opioids in the Subacute Phase	22
(6 and 12 weeks post episode of pain or surgery).....	22
PART III. OPIOIDS FOR PERIOPERATIVE PAIN	25
Preoperative Period	25
Intraoperative Period.....	26
Immediate Postoperative Period	26
At Time of Hospital Discharge.....	27
PART IV. PRESCRIBING OPIOIDS FOR CHRONIC NON-CANCER PAIN	31
Opioids in the Chronic Phase	31
(>12 weeks after an episode of pain or surgery)	31
PART V. REDUCING OR DISCONTINUING CHRONIC OPIOID ANALGESIC THERAPY (COAT)	35
Reason to Discontinue COAT and Considerations Prior to Taper.....	35
How to Discontinue Opioids	36
PART VI. RECOGNITION AND TREATMENT OF OPIOID USE DISORDER	39
PART VII. CHRONIC PAIN MANAGEMENT IN SPECIAL POPULATIONS	41
Managing Chronic Pain during Pregnancy and Neonatal Abstinence Syndrome	41
Managing Chronic Non-cancer Pain in Children and Adolescents.....	44
Managing Chronic Pain in Older Adults	46
Managing Chronic Pain in Cancer Survivors	48
PART VIII. APPENDICES	53
Appendix A: Opioid Dose Calculations.....	54
Appendix B: Validated Tools for Screening and Assessment.....	57
Appendix C: How to use the Prescription Monitoring Program	58

Appendix D: Urine Drug Testing for Monitoring Opioid Therapy	60
i. Monitoring Opioid Therapy with Urine Drug Testing (UDT)	60
ii. UDT Algorithm for Monitoring Opioid Therapy	60
iii. UDT Clinical Vignettes	60
iv. Frequently Asked Questions (FAQs) about UDT.....	60
Appendix E: Chronic Pain Syndromes in Cancer Survivors	70
Appendix F: Diagnosis-based Pharmacotherapy for Pain and Associated Conditions	72
Appendix G: Patient Education Resources.....	74
Appendix H: Clinical Tools and Resources	76
Appendix I: AGREE Criteria.....	79
ACKNOWLEDGEMENTS	84
REFERENCES.....	86

Table of Figures and Tables

Figure A. Three Item PEG Assessment Scale.....	9
Figure B. Two Item Graded Chronic Pain Scale.....	9
Figure C. Risk of Overdose Events in Four Different Populations	11
Figure D. Infant Hospitalizations for Neonatal Abstinence Syndrome in WA State 1990-2013	43
Figure E: UDT Algorithm for Monitoring COAT for CNCP.....	65
Table 1. Cognitive Behavioral and Non-pharmacological Therapies for Chronic Pain	13
Table 2. "Red Flags" Indicating Need for Further Patient Evaluation.....	14
Table 3. Recommended Sleep Hygiene Habits	15
Table 4. Risks for Over-sedation and/or Respiratory Depression from Postoperative Opioids ¹⁴⁶⁻¹⁵⁵	28
Table 5. Risks for Difficult-to-control Postoperative Pain ¹⁵⁶⁻¹⁶⁴	28
Table 6. How Often to Evaluate Function and Pain in Patients on COAT	33
Table 7. Prescribing Methadone for Pain Management.....	33
Table 8. When to Reduce, Taper, or Discontinue COAT	35
Table 9. Aberrant Behaviors.....	37
Table 10. Symptoms and Treatment of Opioid Abstinence Syndrome (withdrawal).....	37
Table 11. Common Pain Syndromes Resulting from Cancer Treatment*	50
Table 12. Signs and Symptoms Associated with Malignancy that Warrant Assessment for Cancer Recurrence	51
Table 13. Signs and Symptoms of Spinal Cord Compression	52
Table 14. Dosing Threshold for Selected Opioids	54
Table 15. MED for Selected Opioids	55
Table 16. MED for Methadone	56
Table 17. Morphine Equivalent Dose Calculation.....	56
Table 18. Recommended Frequency of PMP Checks during COAT	59

Comparison of 2010-2015 Guidelines

2010 Guideline	2015 Guideline
<p>Primary focus was on chronic non-cancer pain</p> <p>Two main sections:</p> <ol style="list-style-type: none"> I. Initiating, transitioning, and maintaining patients on chronic opioid analgesic therapy (COAT) with principles of safe prescribing, and II. Optimizing treatment for patients on > 120mg daily MED with brief sections on getting consultations, aberrant behaviors, tapering, and discontinuing COAT. <p>Appendices:</p> <ol style="list-style-type: none"> A. Opioid Dose Calculations & Calculator B. Screening Tools C. Tools to Assess Pain and Function D. Urine Drug Testing for COAT E. Consultative Assistance for WA State Payers F. Patient Education Resources G. Sample Doctor-patient Agreement for COAT H. Additional Resources to Streamline Clinical Care I. Emergency Department Opioid Guidelines <p>Recommended 120mg daily MED as a “yellow flag” dose as a strategy to prevent adverse events and overdose by advising providers to seek a consultation with a pain specialist.</p> <p>Organized as narrative information and recommendations with evidence in citations.</p>	<p>Expands focus to include opioid use in acute, subacute, and perioperative pain phases and in special populations.</p> <p>New and modified sections:</p> <ol style="list-style-type: none"> I. Recommendations for All Pain Phases <ol style="list-style-type: none"> a. Clinically Meaningful Improvement in Function b. Expanded discussion on dosing threshold c. Non-opioid Options for Pain Management II. Opioids in the Acute and Subacute Pain Phases III. Opioids in the Perioperative Phase IV. Opioids in Chronic Non-cancer Pain (similar to previous guideline) V. New section on tapering / discontinuing COAT VI. New section on recognizing and treating substance use disorder VII. New sections on opioid use during pregnancy, neonatal abstinence syndrome, opioid use in children and adolescents, in older adults, and in cancer survivors. <p>Appendices:</p> <ol style="list-style-type: none"> A. Opioid Dose Calculations & Calculator B. <i>Renamed:</i> Validated Risk Factor Screening Tools and combines former appendices B and C. C. How to use the Prescription Monitoring Program D. Urine Drug Testing for COAT E. Chronic Pain Syndromes in Cancer Survivors F. Diagnosis-based Pharmacotherapy for Pain G. Patient Education Resources (updated) H. <i>Renamed:</i> Clinical Tools and Resources and combines former appendices G, H, and I I. AGREE criteria <p>Remains the same, plus adds guidance for safe prescribing <u>at any dose</u>, based on new studies showing significant risks occurring at lower doses.</p> <p>Organized with each section having specific clinical recommendations with supporting narrative evidence sections with citations.</p>

Introduction

This is the 3rd Edition of the Washington State (WA) Agency Medical Directors' Group's (AMDG) interagency opioid guideline. First developed in 2007, and updated in 2010, all guidelines were developed in collaboration with a broad advisory group of the state's academic leaders, pain experts, and clinicians in both primary care and specialty areas in response to the growing epidemic of opioid-related unintentional overdoses.⁵ This guideline followed a rigorous and transparent development process and is designed as an easy-to-use reference to help primary care clinicians; each section includes a set of clinical recommendations, followed by supporting evidence, and there are several resources in the appendices.

This guideline offers a **balanced approach** to pain management that includes recommendations for using opioids when appropriate, such as with acute injuries and flare ups, for postoperative pain management, and during painful procedures; and recommending multimodal non-opioid therapies in general for all chronic pain patients. This guideline supplements the WA State Department of Health's pain management rules¹ requiring best practices in the prescribing of opioids for chronic non-cancer pain. In keeping with these rules, use of opioids for patients receiving hospice and palliative care during active cancer or terminal conditions is outside the scope of this guideline.

Monitoring and vigilance are critical to ensure effective and safe use of opioids for the thousands of WA citizens who are on opioids chronically, especially for those on high doses.

Correct Diagnosis and Realistic Expectations

Effective treatment of pain begins with an accurate diagnosis. Beyond the acute injury, the underlying cause of ongoing pain can be difficult to identify. Pain is generally described as either nociceptive (somatic) or neuropathic, but symptoms may not fit neatly into one group, often overlap and may change over time. Another common way to categorize pain is based on chronicity. Acute pain, whether related to disease, injury, or recent surgery, usually diminishes with tissue healing, whereas chronic pain typically lasts >3 months and involves neurological, emotional, and behavioral features that often impact a patient's quality of life, function, and social roles.⁶

Studies of interventions for chronic pain have often been of low quality, including problems associated with an increased risk of bias including difficulty with randomization and inadequate blinding.⁷ The best recent systematic reviews have shown only modest benefits.^{8,9} Patient expectations regarding expected outcomes may be unrealistic; expected outcomes should be balanced by potential risk of harm. Pursuing greater pain reduction via escalating opioid doses may contribute further to unrealistic expectations and even iatrogenic injury.

¹ WAC Chapter 246, authorized by ESHB 2876, Chapter 209 Laws of 2010

Uncertain Long-term Efficacy, Clear Evidence of Harm

While the earlier guidelines focused on how prescribers could safely and effectively prescribe and manage chronic opioid analgesic therapy (COAT), more recent data suggests that the focus should also be on preventing the inappropriate transition from acute and subacute opioid use to chronic opioid use and to avoid COAT altogether when other alternatives for treating pain may be equally effective and safer in the long-term.

Three recently published systematic reviews, which examine the effectiveness of opioids for chronic pain, provide little support for COAT: A review of randomized controlled trials (RCTs) of opioids for chronic non-cancer pain concluded that the overall effectiveness of opioids for pain was only modest, and that the effect on function was small.¹⁰ In a Cochrane review of observational studies of cases on longer duration treatment¹¹ the authors concluded, “The findings of this systematic review suggest that proper management of a type of strong painkiller (opioids) in well-selected patients with no history of substance addiction or abuse can lead to long-term pain relief for some patients...However, the evidence supporting these conclusions is weak, and longer-term studies are needed to identify the patients who are most likely to benefit from treatment.” The Agency for Healthcare Research and Quality’s (AHRQ) recent draft report, “The Effectiveness and Risks of Long-term Opioid Treatment of Chronic Pain,” which focused on studies of effectiveness measured at > 1 year of COAT use, found *insufficient* data on long-term effectiveness to reach any conclusion.¹²

Adverse events most commonly reported in randomized trials include constipation, nausea and vomiting, dizziness, and drowsiness.¹³ Much more serious long-term consequences of opioids have only been identified from observational and epidemiological investigations; these include abuse, inhibition of endogenous sex hormone production with resulting hypogonadism and infertility,¹⁴ immunosuppression,¹⁵ falls and fractures in older adults,¹⁶ neonatal abstinence syndrome,¹⁷ cardiac arrhythmia related to methadone,¹⁸ sleep disordered breathing,¹⁹ opioid-induced hyperalgesia,²⁰ nonfatal overdose hospitalizations,²¹ emergency department visits,²² and death from unintentional poisoning.²³

Opioid therapy is also associated with the development of physical dependence and addiction²⁴ ([DSM 5 Opioid Use Disorder](#)). The true incidence of these serious complications is unknown but is likely to affect more patients than was previously reported.^{12,25,26} In addition, the lack of a useful case definition for any of these dependent states makes it challenging for a primary care provider to identify and intervene appropriately.²⁰ Even with acute low dose opioids (1 – 36 mg/day morphine equivalent dose or MED), patients are at increased risk for developing opioid use disorder (OUD). The likelihood of developing OUD ranges from a 3-fold increase for acute low dose opioids, to a 122-fold increase for chronic high dose opioids (≥ 120mg/day MED) compared to patients who are not prescribed opioids.²⁶

Because there is little evidence to support long term efficacy of COAT in improving function and pain, and there is ample evidence of its risk for harm, prescribers should proceed with caution when considering whether to initiate opioids or transition to COAT.

Opioids and Chronic Disability

Despite evidence based guidelines recommending against their use, opioids are frequently prescribed as first line agents for low back sprain and other routine musculoskeletal conditions.^{9,27-29} In addition, there is evidence in the workers' compensation population that early opioid use increases the risk of disability³⁰ and it is difficult to discontinue COAT once initiated as over 60% of patients taking opioids for at least 3 months are still on opioids 5 years later.³¹ More effective early intervention strategies for acute low back pain are recommended to avoid transitioning to chronic low back pain.³² Routine musculoskeletal conditions are among the top causes of disease burden in the US as measured by Years Lived with Disability (YLD), accounting for nearly 8 million YLD in 2010.³³ By 2011, nearly 25% of disabled Medicare beneficiaries under 65 were on opioids chronically. Preventing the transition from acute and subacute pain to chronic pain and disability could have a significant impact on saving productive lives.³⁴

Although opioids benefit some patients if prescribed and managed properly for appropriate conditions, from a public health perspective, preventing the next group of Washington citizens from developing chronic disability due to unnecessary, ineffective, and potentially harmful COAT is a key objective of this guideline.

Part I. Recommendations for All Pain Phases

Clinically Meaningful Improvement in Function (CMIF)

Tracking function as well as pain is critical in determining the patient's ongoing response to opioids and whether any improvement is consistent with potential changes in opioid dosing. Because of the well documented evidence of risk and the limited evidence of effectiveness beyond the period of acute pain, the use of opioids should result in clinically meaningful improvement in function and pain and therefore, quality of life.

Clinically meaningful improvement is defined as an improvement in pain AND function of at least 30% as compared to the start of treatment or in response to a dose change. **A decrease in pain intensity in the absence of improved function is not considered meaningful improvement except in very limited circumstances such as catastrophic injuries (e.g. multiple trauma, spinal cord injury, etc.).**

COAT that focuses only on pain intensity can lead to rapidly escalating dosage with deterioration in function and quality of life. During the chronic phase, providers should routinely review the effects of opioid therapy on function to determine whether opioid therapy should continue. A brief but effective way to assess function is to determine the degree to which pain interferes with a patient's activities, as this is highly correlated with pain intensity when changes are tracked over time ([Figure A](#) and [Figure B](#)).

Continuing to prescribe opioids in the absence of clinically meaningful improvement in function and pain, or after the development of a severe adverse outcome (e.g. overdose event) is not considered appropriate care. In addition, the use of escalating doses to the point of developing opioid use disorder, as defined by DSM 5, is not appropriate.

Clinical Recommendations

1. Assess and document function and pain using validated tools ([Figure A](#) and [Figure B](#)) at each visit where opioids are prescribed.
2. Expect patients to improve in function and pain and resume their normal activities in a matter of weeks after an acute pain episode. Strongly consider re-evaluation for those who do not follow the normal course of recovery.
3. Evaluate function and pain using brief validated instruments at these three critical decision-making phases:
 - a. At the end of the acute phase (6 weeks following an episode of pain or surgery), to determine whether continued opioid therapy is warranted.
 - b. At the end of the subacute or perioperative phase (12 weeks following an episode of pain or surgery), to determine whether non-opioid treatment will help or if prescribing COAT is warranted.
 - c. During chronic use with regular assessment and documentation of function and pain ([Table 6](#)).

4. Use only validated instruments to measure clinically meaningful improvement in function and pain. The following tools have been validated and are easy ways to track function and pain:
 - a. PEG – A 3-item tool to assess Pain intensity, interference with Enjoyment of life, and interference with General activity.³⁵
 - b. Graded Chronic Pain Scale – A 2-item tool to assess pain intensity and pain interference.³⁶

Figure A. Three Item PEG Assessment Scale

1. What number best describes your <u>pain on average</u> in the past week:											
0	1	2	3	4	5	6	7	8	9	10	
No pain						Pain as bad as you can imagine					
2. What number best describes how, during the past week, pain has interfered with your <u>enjoyment of life</u>?											
0	1	2	3	4	5	6	7	8	9	10	
Does not interfere						Completely interferes					
3. What number best describes how, during the past week, pain has interfered with your <u>general activity</u>?											
0	1	2	3	4	5	6	7	8	9	10	
Does not interfere						Completely interferes					

Krebs 2009

Figure B. Two Item Graded Chronic Pain Scale

Graded chronic pain scale: a two-item tool to assess pain intensity and pain interference											
<p>In the last month, on average, how would you rate your pain? Use a scale from 0 to 10, where 0 is "no pain" and 10 is "pain as bad as could be"? [<i>That is, your usual pain at times you were in pain.</i>]</p>											
No pain						Pain as bad as could be					
0	1	2	3	4	5	6	7	8	9	10	
<p>In the last month, how much has pain interfered with your daily activities? Use a scale from 0 to 10, where 0 is "no interference" and 10 is "unable to carry on any activities."</p>											
No interference						Unable to carry on any activities					
0	1	2	3	4	5	6	7	8	9	10	

Patients who used opioids for at least 90 days were more than 60% likely to still be on chronic opioids in 5 years.

(Martin et al 2011 J Gen Int Med 2011; 26: 450-7)

Evidence

There is a broad consensus in published studies that a combination of outcome measures is superior to any single measure.^{37,38} A major emphasis in earlier studies has been on the MINIMUM clinically important difference (MCID) in outcome. This measure has been tailored to clinical trials of drugs and other interventions, however, more robust definitions may be necessary to clearly define outcomes important to patients. For example, one study prospectively defined a minimally acceptable degree of improvement in patients undergoing lumbar fusion, and found that these predefined outcomes established by patients themselves were not achieved.^{39,40} For this cohort of patients, a combination of four outcomes included:

1. At least a 3/10 decrease in pain, AND
2. An improvement of at least 20 points on the Oswestry Disability Index, AND
3. Discontinuation of opioid medications, AND
4. Return to some occupational activity.

There is no completely safe opioid dose. COAT patients should be routinely assessed for risk as medical conditions and life circumstances may change during treatment.

(Fulton-Kehoe et al 2015 in press)

Based on the literature and expert consensus for low back pain, a 30% improvement in principal outcome measures (pain and function) was considered clinically meaningful.⁴¹ This degree of improvement has also been validated in low back pain compared to actual measures of physical function.⁴² For acute post-op pain, a 35-45% decrease in pain was associated with reported acceptable improvement to patients.⁴³ In a short term prospective study of patients with arthritis undergoing steroid injections, patient-perceived satisfactory improvement was associated with a 55% improvement on a visual analogue scale.⁴⁴ Considering the potential long-term risks of opioid therapy and based on the published literature and expert consensus, two other groups have chosen a 30% improvement in pain and function to be critical for assessing changes from baseline for both acute/subacute and for chronic pain in patients placed on opioids: Washington (final) and California (draft) State Workers' Compensation Programs.ⁱⁱ

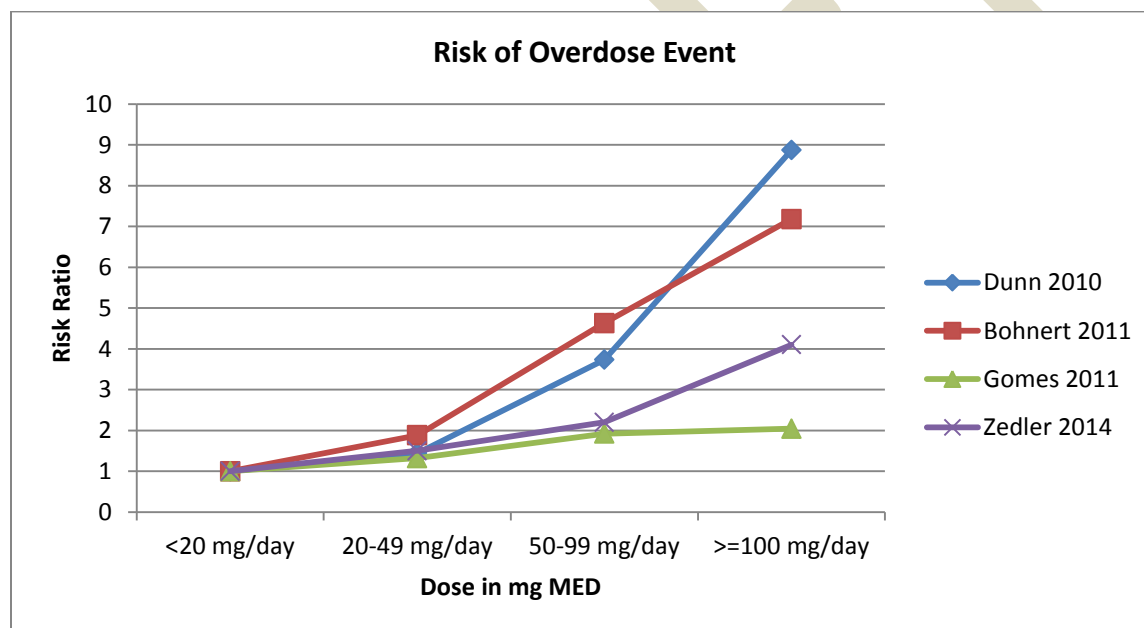
ⁱⁱ <http://www.lni.wa.gov/ClaimsIns/Files/OMD/MedTreat/FINALOpioidGuideline010713.pdf> and <http://www.dir.ca.gov/dwc/dwcwcaforum/Opioids.htm>

Dosing Threshold

While there is evidence that opioids can provide significant pain relief in the short term there is little evidence for sustained improvement in function and pain relief over longer periods of time. COAT is associated with the development of tolerance, a decrease in analgesic effect with the same dose over time. Providers must pay attention to the development of tolerance and avoid ongoing dose escalation to overcome this effect.

The 2010 edition recommended a 120 mg/day MED threshold to seek a consultation with a pain specialist as a strategy to prevent serious adverse outcomes including fatal overdoses. Subsequent studies have supported this dose-related risk and have shed new light on significant risks occurring at even lower doses. Overdose risk approximately doubles at doses between 20 and 49 mg/day MED, and increases nine-fold at doses of 100 mg/day MED or more (Figure C). There is no completely safe opioid dose. Some states and organizations have chosen lower dose thresholds ranging from 50 to 90 mg/day MED, but this edition has maintained the 120 mg/day MED threshold for consultation.

Figure C. Risk of Overdose Events in Four Different Populations



Providers should be especially cautious and assess risk for ongoing opioid therapy when transitioning patients from acute opioid use to COAT, continuing COAT at a dose to which a patient has already become accustomed, or escalating the opioid dose. This guideline provides an electronic [morphine equivalent dose \(MED\) calculator](#) for determining dose when a patient is on one or more opioids. The calculator should not be used to determine doses when converting a patient from one opioid to another.

There is a correlation between the amount of opioids prescribed for patients and their potential availability for diversion, with associated risks for individuals in the community. The recommendations below are intended to reduce the risks to both patients and the community.

Clinical Recommendations

1. **Avoid** COAT if the patient has any of the following FDA or clinical contraindications:
 - a. Significant respiratory depression (e.g. respiratory failure), acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected paralytic ileus or hypersensitivity (e.g. anaphylaxis)
 - b. Current substance use disorder as defined by DSM 5 (except tobacco) or past opioid use disorder
 - c. History of prior opioid overdose
 - d. Pattern of aberrant behaviors ([Table 9](#))
2. Use great caution at any dose and monitor more frequently if the patient has one or more of the following risk factors:
 - a. Mental health disorder per DSM 5
 - b. Family or personal history of substance use disorder
 - c. Medical condition that could increase sensitivity to opioid-related side effects (e.g. impaired respiratory function, sleep apnea, high fall risk, altered drug metabolism related to advanced age or impaired renal, hepatic and/or cardiac function)
 - d. Current use of benzodiazepines
 - e. Tobacco use
3. **Do not prescribe** more than 120 mg/day MED without first obtaining a consultation from a trained pain specialistⁱⁱⁱ who agrees that a high dose is indicated and appropriate. Providers must routinely monitor and document sustained improvement in function and quality of life and an absence of the risk factors listed in recommendations 1 and 2.

Evidence

A review of randomized controlled trials (RCTs) of opioids for chronic non-cancer pain, concluded that the overall effectiveness of opioids for pain was only modest, and that the effect on function was small.¹⁰ Recent published systematic reviews examining the effectiveness of opioids for chronic pain found insufficient data to support the wide prescribing of COAT.^{11,12,45} However, epidemiological studies have shown that patients on COAT who are receiving > 100 mg/day MED have up to nine times the risk of overdosing compared to those on 20 mg/day MED, and for every seven overdoses, one was fatal.⁴⁶⁻⁴⁹ These studies further showed that even at doses between 50 and 100 mg/day MED, than the risk was 2.2 to 4.6 times higher compared to doses < 20mg/day MED.^{46,47,49} While the majority of overdose deaths occur in higher dose patients, recent studies in WA workers' compensation and Medicaid have shown that nearly half of all overdose hospitalizations occur in patients who are on intermittent or lower dose opioids.⁵⁰⁻⁵²

ⁱⁱⁱ DOH Prescribing Rules defining [Pain Specialist](#) are listed in five separate rules according to each license type; all are in the Washington Administrative Code Chapter 246, subsections 919 (MDs); 853 (DOs); 922 (DPMs); 817 (Dentists); 840 (ARNPs); and 854 and 918 (PAs – working with DOs or MDs respectively).

Studies have also shown dose-dependent increases in other serious adverse outcomes such as falls, fractures, and motor vehicle accidents.⁵³ At high doses, patients are at higher risk for poor functional status, increased pain sensitivity, and continuation of chronic opioids for a prolonged period.^{20,30,31} While a cause and effect relationship is unclear, patients on high dose opioids are more than likely to have high risk characteristics, such as mental health disorder, a substance use disorder, and/or opioid misuse.³¹

Chronic opioid analgesic therapy is also associated with the development of tolerance to its analgesic effects.^{20,54} Evidence is accumulating that opioid therapy may also paradoxically induce abnormal pain sensitivity, including hyperalgesia and allodynia.⁵⁵⁻⁵⁷ In addition, higher strength opioids may be associated with poorer functional outcomes than lower strength opioids.¹³ Thus, increasing opioid doses may not improve function and pain control but will expose the patients to the risk of dose-dependent adverse outcomes.

The amount of opioids prescribed for patients and their potential availability for diversion has been identified as one of seventeen determinants of opioid-related mortality.⁵⁸ Communities with higher rates of prescribing experience higher overall overdose rates, even amongst individuals without prescriptions.

Non-opioid Options for Pain Management

Non-pharmacological Interventions

Pain is a multidimensional experience; so therefore, pain management is most effective when a multimodal approach is utilized ([Table 1](#)). In addition to medication, therapies should include physical activation and behavioral health interventions (such as cognitive behavioral therapy, mindfulness, coaching, patient education, and self-management.)

Table 1. Cognitive Behavioral and Non-pharmacological Therapies for Chronic Pain

Cognitive: Address distressing negative cognitions and beliefs, catastrophizing (pain coping characterized by excessively negative thoughts and statement about the future)

Behavioral approaches: Mindfulness, meditation, yoga, relaxation, biofeedback

Physical: Activity coaching, graded exercise

Spiritual: Identify existential distress, seek meaning and purpose in life

Education (patient and caregivers): Promote patient efforts aimed at increased functional capabilities

Adapted from Argoff, 2009 & Tauben, 2015

Clinical Recommendations

1. Perform a thorough history and physical examination at initial visit for pain management.
2. Do not pursue diagnostic tests unless risk factors or “red flags” indicate the need for further evaluation ([Table 2](#)), especially getting an MRI in the first 6 weeks following low back injury

<http://www.choosingwisely.org/american-society-of-anesthesiologists-asa-releases-choosing-wisely-list-for-pain-medicine/>.

3. Re-evaluate the patient for other diagnoses if pain persists beyond a few weeks, or if “red flags” develop ([Table 2](#)).
4. Identify functional goals that are important to the patient, as this increases the likelihood that treatment will improve quality of life, even if the pain intensity rating itself does not change.
5. Engage patients in behavior change counseling that promotes self-care and consider emphasizing evidence-based principles of motivational interviewing ([Appendix H: Clinical Tools and Resources](#)).
6. Use powerful interventions such as listening, providing reassurance, and involving the patient in his or her care.
7. Do not prescribe analgesics or perform interventions (e.g. injections) without also tracking pain and function over time using validated instruments.
8. Use validated instruments to assess predictors of suboptimal recovery such as depression, fear avoidance, and catastrophizing, which can lead to persistent pain and functional limitation ([Appendix B: Validated Tools for Screening and Assessment](#)).
9. Consider behavioral interventions to improve patient self-efficacy and address psychosocial barriers to recovery, such as cognitive behavioral therapy, mindfulness based stress reduction (MBSR), yoga, various forms of meditation and chronic pain self-management.
10. Recommend graded exercise unless contraindicated. Group exercise may have significant benefit and is available to most patients. Use of an activity diary may assist the patient and physician in monitoring progress.
11. Consider spinal manipulation in patients with low back pain.
12. Encourage and facilitate those who have work-related injuries, to participate in programs that coordinate efforts to help them get back to work. Do this early in their recovery.
13. Address sleep disturbances by encouraging sleep hygiene ([Table 3](#)) or effective pharmacological therapy (clinical recommendation #6 under Non-opioid Analgesics). Achieving a minimum of 6 hours of restful sleep per night is a reasonable goal.
14. Refer patient to a multidisciplinary rehabilitation program if s/he has significant, persistent functional impairment due to complex chronic pain.

Table 2. "Red Flags" Indicating Need for Further Patient Evaluation

Presence of neurological deficit(s)
History of malignancy
New signs and symptoms of underlying disease
Sudden increase in severity or nature of previous pain complaint
Unexpected results from urinary drug tests e.g. for cocaine, amphetamines, alcohol etc.
Wounds that don't heal within normal time expectations
Evidence of adverse side effects from current treatment regimen

Adapted from Tauben 2015

Table 3. Recommended Sleep Hygiene Habits

Maintain a regular wake/sleep schedule: fixed bed and wake-up times, regardless of weekday or weekend.
Establish a relaxing routine before bedtime.
Refrain from taking naps.
Make the bedroom 'device-free:' no TV, computer, or handheld devices.
Use the bedroom only for sleep, intimacy, and dressing routines
Set environment (light, noise, temperature) at comfortable levels.
No caffeine after noon; some may need to avoid caffeine altogether.
No exposure to TV or computer screens 2 hours prior to bedtime
Exercise - but not within 3 hours of bedtime.
Avoid alcohol close to bedtime

Adapted from Tauben 2015

Evidence

Overtreatment, excess attention, or labeling a patient during the acute pain phase can precipitate or increase "sickness behavior," and avoidance of activity.⁵⁹ For example, in the absence of "red flags" that indicate the need for further evaluation ([Table 2](#)), obtaining an MRI in the first 6 weeks following low back injury, may lead to a cascade of further unnecessary treatments and escalating costs.⁶⁰ Further, there is value in having patients with work-related injuries participate in programs that help them return to work, as these appear to have a small but significant impact on reducing disability among those who have missed at least four weeks of work due to acute or subacute musculoskeletal pain.⁶¹

Importance of Activity: Unless contraindicated, advice to remain active and engaged in usual activity seems to be the most effective intervention early in the course of a pain episode. A well-studied example is low back pain with or without sciatica. For this condition, advice to remain active has been repeatedly shown to predict better pain and functional outcomes than advice to take bed rest, and is as effective as specific exercises.^{62,63} Aerobic and strengthening exercises have also been shown to reduce pain and disability in osteoarthritis of the knee,⁶⁴ but passive PT interventions have not demonstrated sustained benefit.⁶⁵ In subacute or chronic low back pain there is good evidence of moderate efficacy for exercise interventions.⁸ In a recent Cochrane review of interventions for subacute or chronic LBP, exercise obtained the best outcomes when done as part of an individualized regimen with supervision during strengthening and stretching.⁶⁶ Resistance exercise training and aerobic exercise in women with fibromyalgia may improve pain and multidimensional function.⁶⁷ Patient adherence to home exercise programs may be specifically important in evaluating the success of these interventions.⁶⁸ This is where keeping an activity diary can be especially helpful.

Psychosocial Factors: Psychosocial factors, such as fear of normal activity (fear avoidance), catastrophizing, and low expectations of healing are strong predictors of the development of persistent

pain in patient populations.⁶⁹⁻⁷¹ Interestingly, elevated fear-avoidance beliefs by like practitioners seeing similar patient populations can impact treatment outcomes adversely.⁷²

There is good evidence that cognitive behavioral therapy is effective in reduction of subacute or chronic low back pain and other chronic pain conditions, including chronic orofacial pain, chronic pain in children, fibromyalgia, persistent pain in the elderly, inflammatory bowel disease.^{8,73-82} The treatment of depression was shown to have significant benefits in terms of pain reduction, improved functional status and quality of life in a group of older individuals with depression and arthritis.⁸³ Other psychological therapies such as progressive relaxation and biofeedback aimed at muscle relaxation have not been shown to be superior to active exercise therapies in large cohorts for most outcomes in systematic reviews of low back pain treatment⁸ although both do provide benefit.

Group Support Activities: While patients with acute pain may not require medically supervised rehabilitation interventions, there is evidence to support their benefits in groups of individuals with atypical recovery or with chronic musculoskeletal pathology such as arthritis. Among the benefits that group interventions provide, chronic pain self-management programs are having increasing success at reducing the physical and psychosocial burden of chronic pain while reducing healthcare costs.⁸⁴ These evidence based programs teach strategies for understanding chronic pain and provide a support network with both clinician and lay led (by fellow chronic pain sufferers) workshops, 2.5 hours once a week for 6 weeks. These offer a free or low-cost community based model that has demonstrated short term improvements in pain and multiple quality of life variables.⁸⁵ Modeled after a national study of chronic disease self-management programs, these are being heralded as an effective way to meet the “triple aim goals’ of better health, better health care, and better value while reducing health care utilization.⁸⁶ For resources and workshop information, go to <http://livingwell.doh.wa.gov/workshops>.

Spinal Manipulation, Acupuncture, and Yoga: Chou et. al found good evidence of moderate efficacy for spinal manipulation for chronic or subacute low back pain. Acupuncture was associated with moderate short-term improvement in both pain and function, and yoga was associated with moderately superior outcomes in pain and decreased medication use at 26 weeks when compared to self-directed exercise and a self-care education book.⁸ In comparative studies, exercise and spinal manipulation, but not acupuncture, appear to have a beneficial impact on improving both pain and function in chronic low back pain.⁸⁷ Acupuncture does not appear to be effective when compared to sham acupuncture.⁸⁸

Physical Therapies: Although widely practiced, the application of heat and cold therapies for acute musculoskeletal pain has had a mixed evidence basis. The use of superficial heat has a stronger basis in evidence than the application of cryotherapy, or ice.^{8,89} There was insufficient evidence to make conclusive statements about the benefits of massage therapy. There was no evidence that traction, lumbar supports, interferential therapy, diathermy or ultrasound were effective for chronic low back pain. There was good evidence that transcutaneous nerve stimulation (TENS) is ineffective.⁹⁰

Structured Intensive Multidisciplinary Pain Programs: Evidence clearly supports the value of multimodal therapies in improving pain and function and reducing disability.^{91,92} In chronic back pain and in other pain conditions, multidisciplinary, intensive rehabilitation involving physical, psychosocial

and behavioral interventions has good evidence of moderate effectiveness for pain reduction and improvement of function.⁹³ Various tools such as the StarTBack questionnaire⁹⁴ for low back pain or the Functional Improvement Questionnaire (FRQ)⁹⁵ can be used to stratify patients into groups that might require increased attention and rehabilitative interventions and to plan treatment.³²

Sleep Hygiene: There is evidence to suggest that restorative sleep can help predict reduction in pain.⁹⁶ Although sleep treatment is not typically considered “analgesic”, poor sleep and lack of REM sleep in particular, are acutely hyperalgesic.⁹⁷ Further, the DSM 5 has reclassified insomnia as ‘sleep-wake’ disorders and acknowledges that, if occurring concomitantly with medical conditions and mental disorders, they are interactive and bi-directional.⁹⁸ Cognitive behavioral therapy has been shown to be a very effective non-drug strategy for insomnia.⁹⁹ Hence, having a sleep management plan is likely to help improve a patient’s pain experience. Morin and Benca have published an excellent review of chronic insomnia management in Lancet 2012.¹⁰⁰

Mindfulness and Stress Reduction: Mindfulness-based therapy techniques such as meditation and Mindfulness Based Stress Reduction (MBSR) and/or yoga, may be reasonable alternative therapies for chronic pain as they have been successful in helping patients learn to self-manage their pain sensations. Recent systematic reviews have shown these approaches may be as effective as cognitive behavioral therapy, which has consistently been demonstrated in randomized trials to improve chronic pain outcomes.¹⁰¹⁻¹⁰⁴ In addition, the neuroscientific basis of these treatments in alleviating pain has received greater scrutiny, and suggests specific mechanisms in the regulation of pain.¹⁰⁵

Non-opioid Analgesics

For most pain conditions, non-opioid analgesics (e.g. acetaminophen and NSAIDs) and adjuvant analgesics (e.g. antidepressants and anticonvulsants) are equally or more effective with less risk for harm than opioids. Providers should consider these medications during acute and subacute pain episodes and/or before initiating or transitioning patients to COAT. Selection of appropriate non-opioid or adjuvant analgesics requires a thorough history and physical exam, and will depend on the patient’s diagnosis, symptoms, pain type, comorbid conditions, and overall risk for adverse drug events ([Appendix F: Diagnosis-based Pharmacotherapy for Pain and Associated Conditions](#)).

Clinical Recommendations

1. Select acetaminophen for mild to moderate pain, at a maximum daily dose of 4 grams. Less than 2-3 grams per day is safer for prolonged use. Assess for all acetaminophen containing products to avoid inadvertent overdose. Use acetaminophen with caution, and at doses of less than 2gm daily in those at risk for hepatotoxicity, including those with advanced age, and liver disease (e.g. alcohol abuse, hepatitis B and C).
2. Use non-steroidal anti-inflammatory drugs (NSAIDs) for inflammatory, nociceptive pain. Monitor patients for potential renal, gastrointestinal (GI), and cardiac side effects. Consider concurrent H-2 blockers (e.g. famotidine, ranitidine) or proton pump inhibitors (e.g. omeprazole, pantoprazole) to help protect against GI effects. Avoid NSAIDs in patients with a calculated glomerular filtration rate (cGFR) < 60 ml/min/1.73 m².

3. Consider tricyclic antidepressants (TCAs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) and anticonvulsants (e.g. gabapentin, pregabalin) for neuropathic pain, other centralized pain syndromes, or fibromyalgia. Watch for potential cognitive impairment or sedation with anticonvulsants and TCAs.
4. Reserve baclofen or tizanidine for pain associated with spasticity from spinal cord injury or disease of the CNS (e.g. multiple sclerosis). Avoid abrupt discontinuation of baclofen because of the risk of precipitating withdrawal.
5. Do not prescribe muscle relaxants (e.g. methocarbamol, cyclobenzaprine) beyond a few weeks as they offer little long-term benefit. Avoid carisoprodol (Soma) due to the risk of misuse and abuse. Cyclobenzaprine, though not classified as a TCA, is structurally similar, so precautions are the same, and risk of adverse side effects are potentiated when used in combination with TCAs.
6. Prescribe trazodone, tricyclic antidepressants, melatonin, or other non-controlled substances if the patient requires pharmacologic treatment for insomnia.

Evidence

Sleep Medications: If non-pharmacologic options to aid sleep are not effective, treatment with OTC melatonin (1-5 mg) can help, especially since endogenous levels decrease with age.⁹⁸ This naturally occurring hormone plays a pivotal role in the physiological regulation of sleep by reinforcing circadian and seasonal rhythms; side effects can include drowsiness, dizziness, headache, nausea, and nightmares.¹⁰⁰ Tricyclic antidepressants (TCAs) are sedating and may assist with sleep initiation and maintenance.¹⁰⁶ Trazodone, another antidepressant, is widely used for sleep but does not have any analgesic properties; and caution is advised if the patient is taking selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), triptans, or tramadol.¹⁰⁷ SNRIs are much less sedating and may disturb sleep by provoking periodic leg movement disorders; and SSRIs decrease REM sleep, increase REM latency, and fragment sleep so they are not good options for insomnia.^{108,109}

Benzodiazepines: Use of benzodiazepines for sleep is not recommended in chronic pain patients because they do not improve patients' reported pain scores¹⁰⁹ and they increase the risk of rebound insomnia, overdose (especially when combined with opioids), reduced REM sleep, and the development of tolerance, dependency, and addiction.¹⁰⁷ Although benzodiazepine receptor agonists, (e.g. the Z-drugs: zolpidem, Zaleplon, Zopiclone, and eszopiclone) are FDA-approved to treat insomnia, they can potentially impair cognitive and psychomotor skills that can increase the risk of falls, rebound, sleep-walking, sleep-eating, and driving unaware, or dependence and abuse.^{98,107} For these reasons, these should not be used with patients who have Alzheimer's disease and other comorbid disorders.^{98,110,111}

Acetaminophen (APAP): APAP is an effective analgesic and antipyretic agent that is available over-the-counter (OTC). When combined with ibuprofen 200mg, the combination has been demonstrated to be more effective than opioids.¹¹² Hepatotoxicity can result from prolonged APAP use or doses in excess of recommended maximum total daily dose including combined-acetaminophen OTC products. Although the FDA's current maximum daily dose is 4 gm, some manufactures have voluntarily revised their label to recommend a lower maximum of 3 gram daily. The risk of hepatotoxicity increases significantly with age, concomitant alcohol use, comorbid liver disease or dose.¹¹³

Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs recommended for nociceptive pain such as traumatic musculoskeletal pain syndromes from traumatic, infectious or degenerative conditions (e.g. muscle, ligament, and or tendon injuries) with evidence to support effectiveness for spinal pain from disc, facet, or spinal ligament injuries¹¹⁴ and neuritis related to connective tissue disorders.¹¹⁵ In patients with non-specific low back pain, NSAIDs are equivalent to opioids in relief of pain.¹¹⁶ The number needed to treat (NNT) for oxycodone 15mg is approximately 4.6, (95% confidence Interval (CI), 2.9-11) while the NNT for oxycodone 10mg + acetaminophen 650mg is only 2.7, (95% CI, 2.4-3.1). The NNT for naproxen 500mg or naproxen sodium 550mg is also 2.7, and the NNT for ibuprofen 200mg + acetaminophen 500mg is 1.6. Hence, NSAID alone or in combinations can be as or more effective than opioids.¹¹⁷⁻¹¹⁹

Antidepressants (TCAs/SNRIs): TCAs have been studied in many clinical trials with positive results in the treatment of various neuropathic pain conditions and are a good first line option.¹²⁰⁻¹²⁴ Among the drugs reviewed in three different neuropathic pain conditions, low-dose TCAs have the lowest NNT with an average 2.6 (range 2.0 to 5.0). In addition to pain relief, TCAs can offer added benefit to patients who also have depression or whose pain is interfering with sleep. However, caution should be used when prescribing TCAs to elderly patients or those with cardiovascular disorders due to risk of sinus tachycardia, changes in cardiac conduction time or arrhythmias. Besides TCAs, the serotonin norepinephrine reuptake inhibitor (SNRI) duloxetine has been shown to be effective in diabetic peripheral neuropathy, fibromyalgia and chronic musculoskeletal pain.¹²⁵ A systematic review, on indirect comparison, found that there were no differences between venlafaxine and either gabapentin, pregabalin or duloxetine on average pain scores or the likelihood of achieving significant pain relief.¹²⁶

Anticonvulsant drugs (ACDs): Gabapentinoids (*gabapentin* and *pregabalin*) have been found to be moderately superior to other ACDs for achieving pain relief.¹²⁶ They have robust evidence in treating diabetic peripheral neuropathy, other neuropathies and fibromyalgia.^{127,128} Gabapentin was found to be effective in painful polyneuropathy with an average NNT of 6.4.¹²⁹ In another systematic review of antiepileptic drugs used to treat neuropathic pain, gabapentin was found to be effective at doses of 1800mg and 2400mg, although side effects such as dizziness and drowsiness were reported at these doses.¹²⁶ Pregabalin has been studied in neuropathic pain conditions such as diabetic neuropathy and spinal cord injury and is FDA-approved to treat those neuropathies as well as fibromyalgia. The efficacy of pregabalin was found to be comparable to duloxetine, amitriptyline and gabapentin, however, pregabalin is classified as a controlled substance (Schedule V) with the potential for misuse or abuse, so it argues for a more cautious approach to the use of this agent.¹²⁶ Other anticonvulsants such as carbamazepine, oxcarbazepine, and lamotrigine have limited or conflicting evidence of efficacy in spontaneous shooting pain of trigeminal neuropathy, diabetic peripheral neuropathy, HIV-related peripheral neuropathy, and multiple sclerosis.^{121,130} All non-gabapentinoid ACDs are associated with risk of hepatotoxicity, hyponatremia, neutropenia, rash (including Stevens Johnson Syndrome), sedation, and suicidality.

Muscle relaxants and antispasticity drugs: Muscle relaxants have limited evidence for effectiveness for chronic pain and are predominantly sedative.¹³¹ Carisoprodol (Soma) should never be used due to lack of long-term efficacy, a high risk for abuse and misuse, and serious withdrawal symptoms.¹⁰⁷ When true

painful spasticity is present, for instance in spinal cord injury and multiple sclerosis, antispasticity agents e.g. baclofen and tizanidine are good treatment options; however, serious and life threatening reactions can occur with abrupt discontinuation, e.g. rhabdomyolysis.

DRAFT

Part II. Prescribing Opioids in the Acute and Subacute Phase

Opioids in the Acute Phase (0-6 weeks post episode of pain or surgery)

In general, reserve opioids for acute pain resulting from severe injuries or medical conditions, surgical procedures, or when alternatives Non-opioid Options([Non-opioid Options](#)) are ineffective or contraindicated. If opioids are prescribed, it should be for the shortest duration and at the lowest necessary dose (usually less than 14 days). The use of opioids for non-specific low back pain, headaches, and fibromyalgia is not supported by evidence.

Receiving one week supply or ≥ 2 opioid prescriptions after an acute back sprain doubles a patient's risk of long-term disability.

(Franklin et al 2008)

Clinical Recommendations

1. Explore non-opioid alternatives for treating pain and restoring function, including early activation.
2. Prescribe opioids for dental pain only after complex dental procedures and at the lowest dose and duration.
3. Help the patient set reasonable expectations about his or her recovery, and educate the patient about the potential risks and side effects. Provide patient education on safekeeping of opioids, benzodiazepines, and other controlled substances.
4. Expect patients to improve in function and pain and resume their normal activities in a matter of days to weeks after an acute pain episode. Strongly consider re-evaluation for those who do not follow the normal course of recovery.
5. Check the state's Prescription Monitoring Program (PMP) to ensure that the patient's controlled substance history is consistent with the prescribing record. Prescribers may delegate the ability to query the PMP database to any licensed health care professional ([Appendix C: How to use the Prescription Monitoring Program](#)).
6. Assess function and pain at baseline and with each follow-up visit when opioids are prescribed. Document clinically meaningful improvement in function and pain using validated tools.
7. Strongly consider tapering the patient off opioids as the acute episode of pain improves. Taper patient by 6 weeks if clinically meaningful improvement in function and pain has not occurred.

Opioids in the Subacute Phase (6 and 12 weeks post episode of pain or surgery)

With some exceptions, resumption of normal activities should be expected during this period. Use of **activity diaries** is encouraged as a means of improving patient participation and investment in recovery. Non-pharmacological treatments such as cognitive behavioral therapy, activity coaching, and graded exercise are also encouraged ([Recommendations for All Pain Phases](#) and [Non-opioid Options](#)). If the injury is not severe (e.g. catastrophic injuries or severe fractures), opioid use beyond the acute phase (longer than 6 weeks) is rarely indicated. If and when they are prescribed for longer than 6 weeks, the following clinical recommendations should be followed.

Patients with substance use and/or psychiatric disorders are more likely to have complications from opioid use, such as misuse, abuse or overdose.

(Martin et al 2011 Gen Intern Med 26(12): p. 1450-7)

Clinical Recommendations

1. Do not continue to prescribe opioids if use during the acute phase does not lead to clinically meaningful improvement in function or to a pain interference with function level of 4 or less ([Figure B](#)).
2. Prescribe opioids in multiples of a 7-day supply to reduce the incidence of the supply ending on a weekend.
3. Have a plan for how and when to discontinue opioids if treatment has not resulted in clinically meaningful improvement in function and pain or the patient has had a severe adverse outcome.
4. Check the state's [Prescription Monitoring Program](#) (PMP) to ensure that the patient's controlled substance history is consistent with the prescribing record. Prescribers may delegate the ability to query the PMP database to a licensed health care professional ([Appendix C: How to use the Prescription Monitoring Program](#)).
5. Screen for depression using PHQ-9 and for anxiety using GAD-7 or other validated tools. If comorbid mental health conditions exist in the presence of pain, they need to be treated or the patient's pain will not improve regardless of opioid therapy.
6. Administer the 4-item [PC-PTSD](#) screen or other validated tools, if the patient's history suggests PTSD, or if PHQ-9 or GAD-7 remains elevated after treatment.
7. Screen for opioid misuse risk using Opioid Risk Tool, SOAPP-R, DIRE, CAGE-AID or other validated tools. Review the patient's medical records and include the patient's support system (e.g. family, friends etc.) to determine if consistent with risk assessment results.
8. Do not prescribe opioids if results of a baseline UDT reveal "red flags" such as the *confirmed* presence of cocaine, amphetamines, non-prescribed benzodiazepines, alcohol, or any other drugs you did not prescribe or have knowledge of ([Appendix D: Urine Drug Testing for Monitoring](#)).

[Opioid Therapy](#)). If cannabis is present on a UDT, the patient should be screened for cannabis use disorder, as defined by DSM 5.

9. Avoid new prescriptions of benzodiazepines and sedative-hypnotics. Consider tapering or discontinuing benzodiazepines and/or sedative-hypnotics.
10. Discontinue opioids during this phase if
 - a. There is no clinically meaningful improvement in function and pain.
 - b. Treatment resulted in a severe adverse outcome (e.g. overdose, bowel obstruction, central sleep apnea).
 - c. The patient has current or history of substance use disorder (excluding tobacco).

Evidence

Short term use of opioids for severe acute injury (e.g. severe trauma, fracture, crush injury, post-op) is unquestioned and is a standard of care. However, the overall data on effectiveness of opioids for longer term use, especially for improved function, and for routine conditions such as non-specific low back pain, headaches, and fibromyalgia is weak, and the evidence of potential harm is strong. Systematic reviews of efficacy of opioids for low back pain demonstrate modest improvement in pain but little improvement in function and no clear evidence that pain relief will be sustained.^{9,45} For headaches and fibromyalgia, there is a paucity of evidence on effectiveness. Both the European Federation of Neurological Societies and the American Academy of Neurology recommend against the use of opioids for headache.¹³²⁻¹³⁴ There is no evidence from randomized trials to support the use of opioids for fibromyalgia, and some observational data suggest that strong opioids are used in fibromyalgia patients with significant risk factors that would normally mitigate against such use.^{78,135-139}

In addition to these data, evidence from a population-based, prospective study of a low back pain cohort in WA workers' compensation reported that even minimal use of opioids in the first six weeks following an acute low back injury was associated with a doubling of the risk of disability one year later, after adjusting for baseline pain, function, and injury severity.³⁰

Evidence on the use of opioids for subacute pain is limited; thus, most of the recommendations for this period represent a consensus of expert opinion of the advisory group. A systematic review of RCTs on conservative treatments for subacute low back pain (6 weeks-3 months), revealed that only advice on staying active was found to be effective.¹⁴⁰

The use of screening tests prior to starting COAT is important in patients with comorbid medical conditions. Managing pain in patients with complex medical conditions such as substance use disorder or a mental health condition can be a challenge. Research has shown that patients with substance use or psychiatric disorders (e.g. depression), or both, are actually more likely than patients without these disorders to receive COAT.^{141,142} They are also more likely to have complications such as misuse, abuse or overdose.^{143,144} Adults with a history of depression, alcohol or other non-opioid substance use disorder are three to five times more likely to receive COAT.¹⁴⁵

High-risk COAT prescribing practices (high opioid dose, extended COAT duration, concurrent use of sedatives/hypnotics) are associated with increased risks of opioid overdose and serious fractures.^{16,46} Unfortunately, patients who receive high-risk COAT are also more likely to have high-risk characteristics, including younger age, history of substance use disorder and mental disorder and presence of opioid misuse.³¹ Because of the increased risk for adverse outcomes from the use of COAT in patients with mental health disorders, such as borderline personality disorder, depression, bipolar disorder, anxiety, post-traumatic stress disorder or PTSD) or psychotic disorders, providers should be cautious when prescribing COAT for patients with these co-morbid conditions.

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Part III. Opioids for Perioperative Pain

Opioids serve as the cornerstone for severe acute postoperative pain management with proven efficacy for this indication. Nevertheless, patients must be counseled on the limited effectiveness of any analgesics in eliminating pain entirely. A balanced, rational multimodal analgesic approach is most effective to control pain while minimizing analgesic doses and their resultant side effects that interfere with rehabilitation. In addition, patients on COAT who are undergoing elective surgeries present challenges for perioperative pain management. For this reason, it is important to assess patients' risks for both severe postoperative pain and side effects of opioids. The following recommendations are intended to help manage patients' pain and minimize their risk associated with perioperative opioid use.

Preoperative Period

Clinical Recommendations

1. Conduct a thorough preoperative evaluation, including history and physical:
 - a. Ask about past and current use of, response to and preferences for analgesics.
 - b. Consider a check of the Prescription Monitoring Program (PMP), especially for patients with a history of COAT or benzodiazepine use.
 - c. Assess risk for potential postoperative opioid over-sedation and/or respiratory depression ([Table 4](#)) and difficult postoperative pain control ([Table 5](#)). Inform the entire perioperative team of the results of the risk assessment.
 - d. Consider consultation with a specialist (e.g. pain management, addiction medicine, behavioral health), particularly in patients at risk for both over-sedation ([Table 4](#)) and difficult postoperative pain control ([Table 5](#)).
2. Develop a coordinated treatment plan, including a timeline for tapering perioperative opioids. Identify which provider will be responsible for managing postoperative pain and prescribing opioids.
 - a. Generally, in opioid naïve patients, any opioids prescribed during the first 6 weeks postoperatively should be managed solely by the surgeon.
 - b. If a patient was previously using chronic opioids for the condition being addressed by surgery, the surgeon should consult with the prescriber as to whether or not the patient is likely to need continued COAT after surgery. If so, develop a plan for transition of pain care back to the previous prescriber.
 - c. Generally, it is expected that the prescribing provider manages the pain medication even in the immediate postoperative period for patients who are on methadone, buprenorphine/naloxone, or high dose long-acting opioids.
3. Inform patient and family of the perioperative pain plan. Set expectations with them about realistic pain management goals, including functional recovery activities, need for multimodal

treatment, limits of therapy, timely return to preoperative baseline opioid dose (if any) or lower, and the analgesic tapering timeline.

4. Avoid new prescriptions of benzodiazepines, sedative-hypnotics, anxiolytics, or other central nervous system (CNS) depressants.
5. Avoid escalating the opioid dose before surgery. The lowest effective dose should always be sought, but there is insufficient evidence to recommend routinely lowering chronic opioid doses or discontinuing opioids prior to surgery.

Intraoperative Period

Clinical Recommendations

1. Provide balanced multimodal analgesia, including adjuvant analgesics when possible (e.g. acetaminophen, NSAIDs, gabapentin):
 - a. Under specialist direction, ketamine, lidocaine, and regional local anesthetic techniques can also help minimize perioperative opioids and their side effects.
2. Provide sufficient intraoperative opioid doses to avoid acute withdrawal in patients who are on large doses of preoperative opioids.

Immediate Postoperative Period

Clinical Recommendations

1. Reserve the use of opioids for moderate to severe acute pain. If used, utilize the lowest possible dose as part of a multimodal regimen, including NSAIDs, acetaminophen, and non-pharmacologic therapies unless contraindicated.
2. Monitor sedation and respiratory status in patients receiving systemic opioids for postoperative analgesia (e.g. [Richmond Agitation Sedation Scale](#), [Ramsey Sedation Scale](#), or [Comfort Scale](#)). Due to the risk of excessive sedation and respiratory depression, patients should be monitored closely in the initial hours following surgery and with subsequent dose escalations. Monitoring should include assessments of alertness and signs or symptoms of hypoventilation or hypoxia:
 - a. The use of routine oxygen is discouraged as hypoxia is a late sign of respiratory compromise and this sign will be delayed still further by supplemental oxygen.
 - b. There is insufficient evidence to recommend the routine use of more sophisticated currently available noninvasive methods (such as capnography) for monitoring hypoventilation postoperatively.
 - c. Providers should be prepared to change or reduce opioids or administer opioid antagonists in patients who develop excess sedation or respiratory depression ([Table 4](#)).
3. Use oral opioids for managing postoperative pain in patients who can tolerate oral medications, particularly following the first or second postoperative day, as pain levels become less variable with activity:

- a. Consider the use of patient controlled analgesia (PCA) initially in cases where repeated doses of parenteral opioids are anticipated or required. Prescribers should be aware of the doses being self-administered by their patients via PCA to guide adjustments. Routine use of continuous opioid infusions (basal rates with PCA) is NOT recommended:
 - b. Consider consultation with specialists for patients receiving high dose PCA, and when opioids or benzodiazepines are being used in combination with the PCA.
4. Use short-acting “as needed” (PRN) opioids as the foundation for acute severe postoperative pain in the opioid-naive patient. For the opioid tolerant patient, do not add or increase extended release or long-acting opioids for the immediate postoperative period.
 - a. Avoid therapeutic duplication of opioids consisting of more than one type of PRN short-acting opioid (e.g. oxycodone and morphine). Avoid co-administration of parenteral and oral PRN opioids for ongoing pain. If PRN opioids from different routes are needed, provide a clear indication for use (e.g. for a brief, severely painful, closely monitored procedures such as a dressing change).
 - b. Consider scheduling non-opioids for more steady analgesia and to avoid multiple PRNs for pain.
5. Resume chronic regimen as soon as possible if patients were previously on chronic opioids and are expected to continue these postoperatively.
6. Avoid new prescriptions of benzodiazepines/sedative/hypnotics/anxiolytics/CNS depressants. If patients were previously on chronic sedatives, restart these at lower doses in the setting of postoperative opioids to avoid synergies between CNS depressant and opioid side effects.
7. Initiate a bowel regimen as soon as possible postoperatively in those taking opioids for their pain to minimize opioid-induced bowel dysfunction (constipation). This side effect may still require opioid dose reductions if unresponsive to stool softeners, laxatives or enemas.

Do not discharge the patient with more than a two week supply of opioids, and many surgeries may require less. Continued opioid therapy will require appropriate re-evaluation by the surgeon.

At Time of Hospital Discharge

Clinical Recommendations

1. Avoid continuing or adding new prescriptions of benzodiazepines, sedative-hypnotics, anxiolytics or CNS depressants. Counsel patients and families about risks of using alcohol and other CNS depressants with opioids.
2. Inform the patient and family which provider will be responsible for managing postoperative pain, including who will be prescribing any opioids. Instruct the patient and family on the planned taper of postoperative opioids, including a timeline for return to preoperative or lower opioid dosing for those on chronic opioids.

3. Remind the patient of the dangers of prescription opioid diversion and the importance of secure storage of their medications. Sharing medications with others is never appropriate and is illegal. Instruct the patient and family on prompt disposal of controlled substances either through a [DEA-approved take-back program](#) or FDA guideline for [safe disposal of medicine](#).
4. Follow through with the agreed upon preoperative plan to taper off opioids added for surgery as surgical healing takes place. The goal is always the shortest duration and lowest effective dose:
 - a. Most patients with major surgeries should be able to be tapered to preoperative doses or lower within 6 weeks (approximately 20% of dose per week although tapering may be slower in the 1st week or 10 days and then become much more rapid as healing progresses).
 - b. It is important to remember that for some minor surgeries, it may be appropriate to discharge patients on acetaminophen or NSAIDs only or with only a very limited supply of short-acting opioids (e.g. 2-3 days) - even if they were taking opioids preoperatively.
 - c. For patients who were not taking opioids prior to surgery, but who are still on them after 6 weeks, follow the recommendations in the [Subacute Phase](#).

Table 4. Risks for Over-sedation and/or Respiratory Depression from Postoperative Opioids ¹⁴⁶⁻¹⁵⁵

<p>Sleep apnea or high risk sleep disorder (morbid obesity/history of snoring/positive STOP Bang score ≥ 4).</p> <p>Age (<1 and >65 years old).</p> <p>History of previous over-sedation with opioids.</p> <p>Opioid analgesic tolerance or increased opioid dose requirement.</p> <p>Concurrent use of other sedating drugs (e.g. benzodiazepines, antihistamines, sedative/anxiolytics or other CNS depressants).</p> <p>History of difficult to control postoperative pain.</p> <p>Long (>6 hours) duration general anesthetics.</p> <p>Surgery location and/or type (e.g. airway, upper abdominal, thoracic, scoliosis repair) in children.</p> <p>Medical comorbidities (pulmonary disease/smoker, cardiac disease, other major organ failures).</p>
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Table 5. Risks for Difficult-to-control Postoperative Pain ¹⁵⁶⁻¹⁶⁴

<p>History of severe postoperative pain.</p> <p>Opioid analgesic tolerance (daily use for months).</p> <p>Current mixed opioid agonist/antagonist treatment (e.g. buprenorphine or naltrexone).</p> <p>Chronic pain (either related or unrelated to the surgical site).</p> <p>Psychological comorbidities (e.g. depression, anxiety, catastrophizing).</p> <p>History of substance use disorder.</p> <p>History of "all over body pain".</p> <p>History of significant opioid sensitivities (e.g. nausea, sedation).</p> <p>History of intrathecal pump use or nerve stimulator implanted for pain control.</p>
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Evidence

A number of reviews of the literature on Perioperative Pain Treatment have been undertaken and published in the last few years including those from the American Pain Society, the American Society of Anesthesiologists, the Department of Defense, the Veterans Administration, and the Washington State Department of Labor and Industries. These guidelines as well as a PubMed search for additional reviews of this topic in the last 5 years (560, excluding 32 reviews concerning any single surgical procedure) were used and combined with consensus opinions from the experts in the AMDG advisory group) to formulate our final recommendations.

Although opioids are effective for short-term pain relief following surgery, side effects may limit their use.¹⁶⁵ The use of multimodal approach including non-pharmacologic interventions to manage pain can improve treatment and limit side effects from any one class of analgesics.¹⁶⁶⁻¹⁷⁹ Preparation for surgery such as training in relaxation, counseling and education can reduce anxiety, postoperative opioids use and physical therapy needs.¹⁸⁰⁻¹⁸⁴ In addition, adjuvant treatments such as acetaminophen, NSAIDs and gabapentin have been demonstrated to be opioid sparing and help minimize opioid-related side effects.^{179,185-187} The intraoperative use of techniques such as regional local anesthetic, ketamine and intravenous lidocaine can also reduce opioid requirements.¹⁸⁸⁻¹⁹⁰

It is important to assess patients' risk factors for over-sedation and/or respiratory depression and for difficult to control postoperative pain. Predictors of postoperative opioid over-sedation and/or respiratory depression include, but are not limited to, sleep apnea, concurrent use of benzodiazepines or other CNS depressant agents, other medical conditions that affect respiratory function and prolonged anesthesia.^{146,151,152,154,155} Risk factors for difficult to control postoperative pain include, chronic pain, mental health comorbidities (e.g. anxiety, depression, catastrophizing) and history of substance use disorder.^{156-160,162}

Patients on COAT who are undergoing surgery are at increased risk for both of these complications. These patients have higher pain scores, manifest more anxiety and have frequent and more severe respiratory depressive episodes than opioid naïve patients.^{157-160,191}

A Prescription Monitoring Program provides an accurate picture of the patient's history of opioids, benzodiazepine, and other controlled substance use, which is especially helpful for planning perioperative pain management.^{192,193} It is important to collaborate across the care team (surgeon, anesthesiologist, pain management specialist, bedside nurses, treating provider and the patient) to formulate a postoperative pain management plan including risk factors and a timeline for weaning analgesics. Communication of this treatment plan, as well as realistic expectations concerning postoperative pain, is important for the patient, his or her family and the entire care team to help ensure appropriate treatment and avoid dangerous side effects.¹⁹⁴

The first 24 hours of opioid therapy is a significant period of risk for excess sedation and respiratory depression.¹⁵⁴ Assessment of sedation level and monitoring for adequate ventilation and oxygenation allow for early response and intervention.^{153,154,195-199} When the parenteral route is needed beyond the first few hours after surgery, patient-controlled analgesia (PCA) is recommended and can add an

element of safety as the sedated patient is less likely to continue to press the dosing button.²⁰⁰⁻²⁰² However, routine use of PCA is not needed as many patients can resume oral analgesia within hours of operation. Analgesic effects of oral and intravenous opioids are comparable, so patients can be transitioned to oral opioids as soon as oral intake is tolerated.²⁰³ Concurrent, as needed use of intravenous and oral opioids increases the risk of side effects.²⁰⁴ Constipation is a common adverse effect of opioids and if left untreated, could lead to bowel impaction. Initiate a bowel regimen as soon as possible postoperatively in those taking opioids to minimize opioid-induced bowel dysfunction.^{205,206}

The goal of opioid therapy is the briefest, least invasive and lowest dose regimen that minimizes pain and avoids dangerous side effects.¹⁻⁴

DRAFT

Part IV. Prescribing Opioids for Chronic Non-cancer Pain

Opioids in the Chronic Phase

(>12 weeks after an episode of pain or surgery)

Managing chronic pain and providing appropriate opioid therapy is a challenging aspect of both primary care and specialty care practices. This is why it is critical for providers to be very conscious of the risks, and intentional about the treatment plan when prescribing these drugs. The key to effective COAT is sustained improvement in physical function and pain with frequent monitoring to adjust therapy as necessary. Best practice treatment requires ongoing attention to identify adverse outcomes. Providers must balance the need for scientific evidence and skillful clinical decision making in these complex cases.

1 in 5 patients on chronic opioid analgesic therapy will develop opioid use disorder as defined by DSM 5. If tolerance and withdrawal are considered, the prevalence rises to nearly 1 in 3.

(Degenhardt et al. Lancet Psychiatry 2015)

Clinical Recommendations

1. Prescribe COAT only if there is sustained clinically meaningful improvement in function and no serious adverse outcomes or contraindications.
2. Use extreme caution and consider consultation before prescribing COAT in patients with comorbid mental health disorders (especially PTSD and major depressive disorder), family or personal history of substance use disorder, medical condition that could increase sensitivity to opioid-related side effects (e.g. COPD, CHF, sleep apnea, advanced age, or renal or hepatic dysfunction) or concurrent use of benzodiazepines.
3. Reassess the need for COAT in transferred patients who are already using opioids. If current treatment is not benefiting the patient, a dose reduction or discontinuation is warranted. Consider non-opioid options for pain treatment ([Recommendations for All Pain Phases](#) and [Non-opioid Options](#))
4. Discuss the potential benefits and risks associated with COAT including addiction and overdose. Have a signed opioid treatment agreement to document this discussion and set behavioral expectations including the use of a single prescriber and pharmacy.
5. Prescribe opioids at the lowest possible effective dose. If dose is increased but this does not result in CMIF, then significant tolerance or adverse effects to opioids may be developing and opioids should be tapered back to previous dose or possibly discontinued.
6. Prescribe opioids in multiples of a 7-day supply to reduce the incidence of the supply ending on a weekend.

7. Initiate a bowel regimen to prevent opioid-induced constipation, especially in older adults. Use a stimulant laxative on a scheduled basis such as senna, milk of magnesia or magnesium citrate (use caution in patients with kidney failure), polyethylene glycol, lactulose or sorbitol.
8. Use the following best practices to ensure effective treatment and minimize potential adverse outcomes:
 - a. Assess and document function and pain status using validated tools at each visit where opioids are prescribed ([Recommendations for All Pain Phases](#) and [CMIF](#)). This is critical in determining the patient's ongoing response to opioids and to measure effects from any dose changes.
 - b. Check the State's PMP at the frequency determined by the patient's risk category to ensure controlled substance history is consistent with prescribing record. Prescribers may delegate the ability to query the PMP database to any licensed health care professional ([Appendix C: How to use the Prescription Monitoring Program](#)).
 - c. Repeat random UDT at the frequency determined by the patient's risk category to identify aberrant behavior, undisclosed drug use and/or abuse and verify compliance with treatment ([Appendix D: Urine Drug Testing for Monitoring Opioid Therapy](#)).
 - d. Monitor for opioid-related adverse outcomes such as central sleep apnea, endocrine dysfunction, opioid-induced hyperalgesia, opioid use disorder or signs of acute toxicity. Be especially cautious with comorbid conditions that may increase risk for adverse outcomes (including COPD, CHF, obstructive sleep apnea, history of alcohol or substance use disorder, elderly, or renal or hepatic dysfunction).
 - e. Monitor for medication misuse, aberrant drug-related behaviors or diversion ([Table 9](#)).
 - f. Consult with a pain management specialist before exceeding 120 mg/day MED. If the pain management specialist endorses high dose COAT, consider prescribing naloxone as a preventive rescue medication. Counsel family member or other personal contacts in a position to assist the patient at risk of opioid-related overdose.
9. Do not combine opioids with benzodiazepines, sedative-hypnotics or barbiturates.
10. Do not prescribe methadone for chronic opioid therapy unless the provider is knowledgeable of methadone's non-linear pharmacokinetics, unpredictable clearance, multiple drug-to-drug interactions and additional monitoring requirements. Free mentoring services are available for prescribing methadone using the [Providers' Clinical Support System](#) ([Appendix H: Clinical Tools and Resources](#)).
11. Increase the frequency of monitoring for high risk patients on opioids. Monthly visits are often needed.
12. Discontinue opioids during this phase if
 - a. Clinically meaningful improvement in function has not been sustained.
 - b. Treatment resulted in a severe adverse outcome including the development of opioid use disorder as defined by DSM 5.
 - c. The patient has a current substance use disorder (excluding tobacco).

Table 6. How Often to Evaluate Function and Pain in Patients on COAT

Level of Risk	Recommended Frequency
Low risk (no risk factors)	Every 6 months
Moderate risk	Every 3 months
High Risk or opioid doses >120 mg/day MED	Every month

Table 7. Prescribing Methadone for Pain Management

Prescribing methadone is complex. To prevent serious complications from methadone, prescribers should read and carefully follow the methadone (Dolophine®) prescribing information at www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

Deaths, cardiac and respiratory, have been reported during initiation and conversion of pain patients to methadone treatment from treatment with other opioid agonists. It is critical to understand the pharmacokinetics of methadone when converting patients from other opioids.

Respiratory depression is the chief hazard associated with methadone or other opioid administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

In addition, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Evidence

The efficacy of long-term opioid use for chronic non-cancer pain has not been established. However, many primary care providers have patients—in some cases inherited from other providers—who have already been placed on COAT after failing other pain management options.

While this guideline continues to identify 120 mg/day MED as the boundary beyond which specialty consultation is warranted, there is no completely safe opioid dose level. There appears to be a steady increase in overdose risk as the opioid dose rises above 20 mg/day MED.⁴⁶⁻⁴⁹ The cause and effect relationship is unclear, but patients on high dose opioids are more than likely to have high risk characteristics, such as mental health disorder, a substance use disorder, and/or opioid misuse.³¹ Recent evidence also shows that the increased risk from escalating the opioid dose is not balanced by an increased benefit in either functional status or average pain level.²⁰⁷

In addition to dose-associated risks, duration of opioid action (long-acting vs. short-acting) has been linked to unintentional overdose.²⁰⁸ Patients receiving long-acting opioids had a 2.5-fold increased risk of overdose than those receiving short-acting opioids after adjusting for age, sex, opioid dose and other characteristics. The risk was significantly higher during the first two weeks after initiation of long-acting opioids.

Chronic opioid analgesic therapy is also associated with the development of physical dependence and addiction (DSM 5 “opioid use disorder”). The true incidence of these serious complications is unknown but is likely to affect more patients than was previously reported.^{12,25,26} In addition, the lack of a useful case definition for any of these dependent states makes it challenging for a primary care provider to identify and intervene appropriately.²⁰ Even with acute low dose opioids, patients are at increased risk for developing opioid use disorder. This risk ranges from an odds ratio of 3.03 for acute low dose opioids (1 – 36 mg/day MED), to 122.45 for patients on chronic high dose opioids (≥ 120 mg/day MED).²⁶ A recently published large scale study of patients on chronic opioid revealed that the lifetime prevalence of DSM 5 prescription opioid use disorder is 21% (12% mild, 9% moderate to severe).²⁰⁹ These rates do not consider tolerance or withdrawal. If these physiologic responses are considered, the prevalence is 29%.

Other adverse events most commonly reported in randomized trials include constipation, nausea and vomiting, dizziness, and drowsiness.¹³ Much more serious long-term consequences of opioids have only been identified from observational and epidemiological investigations; these include higher risk for poor functional status,³⁰ inhibition of endogenous sex hormone production with resulting hypogonadism and infertility,²¹⁰ immunosuppression,¹⁵ falls and fractures in older adults,¹⁶ neonatal abstinence syndrome,¹⁷ cardiac arrhythmia related to methadone,¹⁸ central sleep apnea,¹⁹ opioid-induced hyperalgesia,⁵⁷ nonfatal overdose hospitalizations,²¹ emergency department visits,²² and death from unintentional poisoning.²³

Part V. Reducing or Discontinuing Chronic Opioid Analgesic Therapy (COAT)

Reason to Discontinue COAT and Considerations Prior to Taper

Not all patients benefit from opioids, and a prescriber frequently faces the challenge of reducing the opioid dose or discontinuing opioids altogether. Patients on COAT can be reluctant to change, and many who agree to try will have difficulty as the dose is reduced. Such reluctance and difficulty in tapering often reflect anxiety. There may be apprehension about worsening of pain and withdrawal symptoms or if there is opioid use disorder, about reduced access to the drug. Exploring each of these possibilities in a non-judgmental manner helps the provider understand the patient’s perspective and helps the patient have realistic expectations. This, in turn, strengthens the therapeutic relationship and helps guide future strategies.

Table 8. When to Reduce, Taper, or Discontinue COAT

<p>Patient requests opioid taper.</p> <p>Patient is maintained on opioids for at least 3 months, and there is no sustained clinically meaningful improvement in function (CMIF), as measured by validated instruments (Appendix B: Validated Tools for Screening and Assessment).</p> <p>Patient’s risk from continued treatment outweighs the benefit, (e.g. decreased function, drug therapy, or medical conditions that could increase risk for opioid-related toxicities.)</p> <p>Patient has experienced a severe adverse outcome or overdose event.</p> <p>Patient has a substance use disorder.</p> <p>Use of opioids is not in compliance with DOH’s pain management rules or consistent with the AMDG Guideline.</p> <p>Patient exhibits aberrant behaviors (Table 9).</p>

Clinical Recommendations

1. Help the patient understand that chronic pain is a complex disease and opioids alone cannot adequately address all of the patient’s pain-related needs. Exploring the patient’s resistance to discontinuing opioids will guide taper strategy. Motivational interviewing skills may be useful when having this conversation.
2. Consider tapering patients in an outpatient setting if they are not on high dose opioids or who do not have comorbid substance use disorder or an active mental health disorder, as this can be done safely and they are at low risk for failing to complete the taper.
3. Seek consultation from a pain management specialist or Structured Intensive Multidisciplinary Pain Program (SIMP; described in [Non-opioid Options](#)) for patients who have failed taper in an outpatient setting or who are at high risk for failure to taper due to high dose opioids, concurrent benzodiazepine use, comorbid substance use or an active mental health disorder. If SIMP is not available, engage patients in activities that emulate the biopsychosocial approach of such a program. Rarely, inpatient management of withdrawal may be necessary.
4. Refer patients with aberrant behaviors ([Table 9](#)) suggestive of substance use disorder for evaluation and treatment.

How to Discontinue Opioids

Selecting the optimal timing and approach to tapering depends on multiple factors. The rate of opioid taper should be based primarily on safety considerations and special attention is needed for patients on high dose opioids, as too rapid a taper may precipitate withdrawal symptoms or drug-seeking. In addition, behavioral issues or physical withdrawal symptoms can be a major obstacle during an opioid taper. Patients who feel overwhelmed or desperate may try to convince the provider to abandon the taper. Although there are no methods for preventing behavioral issues during taper, strategies implemented at the beginning of COAT such as setting clear expectations and development of an exit strategy are most likely to prevent later behavioral problems if a taper becomes necessary.

Clinical Recommendations

1. Consider sequential tapers for patients who are on chronic benzodiazepines and opioids. Taper off opioids first, then the benzodiazepines.
2. Do not use ultra-rapid detoxification or antagonist-induced withdrawal under heavy sedation or anesthesia (e.g. naloxone or naltrexone with propofol, methohexital, ketamine or midazolam).
3. Establish the rate of taper based on safety considerations:
 - a. Immediate discontinuation if there is diversion or non-medical use,
 - b. Rapid taper (over a 2 to 3 week period) if the patient has had a severe adverse outcome such as overdose or substance use disorder, or
 - c. Slow taper for patients with no acute safety concerns. Start with a taper of $\leq 10\%$ of the original dose per week and assess the patient's functional and pain status at each visit.
4. Adjust the rate, intensity, and duration of the taper according to the patient's response (e.g. emergence of opioid withdrawal symptoms ([Table 10](#))).
5. Watch for signs of unmasked mental health disorders (e.g. depression, PTSD, panic disorder) during taper, especially in patients on prolonged or high dose opioids. Consult with specialists to facilitate a safe and effective taper. Use validated tools to assess conditions ([Appendix B: Validated Tools for Screening and Assessment](#)).
6. Consider the following factors when making a decision to continue, pause or discontinue the taper plan:
 - a. Assess the patient behaviors that may be suggestive of a substance use disorder
 - b. Address increased pain with use of non-opioid options.
 - c. Evaluate patient for mental health disorders.
 - d. If the dose was tapered due to safety risk, once the dose has been lowered to an acceptable level of risk with no addiction behavior(s) present, consider maintaining at the established lower dose if there is CMIF, reduced pain and no serious adverse outcomes.
7. Do not reverse the taper; it must be unidirectional. The rate may be slowed or paused while monitoring for and managing withdrawal symptoms.
8. Increase taper rate when opioid doses reach a low level (e.g. < 15 mg/day MED), since formulations of opioids may not be available to allow smaller decreases.

9. Use non-benzodiazepine adjunctive agents to treat opioid abstinence syndrome (withdrawal) if needed. Withdrawal symptoms are rarely medically serious, although they may be extremely unpleasant. Symptoms of mild opioid withdrawal may persist for six months after opioids have been discontinued ([Table 10](#)).
10. Refer to a crisis intervention system if a patient expresses serious suicidal ideation with plan or intent, or transfer to an emergency room where the patient can be closely monitored.
11. Do not start or resume opioids or benzodiazepines once they have been discontinued, as they may trigger drug cravings and a return to use.

Table 9. Aberrant Behaviors

Less suggestive for addiction but are increased in depressed patients	More suggestive of addiction and are more prevalent in patients with substance use disorder
Frequent requests for early refills; claiming lost or stolen prescriptions Opioid(s) used more frequently, or at higher doses than prescribed Using opioids to treat non-pain symptoms Borrowing or hoarding opioids Using alcohol or tobacco to relieve pain Requesting more or specific opioids Recurring emergency room visits for pain Concerns expressed by family member(s) Unexpected drug test results Inconsistencies in the patient's history	Buying opioids on the street; stealing or selling drugs Multiple prescribers ("doctor shopping") Trading sex for opioids Using illicit drugs, +UDT for illicit drugs Forging prescriptions Aggressive demand for opioids Injecting oral/topical opioids Signs of intoxication (ETOH odor, sedation, slurred speech, motor instability etc.)

Adapted from Passik, S. 2006

Table 10. Symptoms and Treatment of Opioid Abstinence Syndrome (withdrawal)

<p><u>Restlessness, sweating, tremors</u>: Clonidine 0.1-0.2mg orally every 6 hours or transdermal patch 0.1-0.2mg weekly (If using the patch, oral medication is required for the first 72 hours) during taper. Monitor for significant hypotension and anticholinergic side effects.</p> <p><u>Nausea</u>: Anti-emetics such as ondansetron or prochlorperazine</p> <p><u>Diarrhea</u>: Loperamide or anti-spasmodics such as dicyclomine</p> <p><u>Muscle pain and myoclonus</u>: NSAIDs or muscle relaxants such as cyclobenzaprine or methocarbamol</p> <p><u>Insomnia</u>: Sedating antidepressants (e.g. nortriptyline 25mg at bedtime or mirtazapine 15mg at bedtime or trazodone 50mg at bedtime. Do not use benzodiazepines or sedative-hypnotics.</p>
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Evidence

Some patients on COAT have adverse effects or the prescriber feels that current treatment is not benefiting the patient, and the patient may do better with tapering of the dose or discontinuing opioid therapy²¹¹⁻²¹³. Reduction in dosage, discontinuation of opioids, or transition to medication-assisted treatment for opioid use disorder frequently improves function, quality of life, and even pain control²¹⁴. Because the experience of pain, and the symptoms of withdrawal that accompany an opioid taper vary from one person to the next, there is not a one size fits all approach. The approach to and rate of taper

in patients on COAT is based on the individual patient's needs and comorbidities. Expert opinion, rather than systematic reviews or RCTs have informed these "best practice" recommendations.

Many pharmacologic therapies have been studied for use as adjunctive agents during opioid taper to palliate opioid abstinence syndrome (withdrawal) as well as emergent insomnia and anxiety.²¹⁵⁻²²⁰

A multidisciplinary approach to pain, including psychotherapy (behavioral activation, problem solving therapy, etc.), physical therapy, chiropractic, social work, and occupational therapy have been proven to improve function. Multidisciplinary pain programs have strong clinical efficacy and empirical data supporting their cost-efficiency.^{91,92,221-224} These programs, while neither widely available nor well reimbursed, provide significant benefit to many patients. In addition, a multidisciplinary approach may be considered to address the psychosocial and cognitive aspects of chronic pain together with patients' physical rehabilitation.²²⁵

High quality evidence of safety and comparative efficacy is lacking in ultra-rapid detoxification, or for the use of antagonist drugs, with or without sedation.²²⁶

Extremely challenging behavioral issues may emerge during an opioid taper.²²⁷ Special care must be taken by the prescriber to preserve the therapeutic relationship during opioid tapering. Otherwise, taper can precipitate doctor-shopping, illicit drug use, or other behaviors that pose a risk to patient safety. Although there are no fool-proof methods for preventing behavioral issues during an opioid taper, strategies implemented at the beginning of the opioid therapy are most likely to prevent later behavioral problems if an opioid taper becomes necessary. Patients who exhibit aberrant behaviors during taper may have ([Opioid Use Disorder](#))²²⁸. Also, serious suicidal ideation (with plan or intent) should prompt engagement of the crisis system or if available, urgent psychiatric consultation.²²⁹

If the patient doesn't have substance use or active mental health disorder and is not on chronic high dose opioids, taper can be done safely in outpatient setting.

Surprisingly, opioid taper rarely causes significant and enduring increases in pain. If these occur, they tend to be during and immediately following completion of the opioid taper. In addition to antidepressant medications, anti-inflammatories and anticonvulsants can be used to address increased pain in patients who have no contraindications.

Office-based buprenorphine treatment is an effective **evidence-based** option which should be considered for patients with both chronic pain and opioid use disorder.²³⁰ Buprenorphine may be the only practical option for patients in rural areas where methadone treatment programs and structured pain programs are difficult to access.

Part VI. Recognition and Treatment of Opioid Use Disorder

Opioid therapy can lead to the development of opioid use disorder. Although the true incidence is unknown, this risk ranges from 3-fold for acute low dose opioids to 122-fold for chronic high dose opioids. As outlined in the DSM 5, substance use disorders including [opioid use disorder](#), are now described as existing across a continuum of severity, from mild to severe. The need for or type of treatment depend on the severity of the condition. According to the broad definition in DSM 5, only two criteria must be met to make a diagnosis of a mild disorder. Two of these criteria, tolerance and withdrawal, are normal physiological consequences of COAT. However, these two criteria do not count toward the DSM 5 diagnosis of opioid use disorder *if the medication is taken appropriately under ongoing medical treatment*. Excluding tolerance and withdrawal, a recently published large scale study found a 21% lifetime prevalence of DSM 5 prescription opioid use disorder (12% mild, 9% moderate to severe) among patients on chronic opioids.²⁰⁹

The remaining DSM 5 criteria for opioid use disorder pertain to maladaptive behavior patterns. Examples include taking opioids in larger amounts than intended, spending a great deal of time trying to obtain opioids, strong craving for opioids, recurrent opioid use in situations where it is physically hazardous, and social impairment such as withdrawal from family and friends, or conflict with medical providers over opioid use. Such behaviors are not unusual in COAT patients and differentiating between physiologic dependence and opioid use disorder can be difficult.²³¹

Often patients will readily acknowledge difficulty due to some of these maladaptive behaviors. These patients may experience an improvement in their quality of life if a transition can be made to medication-assisted treatment for opioid use disorder. However, it is important to recognize the stigma attached to the word “addiction,” and it is generally best to avoid use of that term. “Opioid Use Disorder” may be a more acceptable term to patients who perceive their primary problem to be pain. The term “opioid dependence,” while often acceptable to patients, is best avoided due to possible confusion with its outdated formal definition in DSM-IV.

As efforts to address the prescription opioid overdose epidemic have decreased the supply of prescription opioids, some patients have transitioned to heroin as a cheaper alternative. The numbers of people starting to use heroin have been steadily rising since 2007 with a corresponding increase in heroin overdose (National Institute on Drug Abuse – Research Report Series – Heroin). It is important to recognize this transition and refer high risk patients for appropriate evaluation and treatment.

Clinical Recommendations

1. Assess for opioid use disorder using DSM 5 criteria or refer for a consultation with an addiction specialist if a patient demonstrates aberrant behaviors suggestive of substance use disorder ([Table 9](#) and [Appendix H: Clinical Tools and Resources](#)).

2. Patients diagnosed with opioid use disorder should receive a combination of medication-assisted treatment and behavioral therapies.
3. Contact the Substance Abuse and Mental Health Services Administrations (SAMHSA)'s the [Providers' Clinical Support System for Opioids \(PCSS-O\)](#) and the [Providers' Clinical Support System for Medication Assisted Treatment \(PCSS-MAT\)](#) for treatment issues. Expert physician mentors are available to assist with questions or concerns about opioid tapering and assessment and treatment of substance use disorders and treatment of substance use disorders.
4. Consider prescribing naloxone as a preventive rescue medication for patients with opioid use disorder, especially if heroin use is suspected. Counsel family member or other personal contacts in a position to assist the patient at risk of opioid-related overdose. For more detail on opioid prevention education, visit www.stopoverdose.org.
5. Check the State's PMP to ensure controlled substance history is consistent with prescribing record. Prescribers may delegate the ability to query the PMP database to any licensed health care professional ([Appendix C: How to use the Prescription Monitoring Program](#)).
6. Be knowledgeable about treatment options:
 - a. Medication assisted treatment with either sublingual buprenorphine products or methadone is common in patients who have co-occurring chronic pain and opioid use disorder.
 - b. A [DATA 2000 waiver](#) is needed to prescribe sublingual buprenorphine products for opioid use disorder in an office-based setting. Providers without a waiver should consider getting one or refer the patient to a provider with a waiver to prescribe buprenorphine. This treatment may be the only practical option for patients in rural areas where methadone and other treatment programs are difficult to access.
 - c. Patients who require methadone maintenance must be referred to a federally licensed opioid treatment program.

Evidence

There is very little evidence that outpatient non-medication treatment for opioid use disorder is effective.^{232,233} In these programs, patients are tapered off opioids and are expected to attend a treatment program one or more days per week to learn skills necessary to manage symptoms (e.g., pain, mood and anxiety problems, substance craving) without resorting to substance use.

Once a moderate to severe opioid use disorder has been diagnosed, there is strong evidence for efficacy of methadone or buprenorphine maintenance combined with behavioral therapies compared to non-medication treatment.²³²⁻²³⁴ Maintenance treatment leads to lower rates of illicit opioid use and likely reduces health care utilization and criminal justice involvement.²³⁵⁻²³⁸

There is very little evidence that antagonist therapy with naltrexone is effective for patients with opioid use disorder, and there is no evidence in patients with chronic pain. However, it might be considered in selected, highly motivated patients (e.g., impaired professionals).²³⁹

Part VII. Chronic Pain Management in Special Populations

Managing Chronic Pain during Pregnancy and Neonatal Abstinence Syndrome

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Opioid use during pregnancy complicates the clinical management of an already vulnerable group. Opioid use in pregnancy is increasing at an alarming rate, an estimated 3-4 fold increase between 2000 and 2009.²⁴⁰ Studies of opioid exposure during pregnancy suggest increased fetal, obstetrical and neonatal risks (including neonatal abstinence syndrome). Many pregnancies are unplanned and women of reproductive age may be using opioids prior to a clinically recognized pregnancy. These factors make management of opioid use during pregnancy particularly challenging for healthcare providers.

Clinical recommendations

1. Recommend counseling before (preconception) and during pregnancy for women on COAT to assess and educate about potential maternal, fetal, and neonatal risks.
2. Address underlying contributors to pain syndromes such as stress and anxiety and use non-pharmacologic therapies as appropriate, including stress reduction, exercise, mechanical therapies, activity modification, and complementary and alternative medicine approaches. If appropriate, refer for mental health services ([Non-opioid Options](#)).
3. Use acetaminophen during pregnancy for treatment of pain. NSAIDs anti-inflammatory medications may be considered in consultation with an obstetrical provider for short duration of therapy (<48 hours) prior to the third trimester.
4. Use caution when initiating short-acting opioids for treatment of pain during pregnancy and limit it to women with severe pain for whom other medical treatments have failed.
5. Assess pregnant women taking opioids for opioid use disorder. If present, refer to a qualified specialist for methadone or buprenorphine treatment for pregnant women. Buprenorphine may have improved neonatal outcomes, but availability may be limited due to provider or geographic access ([Appendix H: Clinical Tools and Resources](#)).
6. Monitor fetal growth for women on opioids, using fundal height or ultrasound surveillance, given the risk of intrauterine growth restriction.
7. Consider a perinatal pediatric consultation for pregnant women on opioids to better prepare them for risks of NAS and possible increased hospital stay for the newborn.
8. Use the Finnegan score to assess neonates during the immediate postnatal period if they were exposed to opioids in utero.

9. Weigh carefully the risks/benefits of opioid detoxification during pregnancy, when making the decision to go forward with treatment; and closely monitor the treatment plan for symptoms of withdrawal and risk of relapse.
10. Assess availability of social and community support for women with opioid use disorder or escalating pain symptoms during pregnancy to identify needs for education and services.

Evidence

Ideally, pharmacologic agents would not be needed during pregnancy. However, pain in pregnancy is common and may include musculoskeletal symptoms, exacerbation of previous injuries, headaches and abdominal pain. Some women will require ongoing or episodic opioid treatment for medical conditions, which may be exacerbated by pregnancy. Safety and efficacy data for non-opioid treatments for pain symptoms in pregnancy is limited. Analgesics such as acetaminophen are generally considered safe, while NSAIDs may cause oligohydramnios and premature closure of the ductus arteriosus when used for prolonged periods or during the third trimester.^{241,242} Mechanical therapies, exercise, complementary or alternative medicine, and psychiatric treatment have been beneficial, but each may have risks to a woman's pregnancy based on her history.²⁴³

A 2015 CDC study showed that 39% of women age 15-44 on Medicaid between 2008-2012 had filled an opioid prescription each year, compared with 28% of women with private insurance.²⁴⁴ Of pregnant women enrolled in Medicaid between 2000-2007, 21.6% filled an opioid prescription from an outpatient pharmacy during pregnancy²⁴⁵ as compared to 14.4% of pregnant women with private insurance during 2005-2011.²⁴⁶ These studies do not provide insight on the indications for opioid prescriptions but illustrate remarkably high rates in both the privately and publically insured. Women who use opioids and could become pregnant require counseling regarding maternal, fetal and neonatal risks.

Fetal and Obstetrical Risks

Opioids are known to cross the placenta and can be detected in fetal umbilical cord blood and meconium.²⁴⁷ The window for teratogenicity is from 4 to 10 weeks after the last menstrual period, which is often before a clinically recognized pregnancy. Research on teratogenicity of opioids is limited and heterogeneous as there is a relatively high 2-3% incidence of major congenital malformations in the general population. Studies have shown that opioid exposed fetuses may be at increased risk for neural tube, cardiac and gastrointestinal defects.^{248,249}

Opioid use during pregnancy is associated with adverse pregnancy outcomes such as preterm delivery, poor fetal growth, and stillbirth.²⁵⁰ Additionally, pregnant women who use opioids have higher rates of depression, anxiety, and chronic medical conditions, with increased health care costs.²⁵⁰ There are, however, numerous confounders that challenge the causal relationship between opioids and adverse obstetrical events, such as co-morbid medical conditions, obesity, poor nutritional status, socioeconomic background, and poly-substance abuse (alcohol, tobacco, illegal drugs).

NSAIDs may cause oligohydramnios and premature closure of the fetal ductus arteriosus when used for prolonged periods or during the third trimester.

Risks Associated with Medically Supervised Withdrawal from Opioids

The safety of medically supervised withdrawal from opioids during pregnancy is not well studied, yet there are historical reports of embryonic or fetal loss, preterm labor, and fetal distress during maternal opioid withdrawal.²⁵¹⁻²⁵³ Several recent studies have reported successful inpatient medically supervised withdrawal from opioids during pregnancy with no increased risk of adverse obstetrical outcomes²⁵⁴⁻²⁵⁶ Ideally women discontinue or minimize opioid dose *prior* to pregnancy to decrease the risk of birth defects, obstetrical complications and neonatal abstinence syndrome. The decision to proceed with opioid discontinuation or medically supervised withdrawal during pregnancy is complex and must be individualized.

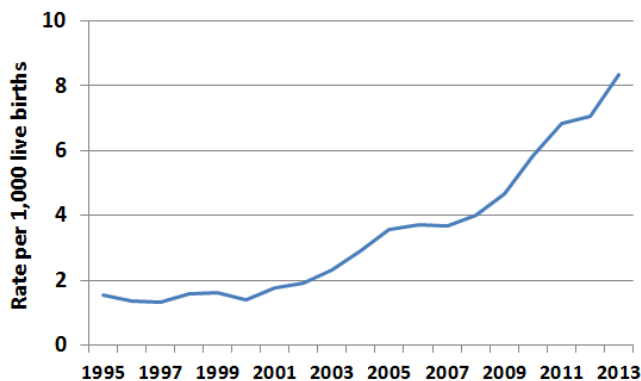
Treatment of Opioid Use Disorder

For women who do have opioid use disorder (as defined by DSM 5), use of methadone or buprenorphine reduces illicit drug use, criminal activity and infectious complications (including sexually transmitted diseases, HIV, hepatitis B and C), while improving adherence to prenatal care.²⁵⁷ The American Academy of Pediatrics supports use of methadone (without limitation) and other opioids during breastfeeding. Active use of illegal drugs, however, is a contraindication to breastfeeding.²⁵⁸

Neonatal Abstinence Syndrome

Long-term opioid therapy during pregnancy can lead to neonatal abstinence syndrome.²⁴⁰ Neonatal abstinence syndrome (NAS) typically occurs in the first 24 hours to 14 days of neonatal life and is characterized by the Finnegan score, which grades the degree of psychomotor irritability, vasomotor and gastrointestinal disturbances.^{259,260} NAS may occur in up to 60-80% of opioid exposed infants²⁴⁰ and has been increasing at an alarming rate ([Figure D](#)). Maternal methadone dose at delivery does not correlate directly with risk of NAS.²⁶¹ Buprenorphine is associated with a lower incidence and shorter duration of NAS, higher birth weights and longer gestation.²⁵⁷

Figure D. Infant Hospitalizations for Neonatal Abstinence Syndrome in WA State 1990-2013



Source: Inpatient Hospital Discharge & Birth Certificate Data,
NAS= ICD diagnosis code of 779.5

Managing Chronic Non-cancer Pain in Children and Adolescents

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The use of opioids to treat pain in infants and children presents challenges for a few key reasons. First, with very rare exception, opioids have not been labeled for use in individuals less than 18 years of age, indicating a dearth of quality studies on pharmacokinetics, pharmacodynamics, safety, and, in the youngest children, clinical effectiveness. Second, although acute pain problems in pediatrics have many characteristics in common with adult presentations, persistent, recurrent, and chronic pain in infants, children, and adolescents are often qualitatively different than chronic pain problems in adults. It is a corollary that treatment approaches may vary accordingly. Finally, it is often said that "children are not little adults," meaning one cannot simply extrapolate from adult medicine to pediatrics; however, "adults are big children" and there is mounting evidence to show that poorly treated pain in childhood and adolescence is strongly associated with chronic pain and other difficulties in the adult years.

Clinical Recommendations

1. Prescribe opioids for acute pain in infants and children only if knowledgeable in pediatric medicine, developmental elements of pain systems, and differences in pharmacokinetics and pharmacodynamics in young children.
2. Avoid opioids in the vast majority of chronic non-cancer pain problems in children and adolescents (e.g. abdominal pain, headache, pervasive musculoskeletal pain), as evidence shows no indication.
3. Opioids are indicated for a small number of persistent painful conditions, including those with clear pathophysiology and when an endpoint to usage may be defined, such as pain associated with most surgical procedures, trauma (including burns), and major reconstructive surgery.
4. Opioids may be indicated for some chronic pain conditions in children and adolescents, when there is clear pathophysiology, and no definable endpoint. This may include treatment at the end of life or for certain ongoing nociceptive mediated painful conditions, such as osteogenesis imperfecta or epidermolysis bullosa.
5. Put safety first when prescribing opioids to younger patients: limit the total dispensed and educate parents about dosing, administration, storage and disposal to minimize risks of diversion or accidental ingestion. Adolescents should undergo similar screening for risk of substance use disorder that one would conduct with adults.
6. Consult or refer to a pediatric pain specialist when chronic pain problems in children and adolescents are complicated or persistent, given the developmental complexities and potential for ongoing pain problems in the future. These problems are best treated by those with specialty training in the area.

Evidence

Labeling of Opioids for Use in Pediatrics

Approximately 80 percent of drugs prescribed for children in the United States are done so “off label,” as they have not been approved by the FDA for use in the younger age groups.^{262,263} Clinicians, therefore, are faced with a difficult dilemma: do we withhold potentially beneficial medications from young patients because they are not labeled for that age group? In the case of analgesics, this means unnecessary suffering. Or do we give the drugs based on extrapolation from adult studies (with some dosage modifications for body mass or surface area) without direct data on safety and effectiveness?

Even with innovations to improve the study of pediatric medications, such as the Best Pharmaceuticals for Children Act^{iv} and the Pediatric Research Equity Act^v, analgesic medications remain quite under-represented. No analgesic medications have been labelled for children less than 6 months of age and only ibuprofen has been labeled for those 6 to 24 months. Based on expert consensus, the effectiveness of opioids may be extrapolated from studies on adults and older children down to those 2 years of age and older. Still lacking, however, are sufficient data on drug metabolism, dose response, and toxicity.^{264,265}

Although the benefits have been deemed to outweigh the risks for using opioids for acute pain in children, such is not the case for chronic pain and thus opioid treatment in this context is generally discouraged.²⁶⁶ For example, the American Pain Society (2012) states, “Opioids are rarely indicated in the long-term treatment of chronic non-cancer pain in children, although they may be beneficial in certain painful conditions with clearly defined etiologies.” The Japanese Pediatric Society guidelines state, “The use of opiates for non-cancer chronic pain is debatable; they are generally reserved for treatment of painful syndromes related to cancer, injury, or other acute types of pain. The use of opiates is not recommended for the types of chronic pain described in the present guidelines.”²⁶⁷ The indications are clearly for those conditions with clear underlying pathophysiology and some endpoint is defined prior to initiation.

Chronic Pain in Pediatrics

The most common presentations of chronic pain in children and adolescents include abdominal pain, headache, and musculoskeletal pain.²⁶⁸ The most common pain problems in adults are rarely seen in pediatric populations, as they are frequently neuropathic in nature and often are related to degenerative aging processes.²⁶⁹ As a consequence, treatment modalities are often quite different, i.e. biopsychosocial models are emphasized in children and opioid medications rarely have a role. The possible exceptions are chronic, non-cancer conditions with known pathophysiology and a defined endpoint (e.g., a patient with avascular necrosis awaiting joint replacement), or conditions with persistent pain with an expected endpoint (e.g. post-trauma or extended post-operative pain).²⁷⁰

iv

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCAct/SignificantAmendmentstotheFDCAct/ucm148011.htm> and <http://bpca.nichd.nih.gov/Pages/Index.aspx>

^v <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077853.pdf>

Developmental Trajectories: Adults are Big Children

A comprehensive review of longitudinal studies focused on the continuity or contiguity of pediatric and adolescent chronic pain problems into adulthood is beyond the scope of this guideline. Certainly adults with chronic pain often recall having had difficulties in their earlier years. More substantial, however, are the prospective longitudinal or cross-sequential studies demonstrating these trajectories. Multiple studies have shown that children with functional abdominal pain are at risk for difficulties as adults that include anxiety or depressive disorders, functional gastrointestinal disorders, and other non-abdominal chronic pain.²⁷¹⁻²⁷⁵ Similar data have been generated for headaches^{276,277} and back pain²⁷⁸⁻²⁸⁰ Although no specific studies on prevention have been reported, it seems clear that by addressing pain complaints in the young, morbidity in the subsequent years will be reduced.

Managing Chronic Pain in Older Adults

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Aging is associated with unique biological, psychological and social factors that all play an important role in pain management. As in all age groups, evidence of long-term effectiveness of opioid therapy is lacking. However, in carefully selected and monitored patients, opioids may provide effective pain relief if used as part of a comprehensive multimodal pain management strategy.²⁸¹ A combination of pharmacologic, non-pharmacologic, and rehabilitative approaches in addition to a strong therapeutic alliance between the older patient and physician is essential to achieve desired treatment outcomes.⁸⁰

Clinical Recommendations

1. Use opioids with short half-lives, as they are usually the best choices for older adults. Drugs with a long half-life can readily accumulate in older adults and result in toxicity (e.g. respiratory depression, sedation).
2. Weigh the individual patient's needs and clinical presentation with known risk factors when deciding whether short or long acting opioids are best
3. Avoid the use of agonist-antagonist opioids in older adults as their side effects can be pronounced.
4. Be vigilant when treating patients over 65 so adequate pain relief is provided and the risk of delirium and postsurgical opioid-related adverse drug events is minimized.
5. Use the least invasive method of drug administration (e.g. oral).
6. Initiate opioid therapy at a 25% to 50% lower dose than that recommended for younger adults, and slowly and carefully titrate dosage by 25% increments on an individual basis balancing pain relief, physical function, and side effects.
7. Have a plan for addressing constipation from the start of opioid therapy. Prophylaxis and/or treatment can include hydration, bulk fiber (only if hydration is maintained), activity, Senna, and Sorbitol (20cc of 70% taken twice daily for 3 days per week).²⁸¹

8. Recognize and manage all potential causes of side effects, taking into consideration medications that potentiate opioid side effects:
 - a. Sedatives, tranquilizers, and anti-emetics can cause sedation.
 - b. Antihypertensives and tricyclics can cause postural hypotension.
 - c. Antihistamines, phenothiazines, tricyclics, and anticholinergics can cause confusion.
9. Avoid using more than one opioid at the same time. This makes it is easier to identify the cause of an adverse effect or toxic reaction. The incidence of delirium and other adverse reactions increases with the number of prescription drugs taken.
10. **Avoid** the following drugs:
 - a. Codeine: the doses required for effective pain relief in older adults are associated with an increased incidence of side effects (e.g. constipation, nausea and sedation).
 - b. Meperidine: the metabolite, normeperidine, is toxic to the CNS and can cause seizures, mood alterations and confusion; more so in older patients, especially if the patient has coexisting CHF or renal impairment.
 - c. Methadone: has a high drug-drug interaction potential and is associated with prolongation of the QT interval and a potential risk of accumulation due to a long elimination half-life. In addition, methadone is difficult to titrate because of its large inter-individual variability in pharmacokinetics, particularly in the frail elderly.

Evidence

Approximately 60% of Americans over age 65 have persistent pain, most commonly from musculoskeletal disorders such as arthritis and degenerative spine conditions²⁸² but painful conditions related to neuropathies, advanced heart, kidney, or lung disease are also reported.^{283,284} Older adults are also more likely to undergo surgeries associated with high incidence of persistent pain.²⁸⁵ Persistent pain or inadequate treatment in older adults is associated with reduced physical performance, falls, decreased sleep and self-rated health, mood, and cognition.²⁸¹

Due to the frequency of chronic disease and potential for polypharmacy among older adults, drug-disease and drug-drug interactions should also be considered when prescribing. Nutritional alterations (e.g., protein deficiency), age-related changes (e.g. reduced hepatic and renal function, reduced body water, altered ratio of lean body mass to total body weight) and altered pharmacokinetics impact treatment options necessitating careful evaluation and monitoring.¹⁴⁸ These age-related changes all make older adults especially vulnerable to opioid side effects and reduce the therapeutic window between beneficial doses and doses that are toxic or lethal.

Though evidence shows that older adults are less likely to misuse and abuse opioids²⁸⁶ they are also likely to have higher levels of pain severity and depressive symptoms, and more physical disability. These can increase misuse and abuse²⁸⁷ so an individual approach weighing risk and benefits is best.²⁸¹

There is insufficient evidence to recommend short-acting versus long-acting opioids, or as-needed versus around-the-clock dosing of opioids. However, one large longitudinal nursing home study showed that extended-release opioids improved functional status and social engagement when compared to short acting opioids.²⁸⁸ An individual's condition and need for proper pain management must be weighed against the risks of developing adverse effects of COAT.

The potential for side effects is high in older adults due to altered ability to distribute and excrete drugs resulting in greater peak and longer duration of action. Common opioid side effects include nausea, vomiting, delirium, respiratory depression, sedation, pruritus, hypotension, and urinary retention (especially if there is coexisting benign prostatic hypertrophy). Older adults are particularly prone to constipation and even ileus, making prevention measures particularly important. Opioids have also been linked to an increased risk for falls and any non-spine fracture in community living older adults.^{289,290}

Patients over 65 who receive opioids for postoperative pain have a higher risk for opioid-related adverse drug events.²⁹¹ Delirium has a significant impact on the medical, functional, and cognitive outcomes of older patients and the risk of delirium increases with inadequate pain control and the use of meperidine.^{292,293} In fact, use of meperidine is listed in the 2012 American Geriatrics Society Beers Criteria as potentially inappropriate for older adults.²⁹⁴

Managing Chronic Pain in Cancer Survivors

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Management of chronic pain in the cancer survivor involves unique issues that require a careful and thoughtful approach from the clinician. Survivors are at risk of recurrent disease, so development of new or worsening pain in the survivor requires rapid evaluation in coordination with the oncologist. In the absence of “red flags” for malignancy, simple exacerbations of chronic pain are treated in a manner similar to chronic non-cancer pain (CNCP). Hence, the best pain management strategy combines diligent monitoring for cancer recurrence with standard chronic pain management therapies, including multimodal and interdisciplinary approaches.

Although the term cancer survivor has a variety of definitions, for this guideline, a survivor is someone who has completed cancer treatment, is cured or in full clinical remission, with no current evidence of disease, and under cancer surveillance only.²⁹⁵

Survivors are primarily older, 45% are over the age of 70, and only 5% younger than age 40.²⁹⁶ The most common cancer sites in survivors are female breast, prostate, colorectal, melanoma, and gynecologic. With this survival benefit comes the burden of long-term and late effects; of cancer and cancer therapy. The most common issues are pain, depression, and fatigue. Other chronic problems include cognitive decline, sexual dysfunction, anxiety, and sleep disorders.²⁹⁷⁻²⁹⁹

Primary care providers will see more patients who are cancer survivors, as their numbers are increasing significantly due to earlier detection and improved cancer therapies.

National Comprehensive Cancer Network Survivorship Guidelines 2014

Clinical Recommendations

1. Make a medical diagnosis for the cause of pain. Promptly address new and worsening complaints to determine the cause. Always consider cancer recurrence or secondary malignancy in the differential diagnosis.
2. Follow the recommendations for treating chronic non-cancer pain once cancer recurrence has been ruled out as the source of pain. This includes using multimodal and multidisciplinary approaches and focusing on non-escalating doses, with attempts to reduce the total opioid dose and discontinue when possible ([Reducing or Discontinuing COAT](#)).
3. Educate the patient about the limited role of opioids in managing chronic cancer-related pain. During active cancer treatment, patients may have been accustomed to receiving escalated opioid doses with any complaint of worsening pain. Therefore it may come as a surprise to the patient when the provider not only declines to escalate an opioid dose, but instead initiates a slow taper once remission has been achieved. Significant education is needed to assist the patient and caregiver to understand the new approach.
4. Encourage the use of non-pharmacologic therapies with a focus on rehabilitation and pain management. This includes a graduated exercise program, physical therapy, thermal therapy, complementary and alternative measures, and counseling to help with anxiety, depression, and coping ([Non-opioid Options](#)).
5. Use an individualized approach to pain management, paying special attention to those who are hyper vigilant about their body sensations and may present with frequent reports of new symptoms.
6. Be alert to a patient being fearful of the cancer recurring, as fear commonly underlies pain behaviors. Reassure and redirect the patient after a thorough evaluation of the pain complaint and consultation with the oncologist for imaging recommendations.
7. Encourage patients to actively engage in their pain management plan and explore options to participate in support groups.
8. If signs and symptoms of spinal cord compression are present ([Table 13](#)), an urgent medical workup with MRI of the spine should be performed within 24 hours.

Chronic cancer-related pain is primarily caused by cancer *treatment*, rather than the neoplasm.

Paice, NCCN Survivorship

Evidence

Chronic cancer-related pain (CCRP) is common in survivors, with an overall incidence of 33% to 40%.^{300,301} Harrington 2014 found that 16-73% of breast cancer survivors experience pain, as well as significant symptom burden of psychological distress and insomnia. Survivors younger than 50 years of age report more pain than older patients.³⁰² CCRP typically is more common and more severe in the first few years after completing treatment, then declines in intensity as time passes.³⁰¹ The Childhood Cancer Survivor Study reported 11% of adult survivors (mean interval from diagnosis 17 years) experienced medium or higher pain intensity;³⁰³ and 6% of Australian adult cancer survivors at 5-6 years post treatment reported moderate to severe pain.³⁰⁴ However, certain *late effects* of therapy may emerge years, or even decades, after completing therapy, such as radiation related plexopathies or fibrosis, producing discomfort, pain, reduced range of motion (ROM) and impacting quality of life.³⁰⁵

Unlike CNCP, identifiable tissue damage caused by the tumor or, more commonly, the cancer treatment, is typically the basis of the pain complaint.³⁰¹ Examples include painful chemotherapy-induced peripheral neuropathy (CIPN) or post-mastectomy pain syndrome. Aromatase inhibitors are used to prevent recurrence of breast cancer and are taken for 2-10 years after completing acute therapy. Nearly half of women experience myalgias and arthralgias,³⁰⁶ which may be of enough severity that 21-38% of patients abandon this potentially life-saving therapy³⁰⁷ ([Table 11](#)).

Table 11. Common Pain Syndromes Resulting from Cancer Treatment*

Chemotherapy-induced peripheral neuropathy (CIPN)
Myalgias and arthralgias from aromatase inhibitors in breast cancer survivors.
Generalized myofascial pain from deconditioning or sleep disorders
Post-operative neuropathic pain syndromes such as post-mastectomy, post-amputation, post-radical neck pain.
Chronic pain from radiation therapy such as plexopathies, lymphedema, and chronic proctitis, cystitis, enteritis, or tenesmus from pelvic radiation.
Dyspareunia from ovarian failure, causing vaginal dryness or atrophy

*For a more extensive description of chronic pain syndromes, the types of cancers they are associated with, along with causes and treatment options, ([Appendix E: Chronic Pain Syndromes in Cancer Survivors](#)).

Managing Chronic Cancer Related Pain

Chronic cancer related pain in the survivor can improve significantly with a variety of pharmacological and non-pharmacological therapies. Pain treatments in the survivor should be modeled after chronic non-cancer pain strategies, rather than palliative therapies. As with CNCP, the primary goal of pain management is improved function.

Pharmacological therapies for chronic cancer related pain (CCRP) rely more on neuromodulators and less on opioids. As in CNCP, neuromodulators, such as serotonin-norepinephrine reuptake inhibitors (SNRI) antidepressants and anticonvulsants are the core of pharmacological therapy. Topical agents, such as lidocaine 5% patch, capsaicin cream, or diclofenac gel may be helpful for post-surgical pain syndromes or radiation fibrosis. Although opioids are the foundation for cancer pain management in the

setting of active disease, COAT in the survivor is typically relegated to third or fourth line therapy, if used at all.²⁰ Occasionally, a stable, non-escalating dose of opioids is required for more severe CCRP.

Non-pharmacological therapies are primary strategies in the management of CCRP. Physical therapy, rehabilitation, and graded exercise programs will help reverse deconditioning and functional loss commonly experienced during cancer treatment. Specialized therapy such as manual lymphatic drainage for lymphedema will improve discomfort from swelling. Counseling for anxiety, depression, and pervasive fear of cancer recurrence is beneficial; as is mindfulness training and other cognitive behavioral strategies to reduce pain. Sleep hygiene education is essential for pain management, as sleep disruption is common in this population.³⁰⁶

All new or worsening pain in the cancer survivor must be promptly evaluated to eliminate the possibility of cancer recurrence as the source of pain. Consultation with the patient's oncologist is recommended to provide guidance as needed.

Recurrent or Secondary Malignancy

Most survivors struggle with a fear of cancer recurrence, and are well aware that pain is an initial symptom.³⁰⁶ The clinician should provide reassurance that all new or worsening pain problems will be investigated to eliminate cancer as the cause, in coordination with the oncologist. Extensive emotional support may be needed, and formal counseling may be required to assist with anxiety related to potential for cancer recurrence.^{295,308}

The oncologist will direct surveillance screening, either through his/her office, or guide the primary care provider through the Cancer Treatment Summary and Survivorship Care Plan.³⁰⁹⁻³¹¹ However, it is essential that all providers involved in the care of cancer survivors know the signs and symptoms associated with cancer, whether from recurrence or secondary malignancy ([Table 12](#)).

Table 12. Signs and Symptoms Associated with Malignancy that Warrant Assessment for Cancer Recurrence

New or worsening pain
Pain worse at night or with recumbency
Unexplained weight loss of 10 pounds (4.5 kg)
Night sweats
Fever and chills
Enlarging masses
Unusual fatigue
Excessive bruising or bleeding
Change in moles or skin
Altered bowel function
Persistent cough or hoarseness
Signs of breast cancer recurrence include: new lumps or skin changes in breast or axilla; new dyspnea; persistent headache; new bone, chest, or abdominal pain.

Kenyon, Davies 2013a; Davies 2013b

Cancer may occasionally present as metastatic disease with spread to the vertebrae causing spinal cord compression. This is most common in lung, breast and prostate cancer. Symptoms include: ([Table 13](#)).

Table 13. Signs and Symptoms of Spinal Cord Compression

New onset of severe back pain	Thoracic spine is most common site. Pain is typically localized to 1-2 vertebrae. Worse at night and with recumbency. Worse with Valsalva maneuver. May present as a “band” of pain around the torso
New weakness in the limbs	May be described as “clumsiness” or “heaviness” of the limbs
New sensory changes in the limbs	Paresthesias, dysesthesias, lancinating pain
Loss of bowel or bladder control	Urinary retention causing overflow incontinence, or fecal incontinence from loss of anal sphincter tone
Saddle anesthesia	Numbness in perineum, lower buttocks, posterior proximal thighs

White 2008; Davies 2013a; Davies 2013b, Prasad & Shift 2005

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Part VIII. Appendices

Appendix A: Opioid Dose Calculations	54
Appendix B: Validated Tools for Screening and Assessment	57
Appendix C: How to use the Prescription Monitoring Program	58
Appendix D: Urine Drug Testing for Monitoring Opioid Therapy	60
i. Monitoring Opioid Therapy with Urine Drug Testing (UDT)	60
ii. UDT Algorithm for Monitoring Opioid Therapy	60
iii. UDT Clinical Vignettes	60
iv. Frequently Asked Questions (FAQs) about UDT	60
Appendix E: Chronic Pain Syndromes in Cancer Survivors	70
Appendix F: Diagnosis-based Pharmacotherapy for Pain and Associated Conditions	72
Appendix G: Patient Education Resources	74
Appendix H: Clinical Tools and Resources	76
Appendix I: AGREE Criteria	79

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Appendix A: Opioid Dose Calculations

Table 14. Dosing Threshold for Selected Opioids

Opioid	Recommended dose threshold for pain consult	Recommended starting dose	Considerations
Buprenorphine Transdermal	Threshold is beyond maximum daily dose	5mcg/hr q 7 days	Maximum dose: 20mcg/hr due to risk of QTc prolongation
Codeine	800mg per 24 hours	30mg q 4–6 hours	See individual product labeling for maximum dosing of combination products. Avoid concurrent use of any OTC products containing same ingredient.
Fentanyl Transdermal	50mcg/hour q 72 hours	12.5mcg/hour q 72 hours	Use only in opioid-tolerant patients who have been taking \geq 60mg MED daily for a week or longer.
Hydrocodone	120mg per 24 hours	Immediate Release 5-10mg q 4–6 hours	See individual product labeling for maximum dosing of combination products. Avoid concurrent use of any OTC products containing same ingredient. Use ER formulation with extreme caution due to potentially fatal interaction with alcohol or medications containing alcohol.
		Sustained Release 10mg q 12 hours	
Hydromorphone	30mg per 24 hours	Immediate Release 2mg q 4–6 hours	Because of its short half-life, hydromorphone is a good choice in older adults with renal impairment.
		Sustained Release 8mg q 24 hours	
Morphine	120mg per 24 hours	Immediate Release: 10mg q 4 hours	Metabolites may accumulate in patients with impaired renal or hepatic function resulting in prolonged effects and toxicity. Use Avinza with extreme caution due to potentially fatal interaction with alcohol or medications containing alcohol.
		Sustained Release: 15mg q 12 hours	
Oxycodone	80mg per 24 hours	Immediate Release: 5mg q 4–6 hours	See individual product labeling for maximum dosing of acetaminophen combination products. Avoid concurrent use of any OTC acetaminophen products.
		Sustained Release: 10mg q 12 hours	
Oxymorphone	40mg per 24 hours	Immediate Release: 5–10mg q 4–6 hours	Use ER formulation with extreme caution due to potentially fatal interaction with alcohol or medications containing alcohol.
		Sustained Release: 10mg q 12 hours	
Tapentadol	300mg per 24 hours	Immediate Release 50mg q 4-6 hours	Dual mechanism of action - binds to mu-opioid receptors and inhibits reuptake of norepinephrine. Use caution when combining with other medications that affect
		Sustained Release 50mg q 12 hours	

			serotonin as it may increase risk of seizures and serotonin syndrome. Do not exceed 600mg/day for immediate release and 500mg/day for sustained release formulation.
Tramadol	Threshold is beyond maximum daily dose	Immediate Release 50mg q 4-6 hours	Dual mechanism of action - binds to mu-opioid receptors and inhibits reuptake of serotonin and norepinephrine. Use caution when combining with other medications that affect serotonin as it may increase risk of seizures and serotonin syndrome. Do not exceed 400mg/day for immediate release and 300mg/day for sustained release formulation.
		Sustained Release 100mg q 24 hours	

*Meperidine should not be prescribed for chronic pain.

**Methadone should only be prescribed for chronic pain if the provider is knowledgeable of methadone's non-linear pharmacokinetics, unpredictable clearance, multiple drug-to-drug interactions and additional monitoring requirements.

***Long-acting formulations should only be prescribed for opioid-tolerant patients who have been taking ≥ 60 mg MED daily for a week or longer

Morphine Equivalent Dose Table

All conversions between opioids are estimates generally based on equianalgesic dose. Patient variability in response to different opioids can be large, due primarily to genetic factors and incomplete cross-tolerance. **It is recommended that, after calculating the appropriate conversion dose, it be reduced by 25–50% to assure patient safety.**

Table 15. MED for Selected Opioids

Opioid	Approximate Equianalgesic Dose (oral & transdermal) *
Morphine (reference)	30mg
Codeine	200mg
Fentanyl transdermal	12.5mcg/hr
Hydrocodone	30mg
Hydromorphone	7.5mg
Oxycodone	20mg
Oxymorphone	10mg
Tapentadol	75mg
Tramadol	300mg

*Adapted from Von Korff 2008 & FDA labeling

Table 16. MED for Methadone

Chronic Methadone Dose	Approximate Conversion Factors to Morphine Equivalent*
Up to 20mg per day	4
21 to 40mg per day	8
41 to 60mg per day	10
>60mg per day	12

*Adapted from Ayonrinde 2000. Equianalgesic dose ratios between methadone and other opioids are complex. Methadone exhibits a non-linear relationship due to the long half-life and accumulation with chronic dosing. Because methadone pharmacokinetics are variable across patient populations, these conversion factors are approximate and doses around the cutoff can have huge differences in calculated MED.

Calculating Morphine Equivalent Dose

This guideline provides an electronic [morphine equivalent dose \(MED\) calculator](#) for determining a patient's daily morphine equivalent dose when patients are on one or more opioids. Table 16 below shows samples of morphine equivalents that can be computed using the calculator.

Table 17. Morphine Equivalent Dose Calculation

For patients taking more than one opioid, the morphine equivalent doses of the different opioids must be added together to determine the cumulative dose ([Table 15](#) in Appendix A for MEDs of selected medications). For example, if a patient takes six hydrocodone 5mg / acetaminophen 500mg and two 20mg oxycodone extended release tablets per day, the cumulative dose may be calculated as follows:

1. Hydrocodone 5mg x 6 tablets per day = 30mg per day.
2. Using the Equianalgesic Dose table in Appendix A, 30mg Hydrocodone = 30mg morphine equivalents.
3. Oxycodone 20mg x 2 tablets per day = 40mg per day.
4. Per Equianalgesic Dose table, 20mg oxycodone = 30mg morphine so 40mg oxycodone = 60mg morphine equivalents.
5. Cumulative dose is 30mg + 60mg = 90mg morphine equivalents per day.

Appendix B: Validated Tools for Screening and Assessment

	Tool Characteristics			
	Administration	Time to Complete	Length	Available for Public Use (Cost)
Assessing Function and Pain				
Pain, Enjoyment of life, General Activity (PEG) http://mytopcare.org/wp-content/uploads/2013/06/PEG-Pain-Screening-Tool1.pdf	Patient self-report	1 minute	3 items	X (Free)
Two Item Chronic Pain Scale	Clinician or patient self-report	1 minute	2 items	X(Free)
Risk of Transitioning to Chronic Pain				
StarTBack http://www.keele.ac.uk/sbst/startbacktool/	Patient self-report	<5 minutes	9 items	X (Free)
Functional Restoration Questionnaire FRQ				X (after email registration)
Screening for Risk of Opioid Addiction and Substance Abuse				
Opioid Risk Tool (ORT) ³¹²	Clinician or patient self-report	1 minute	5 (yes/no) questions	X (Free)
CAGE Adapted to Include Drugs (CAGE-AID) ³¹³⁻³¹⁵	Clinician	< 5 minutes	4 (yes/no) questions	X (Free)
Screeener and Opioid Assessment for Patients with Pain (SOAPP-R) www.painedu.org/soapp.asp	Patient self-report	< 10 minutes	24 items	X (Free, with licensing agreement)
Current Opioid Misuse Measure (COMM) www.painedu.org/soapp.asp	Patient self-report	< 10 minutes	17 items	X (Free, with licensing agreement)
DIRE http://integratedcare-nw.org/DIRE_score.pdf	Clinician interview	<2 minutes	7 items	X(Free)
Alcohol Use Disorders Identification Test (AUDIT)	Clinician or patient self-report	< 5 minutes	10 items	X (Free)
Screening for Mental Health Disorders				
Patient Health Questionnaire 9 (PHQ-9)	Patient self-report	< 5 minutes	10 items	X (Free)
GAD-7 http://www.mpho.org/resource/d/34008/GAD708.19.08Cartwright.pdf	Patient self-report	<5 minutes	7 items	X (Free)
PC-PTSD	Clinician interview	<5 minutes	4 items	X(Free)

*The tools listed in this table have demonstrated good content, face, and construct validity in screening for risk of addiction and monitoring opioid therapy. Further validation studies and prospective outcome studies are needed to determine how the use of these tools predicts and affects clinical outcomes.

Appendix C: How to use the Prescription Monitoring Program

Chris Baumgartner, BS

Prescription Drug Monitoring Programs (PDMPs or PMPs) are now operating in 49 states, and have demonstrated their value on many levels.³¹⁶⁻³²⁰ In Washington State, the Prescription Monitoring Program (PMP) is also known as [Prescription Review](#). This database contains the history of all controlled substances dispensed by Washington licensed facilities and providers since implementation in October 2011. The PMP offers key clinical benefits such as identifying duplicative drug therapy, dangerous drug combinations, other providers involved in the patient’s care, signs of aberrant behaviors and possible misuse, and patient’s medication compliance. Providers or their qualified delegated staff should access the PMP before prescribing and as part of ongoing monitoring of treatment with controlled substances. The PMP is an important tool for providers to improve patient care and prevent opioid misuse when prescribing controlled substances.

How to Access the PMP

Providers can register for access online at www.wapmp.org and the system is available 24/7 daily. For PMP system or program assistance please refer to:

PMP System Help Desk:
Health Information Designs
P.O. Box 529 | Auburn, Alabama 36831
Phone: 877-719-3121
Email: wapmp-info@hidinc.com

Washington State Department of Health
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Additional information, including FAQs, can be found at the [Department of Health’s PMP website](#).

Recommendations for Integrating the PMP into Practice

- Assign someone in your organization the responsibility of ensuring all prescribing and dispensing providers register for access.
- Have all prescribers and dispensers register for master accounts. Prescribers can delegate their authority to licensed staff, e.g. nurses and medical assistants if they register for their own sub-accounts and they are linked to the master accounts.
- Request PMP information as appropriate prior to patient visits and place a copy of the report in the patient’s medical chart.
- Consider training someone as a “PMP Champion,” or “Super-User,” who develops system expertise and can help train new staff or assist with questions.

When to Check the PMP

- Prior to prescribing opioids for a new episode of pain or for transferred patients who are already using opioids.
- During the transition from subacute to COAT.
- Routinely for patients for whom you are prescribing chronic opioids and/or other controlled substances ([Table 18](#)).
- Regularly for patients who are being treated for addiction disorder.
- When conducting a preoperative history and medical exam.
- When there is evidence of aberrant behaviors ([Table 9](#)). Address aberrant behaviors in person, not by telephone.

Table 18. Recommended Frequency of PMP Checks during COAT

Risk Category	Recommended Frequency
Low Risk	At least 1/year
Moderate Risk	At least 2/year
High Risk or opioid doses >120 mg/day MED	At least 3–4/year

Interpreting a PMP Report

Providers should access and review the PMP as part of their complete assessment of the patient when prescribing controlled substances, including opioids for an acute episode or chronic therapy:

- Keep in mind that there could be up to a 2-week lag time for dispensing information so recently dispensed controlled substances may not be reflected in the PMP report. Also, the PMP database does not contain information from the Department of Defense and Opioid Treatment Program.
- Compare the PMP report against your medical records. Any discrepancies should be reconciled with the dispensing pharmacy.
- Estimate the patient's controlled substance consumption with "as needed" or PRN use by reviewing the prescription dispensed dates.
- Coordinate care, which may include requesting medical records, when multiple prescribers are identified on the PMP report.
- Discuss in person with the patient when aberrant behaviors (e.g. early refills) or dangerous combinations of opioids with benzodiazepines and/or carisoprodol are identified on the PMP report. Provide patient education on the [safe use of controlled substances](#).
- Confirm the patient is taking medication as prescribed with the PMP report.

If the PMP report reveals concerns such as aberrant behaviors, dangerous drug combinations or multiple prescribers, the provider should follow the clinical recommendations in the sections: [Reducing or Discontinuing Opioids](#) or [Opioid Use Disorder](#) and take appropriate actions.

Appendix D: Urine Drug Testing for Monitoring Opioid Therapy

- i. Monitoring Opioid Therapy with Urine Drug Testing (UDT)
- ii. UDT Algorithm for Monitoring Opioid Therapy
- iii. UDT Clinical Vignettes
- iv. Frequently Asked Questions (FAQs) about UDT

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i. Using Urine Drug Testing (UDT) to Monitor Opioid Therapy for Chronic Non-cancer Pain³²¹⁻³²³

The purpose of drug testing is to identify aberrant behavior, undisclosed drug use and/or abuse and verify compliance with treatment. If a decision has been made to prescribe opioids for chronic non-cancer pain, the prescriber should get a baseline UDT and screen all patients for risk level to develop an appropriate monitoring plan as well as a basis for consultation or referral. Although UDT and other screening tools are helpful in identifying aberrant behavior, it is also important for prescribers to use their clinical judgment in the development of a monitoring plan. The Prescriber should repeat random UDT based on the patient's risk category. There are several validated screening tools available to assess risk of aberrant behavior. The Opioid Risk Tool (ORT) provides a brief questionnaire that can easily be used in the primary care setting ([Appendix B](#)).

Prior to drug testing, the prescriber should inform the patient of the reason for testing, frequency of testing and consequences of unexpected results. This gives the patient an opportunity to disclose drug use and allows the prescriber to modify the drug screen for the individual circumstances and more accurately interpret the results.

Risk Category	UDT Frequency	Drugs or Drug Classes to Test	Consideration
Low Risk	1/year	<ul style="list-style-type: none"> • Drug you are prescribing if not listed • Amphetamines • Opioids • Cocaine • Benzodiazepines • Alcohol 	<p>Typically, the initial (screening) drug test uses an immunoassay method to identify the presence of a drug (presumptive positive). Because of cross-reactivity and different sensitivity and specificity between immunoassays, a second confirmatory test is required unless result is expected or the patient has disclosed drug use. Confirmatory drug tests use gas chromatography/mass spectrometry or liquid chromatography/tandem mass spectrometry (GC/MS or LC/MS/MS) to verify a presumptive positive result.</p>
Moderate Risk	2/year	<ul style="list-style-type: none"> • Barbiturates • Oxycodone • Methadone • Fentanyl • Marijuana 	
High Risk or opioid doses >120 mg MED/d	3-4/year		
Aberrant Behavior (lost prescriptions, multiple requests for early refills, opioids from multiple providers, unauthorized dose escalation, apparent intoxication, etc.)	<p>At time of visit</p> <p>(Address aberrant behaviors in person, not by telephone)</p>	<p>Testing for all drug classes may not be necessary, depending on clinical situation.</p>	<p>Contact the laboratory director, toxicologist or a certified Medical Review Officer (MRO) in your area for questions about drug testing or result.</p> <p>If a point-of-care (POC) device is used, contact technical support from the manufacturer for questions.</p>

UDT Results

Interpreting UDT results can be challenging, especially when the parent drug can be metabolized to other commonly prescribed drugs. The table on the next page may aid prescribers when interpreting UDT results. The following UDT results should be viewed as a “red flag”, requiring confirmation and intervention:

- Negative for opioid(s) you prescribed
- Positive for drug (benzodiazepines, opioids, etc.) you did NOT prescribe or have knowledge of
- Positive for amphetamine or methamphetamine
- Positive for alcohol
- Positive for cocaine or metabolites

If a **confirmatory drug test** substantiates a “red flag” result AND is:

- **Positive for prescribed opioid(s)**, prescriber should consider a controlled taper and a referral to an addiction specialist or drug treatment program depending on the circumstances.
 - **Negative for prescribed opioid(s)**, prescriber should stop prescribing opioid(s) and consider a referral to an addiction specialist or drug treatment program depending on the circumstances.
-

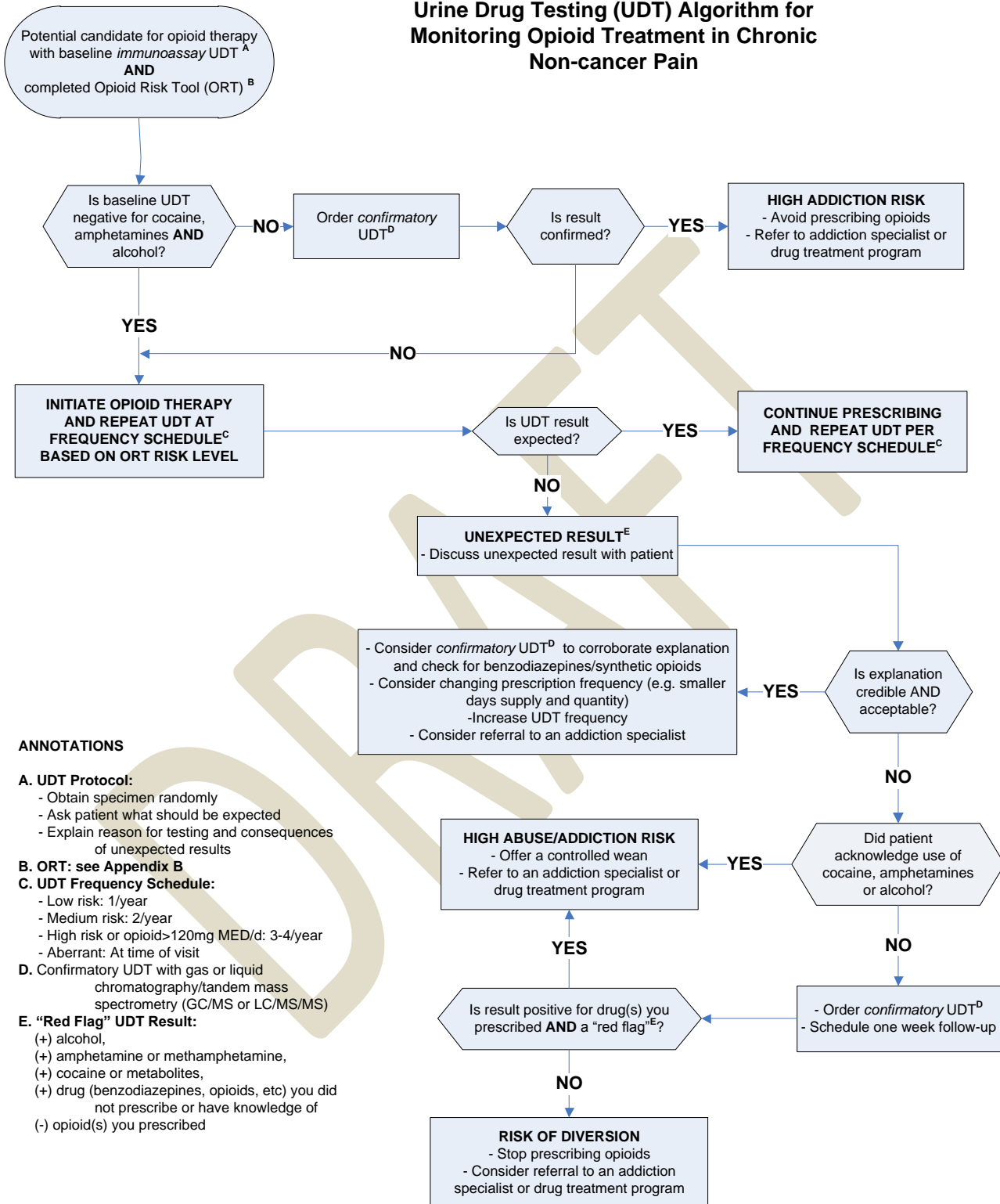
Drugs or Drug Classes	Detection Time in Urine*	Test to Order	Expected Results	Consideration
Opioids or “opiates” – Natural (from opium)				
Codeine (Tylenol #2/3/4)	1-3 days	Opiates Immunoassay + GC/MS or LC/MS/MS Opiates	Opiates Immunoassay – positive GC/MS or LC/MS/MS – codeine, possibly morphine & hydrocodone	Immunoassays for “opiates” are responsive for morphine and codeine but do not distinguish which is present. Confirmatory testing is required to reliably identify drug(s) present. Since codeine is metabolized to morphine and small quantities to hydrocodone, these drugs may be found in the urine. Also, morphine may metabolize to produce a small amount (<10%) of hydromorphone.
Morphine (Avinza, Embeda, MS Contin, Kadian)	1-3 days		Opiates Immunoassay – positive GC/MS or LC/MS/MS – morphine, possibly hydromorphone	
Opioids – Semisynthetic (derived from opium)				
Hydrocodone (Lorcet, Lortab, Norco, Vicodin)	1-3 days	Opiates Immunoassay + GC/MS or LC/MS/MS Opiates	Opiates Immunoassay – positive GC/MS or LC/MS/MS – hydrocodone, possibly hydromorphone	“Opiates” immunoassays may also detect semisynthetic opioids depending on their cross-reactivity pattern. However, a negative result does not exclude use of semisynthetic opioids. Confirmatory testing (GC/MS or LC/MS/MS) is required to verify compliance with the prescribed semisynthetic opioid(s).
Hydromorphone (Dilaudid, Exalgo)	1-3 days	Opiates Immunoassay + GC/MS or LC/MS/MS Opiates	Opiates Immunoassay – positive GC/MS or LC/MS/MS –hydromorphone	
Oxycodone (Roxicet, OxyContin)	1-3 days	Oxycodone Immunoassay + GC/MS or LC/MS/MS Opiates	Opiates Immunoassay – positive GC/MS or LC/MS/MS – oxycodone possibly oxymorphone	Since hydrocodone is metabolized in small amounts to hydromorphone, both may be found in the urine. Likewise, oxycodone is metabolized to oxymorphone, so these may both be present in the urine of oxycodone users. However, the reverse is not true. In other words, hydromorphone and oxymorphone use does not result in positive screens for hydrocodone and oxycodone, respectively.
Oxymorphone (Opana)	1-3 days	Opiates or Oxycodone Immunoassay + GC/MS or LC/MS/MS Opiates	Opiates or Oxycodone Immunoassay – positive GC/MS or LC/MS/MS – oxymorphone	
Opioids – Synthetic (man-made)				
Fentanyl	1-3 days	GC/MS or LC/MS/MS Fentanyl	GC/MS or LC/MS/MS – fentanyl & norfentanyl	Current “opiates” immunoassays do not detect synthetic opioids. Thus confirmatory testing (GC/MS or LC/MS/MS) is needed to identify these drugs. If the purpose is to document compliance with treatment, the laboratory can be instructed to remove the cutoff concentration so that the presence of lower concentrations can be identified.
Meperidine (Demerol)	1-3 days	GC/MS or LC/MS/MS Meperidine	GC/MS or LC/MS/MS – normeperidine, possibly meperidine	
Methadone (Methadose)	3-7 days	Methadone Immunoassay + GC/MS or LC/MS/MS Methadone	Methadone Immunoassay – positive GC/MS or LC/MS/MS – methadone & EDDP	

Propoxyphene (Darvon, Darvocet)	1-3 days	Propoxyphene Immunoassay + GC/MS or LC/MS/MS Propoxyphene	Propoxyphene Immunoassay – positive GC/MS or LC/MS/MS – propoxyphene & norpropoxyphene	
Others				
Alcohol	Up to 8 hours	Alcohol	Alcohol – see Consideration	Additional testing for alcohol metabolites, ethyl glucuronide (EtG) or ethyl sulfate (EtS), can identify alcohol up to 80 hours after consumption.
Amphetamines	2-3 days	Amphetamines, Methamphetamines or MDMA Immunoassay + GC/MS or LC/MS/MS Amphetamines	Amphetamines, methamphetamines or MDMA Immunoassay – see Consideration GC/MS or LC/MS/MS – amphetamine, methamphetamine or MDMA	Amphetamines immunoassays are highly cross-reactive so results should be interpreted cautiously, and may require consultation with the lab. They may detect other sympathomimetic amines, such as ephedrine, pseudoephedrine or selegiline. Confirmatory testing can identify which amphetamine is present.
Barbiturates	1-3 days w/short-acting; up to 30 days w/long acting	Barbiturates Immunoassay	Barbiturates Immunoassay – see Consideration	The clearance half-life of intermediate-acting barbiturates averages 24 hours. It takes about 5 to 7 half-lives to clear 98% of a drug dose. Thus, the presence of an intermediated-acting barbiturate indicates exposure within 5-7 days.
Benzodiazepines	1-3 days w/short-acting; up to 30 days w/long-acting	Benzodiazepines Immunoassay	Benzodiazepines Immunoassay – see Consideration GC/MS or LC/MS/MS – alprazolam, diazepam, clonazepam, lorazepam, etc.	Immunoassays for benzodiazepines have a 28% overall false negative rate and vary in cross-reactivity. Certain benzodiazepines (clonazepam and alprazolam) have limited detectability by most available immunoassays. Confirmatory testing is needed when use is expected or suspected.
Cocaine or benzoylecgonine	2-4 days	Cocaine Metabolites Immunoassay	Cocaine Metabolites Immunoassay – see Consideration	Cocaine immunoassays do not cross-react with other topical anesthetics that end in “caine” (e.g. lidocaine) and are highly specific for cocaine use.
Marijuana	2-4 days; up to 30 days w/chronic heavy use	Cannabinoids (THC) Immunoassay	Cannabinoids Immunoassay – see Consideration GC/MS or LC/MS/MS – THC	THC may be an indicator of the patient’s risk category. Prescribers should have an office policy, discuss with the patients reason for use and adjust monitoring plan accordingly.

*detection time for most drugs depends on the drug, dose, frequency of use and individual metabolism

Figure E: UDT Algorithm for Monitoring COAT for CNCP

Urine Drug Testing (UDT) Algorithm for Monitoring Opioid Treatment in Chronic Non-cancer Pain



ANNOTATIONS

- A. UDT Protocol:**
 - Obtain specimen randomly
 - Ask patient what should be expected
 - Explain reason for testing and consequences of unexpected results
- B. ORT: see Appendix B**
- C. UDT Frequency Schedule:**
 - Low risk: 1/year
 - Medium risk: 2/year
 - High risk or opioid > 120mg MED/d: 3-4/year
 - Aberrant: At time of visit
- D. Confirmatory UDT with gas or liquid chromatography/tandem mass spectrometry (GC/MS or LC/MS/MS)**
- E. "Red Flag" UDT Result:**
 - (+) alcohol,
 - (+) amphetamine or methamphetamine,
 - (+) cocaine or metabolites,
 - (+) drug (benzodiazepines, opioids, etc) you did not prescribe or have knowledge of
 - (-) opioid(s) you prescribed

iii. UDT Clinical Vignettes in Chronic Non-cancer Pain

Case Studies	Discussion
<p>New Patient: A 31-year-old female with low back pain from an injury 2 months ago. She wants to establish care. According to the patient, she was initially prescribed naproxen and hydrocodone in the emergency room. She is currently taking naproxen OTC, but no reported opioids. Her other medical conditions include depression for which she takes citalopram. You are considering prescribing opioid(s) and your suspicion for drug abuse is low. What should you do?</p>	<p>IF you have decided to initiate chronic opioid therapy AND prior to prescribing, you should:</p> <ol style="list-style-type: none"> 1. Obtain a baseline UDT; 2. Assess risk of aberrant behavior with ORT; 3. Assess psychiatric status (e.g. PHQ-9); 4. Obtain a signed opioid agreement; 5. Establish treatment goals including improvements in both function and pain; 6. Describe expectations for behavior related to use of opioids (take as prescribed, use one pharmacy, one prescriber, no early refills, no self-escalation, no sharing of drugs, etc.) 7. Develop a follow-up plan to monitor treatment, including the frequency of UDT's based on ORT
<p>New Patient on Opioids: A 45-year-old male presents with severe neck pain from a motor vehicle accident 2 years ago. He has been treated with OxyContin 30mg BID and oxycodone 5mg 1 tab Q3H PRN (MED = 150mg/day). He reports no history of substance abuse. Due to "personality differences" with previous provider, he would like you to assume care and continue prescribing OxyContin and oxycodone for his neck pain. You have no medical records to confirm previous treatment. What should you do?</p>	<p>Do not prescribe opioids at initial visit since records are unavailable:</p> <ul style="list-style-type: none"> • Comprehensively evaluate the patient, • Order a baseline UDT, • Inform patient that a signed release of information form is required prior to prescribing opioids. Also request medical records from previous provider(s) or consider contacting the previous prescriber for information on treating this patient and • Schedule a follow-up visit for when UDT results and medical records are available. <p>On follow-up visit, if UDT is consistent and prior medical records show improved pain and function with no history of aberrant behaviors, follow steps 2 – 7 above before prescribing.</p>
<p>Compliance Testing in a patient on < 120mg MED/day: A 55-year-old male with chronic knee pain comes in for a routine visit. His opioid regimen consists of methadone 5mg QID and hydrocodone/acetaminophen 5/500mg 1 tab Q6H PRN (MED = 100mg/day). He has moderate risk on ORT and last random UDT was a year ago. What should you do?</p>	<p>Assess the risks and benefits of current opioids. Discuss with the patient reason for testing, frequency of testing and consequences of unexpected results, order an immunoassay test for the drug classes below, and follow the UDT algorithm.</p> <ul style="list-style-type: none"> • Amphetamines • Opiates • Cocaine metabolites • Methadone • Benzodiazepines • Alcohol metabolites • Oxycodone
<p>Unexpected Results: The immunoassays from the above vignette were positive for methadone, opiates and cocaine metabolites but negative for the remainder of the drug classes tested. Confirmatory testing with GC/MS was done per laboratory protocol. The confirmatory results show methadone, hydrocodone and benzoylecgonine (cocaine metabolite). What should you do?</p>	<p>Discuss the unexpected results with the patient and offer a controlled taper and referral to an addiction specialist.</p>

Case Studies	Discussion
<p>Point of Care Testing: A 47-year-old male with rotator cuff tendonitis has chronic shoulder pain managed with morphine SR 30mg TID and oxycodone/acetaminophen 5/325mg 1 tab Q4H PRN (MED = 135mg/day). He reports no other drug therapy. A treatment agreement has been signed by you and the patient recently. You perform a random UDT using a point-of-care testing kit. The immunoassays are positive for opiates but also positive for benzodiazepines. What should you do?</p>	<p>Discuss the unexpected results with the patient:</p> <ul style="list-style-type: none">• If explanation is credible (e.g. receiving treatment for anxiety from another provider), you may want to send the urine sample to laboratory to confirm his story. You may also want to discuss future expectations with the patient and request records from other treating providers for possible specialty consultation.• If explanation is not accepted (e.g. patient admits benzodiazepine use that is not prescribed for the patient), confirmatory testing is not necessary but offer a controlled taper and/or referral to an addiction specialist depending on the circumstances.• If result cannot be explained, send original urine sample to laboratory for confirmatory testing.

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iv. UDT Frequently Asked Questions (FAQ)

Q Drug screening implies that I don't trust my patients. How do I get around this?

A Self-report of drug use has limited validity, and monitoring behavior alone can fail to detect problems revealed by UDTs. Creating a UDT policy in advance and applying it consistently to all patients on opioids may help de-stigmatize the testing. Inform patients that drug testing is a routine procedure for all patients starting or maintained on opioid therapy and it is an important tool for monitoring the safety of opioid therapy. Possible language for explaining to patient includes:

- "Ensures my capacity to provide treatment for your pain while balancing the need for safety."
- "Provides critical information needed to assess the success of your therapy."
- "Prescription medications are a common form of treatment for chronic pain. However, each person reacts differently to them. UDT enables us to identify individual risks related to your medications and avoid problems."
- "Our clinic uses 'universal precautions' in opioid prescribing, which includes UDT. This is the same as wearing gloves on all patients when drawing blood."

Q Can I tell whether my patient has taken the dose of opioid(s) I prescribed?

A No. It is very difficult to correlate urine drug concentration with a patient's dose. UDT can detect the parent drug and/or its metabolite(s) and demonstrate recent use of prescribed drugs and illegal substances. However, it CANNOT determine the amount of drug used and when the last dose was taken, nor can it identify the source of the drug.

Q My patient says he is a "high metabolizer" and that is why the expected drug is not found in the urine. Is this possible?

A A small percentage of persons are ultrarapid metabolizers. They metabolize specific drugs more rapidly than typical patients. It would be rare to take an opioid as prescribed and have a totally negative UDT. It is important that you use testing that is specific to the medication of interest and with cutoff thresholds that are extremely low.

Q How do I deal with marijuana?

A This is a complex issue. Marijuana is currently classified as a Schedule I drug by the DEA. For that reason, many providers will not prescribe opioids to patients using cannabis. Other providers reference State "Medical Marijuana" laws (<http://apps.leg.wa.gov/RCW/default.aspx?cite=69.51A&full=true>) and feel comfortable prescribing opioids to cannabis users. Some providers adopt a "don't ask, don't tell" policy, and request the lab to remove marijuana from the UDT so that positive results are not seen. Do your homework and create an office policy. Then disclose this policy to your patients.

Q Would short-acting opioids show up in UDT?

A Urine testing typically has a 1 to 3-day window of detection for most drugs depending on dose and individual differences in drug metabolism. Short-acting opioids can be detected if the lab removes the cutoff concentration so that the presence of lower concentrations is detected. If the laboratory uses LC/MS/MS, then it will have a lower limit of detection (LOD) with less interference.

Q Why confirm results?

A Immunoassays used in drug screening can cross-react with other drugs and vary in sensitivity and specificity. Thus, confirmation with a more accurate method may be required for clinical decision making. Confirmatory drug testing (GC/MS or LC/MS/MS) of the original specimen is recommended for unexpected

results, or in cases where patients are known to be high risk. However, on occasion, even confirmatory testing requires expert assistance for interpretation. Consider consultation with the lab before discussing/confronting the patient with unexpected test results and discontinuing opioid therapy.

Q Should I use temperature and adulteration strips?

A It depends. Drug testing for clinical compliance, unlike employment testing, does not require a strict “chain-of-custody”. However, if tampering is a concern, the specimen should be monitored for temperature and/or adulterants. Normal human urine should have a temperature between 90°F – 100°F, pH between 4.5 – 8.5 and creatinine >20mg/dL. Be aware that there are multiple websites and devices devoted to getting a “clean” urine drug screen.

Q Should I perform a drug screen on every visit for patients using opioids for chronic pain?

A No. Random screening based on the frequency recommended in the guideline should suffice for most patients. Those patients who you feel require drug screening on every visit, are perhaps not candidates for chronic opioid therapy.

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Appendix E: Chronic Pain Syndromes in Cancer Survivors

Sources: Davies 2013a. Paice. Glare. Kenyon. Smith, Bridges et al 2015. Smith, Pang et al 2013. Barton 2011. NCCN Survivorship 2014.

Pain Syndrome	System	Type of Cancer	Cause of Pain	Treatment Options & Notes
Chemotherapy-induced peripheral neuropathy (CIPN)	Neurological	Breast Ovarian Colorectal Lymphoma Multiple myeloma	Vinca alkaloids (vincristine), platinum compounds (cisplatin), taxanes (paclitaxel), bortezomib	Antidepressant: SNRI: duloxetine . TCA: nortriptyline, desipramine Anticonvulsants: pregabalin, gabapentin Compounded topical creams, such as baclofen/amitriptyline/ketamine Opioids, if used, non-escalating/stable doses <120 mg MED PT/OT/ Rehabilitation Acupuncture CBT
Chronic post-operative neuropathic pain syndromes	Neurological	Breast Neck Lung Sarcoma	Post-mastectomy, post-radical neck, post-thoracotomy, post-amputation pain syndromes Neuroma	Antidepressant: SNRI: duloxetine TCA: nortriptyline, desipramine Anticonvulsants: pregabalin, gabapentin Opioids, if used, non-escalating/stable doses <120 mg MED Topical: lidocaine 5% patch, capsaicin cream Interventional nerve blocks (intercostal, stellate ganglion block, lumbar sympathetic block) PT/OT for ROM CBT
Chronic radiation fibrosis	Integumentary	Breast Neck	Long-term and late radiation effects, fibrosis causes decreased ROM, tightness, discomfort	PT/OT Massage for myofascial release Trigger point injection May develop years after completion of therapy
Lymphedema	Integumentary	Breast Pelvic tumors	Surgery or radiation may interfere with lymph drainage from affected limb	Compression garments PT for ROM Manual lymphatic drainage Diuretics are not helpful May be discomfort more than pain
Scar pain from surgery or radiation	Integumentary	Breast All	Tissue fibrosis leading to pain and decreased ROM	Massage for scar release
Myalgias and arthralgias	Musculo-skeletal	Breast	Aromatase inhibitors, used to prevent recurrence of breast cancer, cause symmetrical pain aching or stiffness in shoulders, elbows, wrists, fingers, knees, ankles	Exercise Thermal PT/OT/Rehabilitation Medicine Massage Acetaminophen

Pain Syndrome	System	Type of Cancer	Cause of Pain	Treatment Options & Notes
				NSAIDs Antidepressants: duloxetine, desipramine Anticonvulsants: pregabalin, gabapentin Change to another aromatase inhibitor
Myofascial pain	Musculo-skeletal	Hematopoietic cell transplant All cancers may cause myalgias and arthralgias from deconditioning	High dose Corticosteroids High dose cyclophosphamide Deconditioning Radiation fibrosis	Exercise, aerobic, stretching and strengthening PT/OT/Rehabilitation Medicine Thermal Massage Acupuncture Acetaminophen NSAIDs Antidepressant: duloxetine, nortriptyline Anticonvulsants: pregabalin, gabapentin Topical: lidocaine 5% patch, capsaicin cream Trigger point injections
Vertebral compression fractures	Skeletal	Ovarian failure from chemotherapy or surgery, prostate, all cancers at risk, especially GYN, prostate, myeloma, hematopoietic cell transplant	Painful vertebral compression fractures	Opioids (acute) NSAIDs PT/Rehabilitation Weight bearing exercise (subacute & chronic) Bisphosphonates Consider vertebroplasty/kyphoplasty
Avascular necrosis of femoral head, knee, humeral head	Skeletal	Hematopoietic cell transplant, especially unrelated donor allogeneic transplant Acute lymphoblastic leukemia	High dose steroids can lead to painful (aseptic) degeneration of joint of such severity that joint replacement may be required in young adults	Opioids at stable non-escalating dose Exercise, especially swimming PT Off-weight joint with cane/crutches Thermal Surgery: joint replacement or cortical bone drilling
Dyspareunia	Genital	Breast, ovarian, any cancer treatment causing ovarian failure	Decreased vaginal lubrication, vaginal stricture from pelvic surgery or radiation	Vaginal lubricants PT for Pelvic floor exercises and vaginal dilators Sexual therapy Low-dose vaginal estrogen cream #
<p>* FDA approved for this condition. All other pharmaceuticals are not FDA approved. # Recommend contacting the oncologist prior to initiating vaginal estrogen cream, especially if patient had estrogen-receptor positive breast cancer.</p> <ul style="list-style-type: none"> • NSAIDs = non-steroidal anti-inflammatory agents (e.g. naproxen, ibuprofen). • PT/OT = physical therapy or occupational therapy • ROM = range of motion • Thermal = hot packs, ice packs • CBT = cognitive behavioral therapy 				

Appendix F: Diagnosis-based Pharmacotherapy for Pain and Associated Conditions

Best Used For...	Adjuvant Drug	Key Points
Minor arthritis, backache, muscle and joint pain	Topical menthol, methyl salicylate, or trolamine salicylate	
Minor to moderate pain	Acetaminophen (APAP)	APAP 325mg + ibuprofen 200mg provides better pain relief than oral opioids Caution: Hepatotoxicity increases with dose, age, use of alcohol, and co-occurring liver disease. Keep to < 2gm daily if at risk for hepatotoxicity. Some manufacturers have voluntarily revised their label to recommend a lower maximum of 3 gram daily.
Pain from spasticity (spinal cord injury or multiple sclerosis)	Tizanidine or baclofen	Caution: Do not abruptly discontinue baclofen due to potential for severe rhabdomyolysis and fever
Neuropathic pain conditions (diabetic peripheral neuropathy, post herpetic neuralgia, spinal cord injury, cauda equina syndrome, phantom limb pain, HIV neuropathy, chemotherapy induced neuropathy, etc.)	Tricyclic antidepressants (amitriptyline, nortriptyline, doxepin, desipramine), serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine), anticonvulsants (gabapentin, pregabalin)	Low dose TCAs and gabapentin are good first line therapy option especially helpful with sleep disturbance Caution: Gabapentin and pregabalin can cause cognitive slowing, weight gain, and edema. Also, pregabalin is a controlled substance
Trigeminal neuralgia	Carbamazepine	Caution: Monitor for hematologic (aplastic anemia, agranulocytosis) and dermatologic (toxic epidermal necrolysis, Stevens-Johnson syndrome) complications. Because there is a strong association between dermatologic complication and the presence of human leukocyte antigen (HLA-B*1502), the FDA and the manufacturers of carbamazepine recommend that patients with ancestry in genetically at-risk populations be screened for the presence of the HLA-B*1502 allele prior to initiating carbamazepine therapy.
Neuropathic pain condition + depression or anxiety	Tricyclic antidepressants (amitriptyline, nortriptyline, doxepin, desipramine) or serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine)	Caution: Monitor for dose related QTc prolongation (TCAs > SNRIs). Also, SNRIs can provoke leg movement disorders.
Non-specific low back or nociceptive pain or pain from traumatic, infectious, or degenerative conditions, or pain from connective tissue disorders	Nonsteroidal anti-inflammatory drugs (naproxen, ibuprofen, meloxicam, diclofenac, etodolac, nabumetone, ketoprofen, piroxicam, sulindac, tolmetin, etc.)	Naproxen 500mg or naproxen sodium 550mg alone and ibuprofen 200mg + acetaminophen 500mg are as effective, or more effective than opioids Caution: Monitor patients for potential renal, gastrointestinal (GI), and cardiac side effects. Risk increase with age and dose.
Fibromyalgia	Duloxetine, gabapentin, pregabalin,	
Minor arthritis, backache, muscle and joint pain	Topical menthol, methyl salicylate, trolamine salicylate or capsaicin	May experience burning, stinging or itching sensations during and following application but high concentration capsaicin or repeat applications will produce a loss of responsiveness to stimuli

Best Used For...	Adjuvant Drug	Key Points
Localized neuropathic pain (HIV polyneuropathy, postherpetic neuralgia)	Topical lidocaine or capsaicin	<p>Caution: Wash hands or use gloves when handling capsaicin.</p> <p>May experience burning, stinging or itching sensations during and following capsaicin application but high concentration or repeat applications will produce a loss of responsiveness to stimuli</p> <p>Caution: Wash hands or use gloves when handling capsaicin.</p>
Insomnia	<p>Melatonin 1-5mg</p> <p>Tricyclic antidepressants (TCAs)</p> <p>Trazadone</p> <p>Benzodiazepine receptor agonists e.g. the Z-drugs: zolpidem, Zaleplon, Zopiclone, eszopiclone</p>	<p>Side effects of melatonin = drowsiness, dizziness, headache, nausea, and nightmares</p> <p>Caution: Trazadone is not advised when patient is taking SSRIs or SNRIs.</p> <p>Caution: Z-drugs can potentially induce unsafe behaviors like sleep-driving or preparing and eating food when not fully awake; have limited value with reducing chronic pain.</p>

Appendix G: Patient Education Resources

Providing quality treatment for your patients is critical, and so is educating them about the risks of taking opioid medications. Resources that can help you provide this education are listed here.

Resource	Description
<p>Chronic Pain American Chronic Pain Association website</p> <p>Chronic Pain Self-Management Program</p> <p>Substance Abuse and Mental Health Services Administration (SAMHSA)</p> <p>Evans Health Lab’s Advice for Patients Taking Opioids</p>	<p>Patients and their families can access plain-language fact sheets, worksheets, communication tools and videos on topics such as medications, pain management programs, and going to the ER. Addresses health literacy with tools for how to read an OTC label, how to store medications safely.</p> <p>Find a local six-week workshop, developed by the Stanford Patient Education Research Center.</p> <p>Downloadable booklet <i>You Can Manage Your Chronic Pain to Live a Good Life</i></p> <p>Dr. Mike Evans’ video on Opioids</p>
<p>Fibromyalgia Fibromyalgia Information Foundation</p>	<p>Overview of fibromyalgia, diagnosis, treatment, preventive advice and new research discoveries. The site does mention the use of opioids and benzodiazepines for fibromyalgia, which is not supported by this guideline.</p>
<p>Headaches National Headache Foundation</p>	<p>Contains topic sheets, educational modules, and videos on all kinds of headaches. Useful for providers also; contains links to research.</p>
<p>Medications National Institute of Health’s Daily med UpToDate</p>	<p>Sponsored by the National Library of Medicine, this site contains information for professionals as well as patients on almost all drugs.</p> <p>This is a paid subscription service, which consumers are not likely to use directly. Providers who have access can download patient information on the basics of: narcotic pain medicines, prescription drug abuse, opioid use disorder, and alcohol and illegal drug use in pregnancy</p>
<p>Stress and Mental Health Anxiety Disorders Association of America National Institute of Mental Health Depression screening.org</p>	<p>Information for healthcare providers and consumers. Detailed information about anxiety disorders, how to find help, and tips for managing anxiety.</p> <p>Information on mental health topics including signs and symptoms, treatment, locating local services, and research.</p> <p>Confidential online depression screening test, symptoms and treatments, personal stories and sources of help.</p>
<p>Sleep National Sleep Foundation</p>	<p>General information about sleep health and safety, and sleep-related problems.</p>
<p>Setting Patient Health Goals Swedish’s Structuring Your Own Management of Pain (STOMP) brochure</p>	<p>Brochure is designed to help patient set health goals to alleviate pain and improve quality of life. It includes general information about pain, goal-setting ideas and steps to take to achieve those goals.</p>
<p>Opioid Safety Washington Department of Health’s Take as Directed website The Addiction Technology Transfer Center Network</p>	<p>Includes opioid safety, possible risks from taking opioids, and warning signs of drug abuse or addiction. Tips on preventing overdoses, signs of overdose and problematic opioid use.</p> <p>A fact sheet with six tips for preventing others from stealing your prescription medicines; good for printing.</p>

Books	
<i>Treat Your Own Neck and Back</i> (5 th Ed.) by R. McKenzie	Patient handbook for common neck pain will help patients learn to relieve their problems and prevent recurrence of their symptoms in the future. It covers a step-by-step system of education, awareness, exercise and prevention.
<i>Managing Pain Before It Manages You</i> (3 rd Ed.) by M Caudill	Simple set of tools to help patients live with their pain more effectively and independently.
<i>Mind Over Mood: Change How You Feel by Changing the Way You Think</i> by D Greenberger and C Padesky	Step by step worksheets teach specific skills to conquer common mental health issues such as depression, anxiety, and low self-esteem.
<i>Thoughts and Feelings: Taking Control of Your Moods and Your Life</i> by M. McKay, M.Davis, and P.Fanning	Adapts the powerful techniques of cognitive behavioral therapy into a set of tools readers can use against anxiety, depression, and obsessiveness.
<i>The War on Pain</i> by S. Fishman & L. Berger	An introduction to interdisciplinary pain management that integrates traditional and alternative techniques.
<i>Heal Your Headache: The 1-2-3 Program for Taking Charge of Your Pain</i> by D. Buchholz & S.G. Reich	Information on how to avoid triggers, use of preventative medications rather than pain relievers which can cause rebound headaches.
<i>Chronic Pain Solution: Your Personal Path to Pain Relief</i> by J.N. Dillard & L.A. Hirschman	Useful information on how to approach and relieve chronic pain.
<i>Snoring and Sleep Apnea: Sleep Well, Feel Better</i> by R. Pascualy	This book is for people with sleep apnea, family, friends and health care professionals. Covers causes, diagnosis, treatment, and surgical techniques.

Appendix H: Clinical Tools and Resources

Consultation Resources

The WA State Department of Health maintains a webpage specifically for pain management^{vi} where the rules for opioid prescribing (including obtaining consultations with pain specialists) are referenced in five separate places, each for the different specialists who can prescribe opioids: MDs, DOs, PAs (within the MD or DO rules), ARNPs, DPMs, and Dentists. They are codified in Washington Administrative Code Chapter 246, and can also be found at the state's legislative website (www.leg.wa.gov).

UW School of Medicine and its academic medical centers offer a toll free consultation and referral service available 24 hours per day 7 days per week. This service helps link you with a faculty physician with expertise in any particular area. To access these services visit, call 800.326.5300, email medcon@u.washington.edu or visit, <http://uwmedicine.washington.edu/Patient-Care/Referrals/Pages/MEDCON.aspx>. Click on "Refer a Patient." The entire process can be done online, including transfer of records and images.

UW TelePain offers weekly (with few seasonal exceptions), a free teleconference where primary care providers can call and present actual complex pain management cases (with personally identifiable patient information redacted) and receive consultative advice from a multidisciplinary group of pain specialists. There is also a 20-30 minute didactic section on pain related topics before cases are presented. Visit: <http://depts.washington.edu/anesth/care/pain/telepain/index.shtml>

Mentoring Resources

Physician Clinical Support System has mentors available to help you, by phone or email, with questions on methadone or buprenorphine. In addition, guidance on specific clinical questions and helpful tools can be downloaded from the website. There is no cost for this service. Once you register at <http://pcssmat.org/mentoring/> a mentor will be assigned to you within 2 days.

UW offers a free online course called COPE-REMS that is designed to educate healthcare providers on how to better treat and manage patients with chronic pain in order to improve patient outcomes. Its goal is to increase knowledge and confidence among providers about how to best treat chronic pain, including whether and when to start, modify or stop opioid therapy. The course contributes to national health goals of preventing opioid misuse, abuse and overdose. It is aimed at physicians, registered nurses, ARNPs, physician assistants, psychiatrists, and other care managers who treat patients with chronic pain. Visit: <https://trainingexchange.org/our-programs/cope-rem>s

vi

<http://www.doh.wa.gov/ForPublicHealthandHealthcareProviders/HealthcareProfessionsandFacilities/PainManagement>

Treatment and Referral Resources

There are several treatment options available for opioid use disorder. A combination of medication and behavioral therapies has been found to be most successful (SAMSHA Medication Assisted Treatment for Opioid Addiction in Opioid Treatment Program

www.kap.samhsa.gov/products/trainingcurriculum/pdfs/tip43_curriculum.pdf).

- Department of Social and Health Services (DSHS) Tool Kit to help address drug and alcohol issues in Medicaid patients <http://maa.dshs.wa.gov/pharmacy/ToolKit.htm>
- DSHS Division of Alcohol and Substance Abuse at 877-301-4557. A referral for treatment may be made to any one of the licensed opioid therapy programs (OTPs) in Washington State: <http://www.dshs.wa.gov/dbhr/dadirectory.shtml>
- A list of treatment centers certified by the Division of Behavior Health and Recovery is available at www.dshs.wa.gov/dbhr/dadirectory.shtml.
- A partial list of physicians authorized by SAMHSA and the DEA to prescribe buprenorphine for treatment of opioid use disorder and treatment programs that also provide it can be found at: http://buprenorphine.samhsa.gov/pls/bwns_locator/provider_search_process_query?alternative=C&HOICEG&one_state=WA

Sample Doctor-Patient Agreements for Chronic Opioid Use (links only)

L&I's Opioid Treatment Agreement in English <http://www.lni.wa.gov/Forms/pdf/F252-095-000.pdf> and Spanish <http://www.lni.wa.gov/Forms/pdf/F252-095-999.pdf>

HCA's Medicaid Chronic Pain Agreement <http://www.hca.wa.gov/medicaid/pharmacy/pages/toolkit.aspx>

DSM 5 Criteria for Substance Use Disorder, by the American Psychiatric Association:

<http://pcssmat.org/wp-content/uploads/2014/02/5B-DSM-5-Opioid-Use-Disorder-Diagnostic-Criteria.pdf>

Everyday Helpful Resources

- UW Department of Anesthesiology and Pain Medicine keeps a useful [Pain Medicine Provider Toolkit](#) on their website with educational and resource information.
- For tips on motivational interviewing, check out: *Motivational Interviewing in Health Care: Helping Patients Change Behavior* by Stephen Rollnick, William R. Mill, and Christopher C. Butler, Guilford Press 2007, (Review at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2779641/>) .

Emergency department guidelines help coordinate care with primary care providers

The emergency department (ED) is a significant outpatient source of prescription opioids, yet there has been little guidance on how to treat pain in the emergency department while minimizing the potential for overdose and abuse. The Washington Chapter of the American College of Emergency Physicians (WA-ACEP) has developed a set of guidelines that outline good prescribing practices for the ED providers. The guidelines have patient information brochure that explains to patients the purpose of the guidelines and the risks associated with prescription opioids. More information can be obtained at

<http://www.washingtonacep.org/painmedication.html> and <http://here.doh.wa.gov/materials/pain-medication-guidelines/?searchterm=emergency%20department>.

Washington has implemented ED care coordination programs across the state. These programs take advantage of an ED visit tracking system used by every ED in the state to notify the ED provider of a patient's ED visit history. A randomized clinical trial of citywide ED care coordination performed in Washington by Washington State University and funded by the Centers for Disease Control shows this approach is effective. The trial demonstrated a statistically significant reduction in ED visits made by frequent ED users and a large reduction in opioid prescribing to these patients by ED providers. The results of this trial are pending publication. Coordinating the ED care of patients that frequent the ED with pain complaints across all the ED in a region is a promising approach to address high risk opioid prescribing from the ED

DRAFT

Appendix I: AGREE Criteria

This guideline meets the specific criteria for the “Appraisal of Guidelines for Research and Evaluation,” (AGREE), which is the industry standard for ensuring its development followed a rigorous strategy, appropriate methodology, and high quality systematic development and implementation process. This standard was developed by the Canadian Institute of Health Research and is used by the United States Agency for Healthcare Research and Quality and the National Guideline Clearinghouse.

DOMAIN 1: SCOPE AND PURPOSE
1. The overall objective(s) of the guideline is (are) specifically described.
Where found: Introduction
<ul style="list-style-type: none"> The key objectives of this guideline are to prevent unnecessary, ineffective, and often harmful COAT in chronic non-cancer pain conditions. <ul style="list-style-type: none"> This guideline is designed to be an easy-to-use reference to help primary care clinicians and supplements the WA state pain management rules requiring best practices in the prescribing of opioids for chronic non-cancer pain (WAC Chapter 246, authorized by ESHB 2876 Chapter 209 Laws of 2010). Although opioids may benefit some patients if prescribed and managed properly for appropriate conditions, the key objectives of this guideline is to prevent unnecessary, ineffective, and often harmful COAT in chronic non-cancer pain conditions.
2. The health question(s) covered by the guideline are specifically described.
Where found: Introduction
While the earlier guidelines focused on how prescribers could safely and effectively prescribe and manage chronic COAT, more recent data suggests that the focus should also be on preventing the inappropriate transition from acute and subacute opioid use to chronic opioid use, and to avoid COAT altogether when other alternatives for treating pain may be equally effective and safer in the long-term. This new edition also expands guidance to address non-opioid alternatives and opioid use in cancer survivors, geriatrics, pediatrics, and pregnancy and neonatal abstinence syndrome.
3. The population (patients, public etc.) to whom guideline is meant to apply is specifically described
Where found: Title page and Introduction
<ul style="list-style-type: none"> Patients with chronic non-cancer pain Opioid use in cancer survivors, geriatrics, pediatrics, and pregnancy and neonatal abstinence syndrome.
DOMAIN 2: STAKEHOLDER INVOLVEMENT
1. The guideline development group includes individuals from relevant professional groups.
Where found: Introduction and Acknowledgements
<ul style="list-style-type: none"> The Guidelines were developed in collaboration with a broad advisory group of the state’s academic leaders, pain specialists, and clinicians in both primary care and specialty areas in response to the growing epidemic of opioid-related unintentional overdoses. Acknowledgements or appendix: We will list all the group members, specialties, and affiliations.
2. The views and target preferences of the target population (patients, public, etc.) have been sought.
Where found: The guideline was posted on a public website.
3. The target users of the guideline are clearly defined.
Where found: On Title Page and Introduction

- Written for the primary care provider treating patients with complex chronic pain.
- This guideline is designed to be an easy-to-use reference to help primary care clinicians.
- The main target population is primary care providers and any provider who treats patients with chronic pain. Primary care providers as well as specialists were included in the guideline advisory group, the names of which are documented in the acknowledgements section.
- A secondary target population is WA state medical directors, clinicians, and policy leaders and staff who implement the guideline in various ways. Before finalization, the guideline was shared with all of them and was posted on a public website for public comment. Responses were provided to all comments received

DOMAIN 3: RIGOR OF DEVELOPMENT

1. Systematic methods were used to search for evidence

Where found: In evidence tables

A literature review was done in Medline – PUBMED. Searches began in March of 2014. Search terms included “opioids and chronic pain”, “chronic pain and treatment”, “opioid related adverse events”, “risk and dose and opioids”, “opioids and overdose and deaths”, “chronic pain management”, “non-pharmacologics and pain management”, “alternatives to opioids and chronic pain”. The search was limited to English, humans, the last 10 years and in some cases, to systematic reviews and meta-analysis. Additional hand searches of relevant studies in reference lists were done.

The National Guideline Clearinghouse was searched for relevant guidelines. Guidelines selected for review addressed the use of opioids in the treatment of chronic non-cancer pain.

Methods- CMIF

PubMed was searched for relevant studies on methodology and measuring pain and function. Key search terms included “meaningful improvement” and “pain” and “function” or “MCID” and “pain” and “function.” This search yielded 240 abstracts, 15 of which were used in this guideline. The final recommendations are based on a combination of these studies and a consensus of expert opinion of the AMDG advisory group.

Methods - Acute

PubMed was searched for randomized trials and systematic reviews of randomized trials, in the treatment of low back pain, headaches, and fibromyalgia. Key terms used included “systematic reviews” and “opioids” and either “low back pain” or “headaches” or “fibromyalgia”. Relevant papers were: 7/180 for low back pain; 3/219 for headache; and 3/60 for fibromyalgia. The final recommendations are based on a combination of these studies and a consensus of expert opinion of the AMDG advisory group.

Methods - Subacute

A search of the literature on specific use of opioids during the subacute pain period yielded no randomized trials; thus, the recommendations for this period represent a consensus of expert opinion of the advisory group. In addition, the use of screening tests prior to starting COAT is covered earlier in this AMDG guideline. One systematic review of this specific period (6 weeks – 3 months) revealed evidence only for advice to stay active (Pengel et al Clin Rehabil 2002; 16:811-20).

Methods – Alternatives to Opioids

The evidence for this section is derived from systematic reviews of randomized trials published since the Chou et al (2007) review of RCTs for pharmacologic and non-pharmacologic treatments of acute, subacute, and chronic low back pain. Using key terms “chronic pain”, “randomized”, and “systematic review”, we reviewed 976 abstracts, 42 of which were relevant to this review. More recent reviews that incorporated older RCT results took precedence over older systematic reviews. In addition, we used key words “systematic review” and “cognitive behavioral therapy” and “chronic pain” to identify systematic reviews, without data limitations, of conditions other than chronic low back pain for which cognitive behavioral therapy may have been effective; we reviewed 586 abstracts,

<p>and included 8 additional studies.</p> <p>Methods – Opioid Use in a Geriatric Population</p> <p><u>Literature search</u></p> <p>Performed 10/28/2014, PubMed, search terms “opioids and older adults”</p> <p>Results 887 abstracts</p> <p>References pulled =31</p> <p>Additional guidelines reviewed = 2</p>
<p>2. The criteria for selecting the evidence are clearly described.</p> <p>Where found: In evidence tables and narrative.</p> <p>Studies were included for review if they were well conducted large randomized controlled trials (RCTs), high quality meta-analyses, systematic reviews, and prospective studies published in English with patient populations relevant to chronic pain patients, interventions and objective outcome measures. Outcomes included were pain, function, activity limitation, quality of life, and adverse events (death, overdose, and other opioid related harms). Studies were excluded if they were published as conference abstracts, non-English, non-human, case series and case reports.</p>
<p>3. The strengths and limitations of the body of evidence are clearly described.</p> <p>Where found: in evidence tables</p> <p>Based on review of available literature, the strengths and limitations of each included study were noted in the evidence tables.</p>
<p>4. The health benefits, side effects and risk have been considered in formulating the recommendations.</p> <p>Where found: Chapter on Long-term Efficacy and Clear Evidence of Harm</p> <p>The goal of pain treatment obviously extends beyond the elimination of pain. There is evidence for significant pain relief in the short term (average 5 weeks), but there is no substantial evidence for sustained pain relief or improved physical function over longer periods. Three recently published systematic reviews which examine the effectiveness of opioids for chronic pain provide little support for this drug therapy.</p> <p>Adverse events most commonly reported in randomized trials include constipation, nausea and vomiting, dizziness, and drowsiness. Much more serious long-term consequences of opioids have only been identified from observational and epidemiological investigations; these include abuse, the development of addiction (opioid use disorder), inhibition of endogenous sex hormone production with resulting hypogonadism and infertility, immunosuppression, falls and fractures in older adults, neonatal abstinence syndrome, cardiac arrhythmia related to methadone, sleep disordered breathing, opioid-induced hyperalgesia, nonfatal overdose hospitalizations, emergency department visits, and death from unintentional poisoning.</p>
<p>5. There is an explicit link between the recommendations and the supporting evidence.</p> <p>Where found: In each clinical chapter</p> <p>All recommendations made in the guideline were based on high quality evidence. Recommendations include but are not limited to:</p> <ul style="list-style-type: none"> • Dosing threshold • Alternative non-opioid treatment for CNCP • Opioids and disability • Opioids during the acute, subacute, chronic, and perioperative phases • Methadone for pain management • Tapering and discontinuing opioids
<p>6. The guideline has been externally reviewed by experts prior to its publication.</p> <p>Where found: Guideline Process Documentation (Appendix ___)</p>

Practicing providers with extensive experience in the evaluation and treatment of patients with chronic pain, professional groups and the public provided internal and external review and comment on this guideline. The draft of the guideline was posted on the AMDG website for 4 weeks for public comment. A response to the public comments is made available after the after the final guideline is posted on the AMDG website.
7. The procedure for updating guideline is provided.
Where found: Appendix ___
The guideline is updated every 5 years or when there is substantial new evidence on COAT to warrant a review of the guideline. When convened, the advisory committee usually involves the same provider and specialty mix, including primary care. Together, with much preparation, key issues that have arisen in medical literature and in state and national databases regarding chronic opioid use will be discussed. The updates will usually supplement the previous guideline.
DOMAIN 4: CLARITY OF PRESENTATION
1. The recommendations are specific and unambiguous.
Where found: Throughout the guideline
<ul style="list-style-type: none"> • Recommendations are clearly identified and can be found within each clinical section • Supporting evidence and strength of evidence for recommendations are clearly documented • Tables and algorithms are used to illustrate processes and decision making • Appendices are used for more detailed references so key recommendations are not obscured.
2. The different options for the management of the condition or health issues are clearly presented.
Where found: Each clinical section provides a variety of pain management recommendations, including screening for risk factors, making a correct and timely diagnosis, dose recommendations, and possible non-opioid options for treating pain.
3. Key recommendations are easily identifiable.
Where found: Each clinical section is consistent in presenting:
Key Clinical Recommendations Supporting Evidence Recommended Tools and Resources
Clinical Sections: <ul style="list-style-type: none"> • Prescribing Opioids in Acute and Subacute Phase • Opioids for Perioperative Pain • Prescribing Opioids for Chronic Non-cancer Pain • Opioid Use in Cancer Survivors • Opioid Use during Pregnancy and Neonatal Abstinence Syndrome • Opioid Use in a Pediatric Population • Opioid Use in a Geriatric Population • Recognizing and Treating Substance Use Disorders
DOMAIN 5: APPLICABILITY
1. The guideline describes facilitators and barriers to its application.
Where found: Need new section, or work into every section
This is not yet really addressed in the guideline. Suggestions: add tips for providers who may not have ready access to pain specialists (tele-medicine?), urine drug testing facilities, or mental health treatment. Acknowledge difficulty of implementing the guideline in busy daily practice. What if insurance doesn't pay for drug testing?
2. The guideline provides advice and/or tools on how the recommendations can be put into practice.

Where found: Within each clinical chapter, in appendices, and on the AMDG website
Bulleted list under “opioids in the acute phase”, and “opioids in the subacute phase”. A few other places throughout. Contains tools in links (p. 7) and in appendices. Tools under “screening and monitoring your patient”. Needs more work.
3. The potential resources implications of applying the recommendations have been considered.
Where found: p. 22 --“Consultations do not necessarily have to be done face to face with the patient. See Appendix E for alternate forms of consultative assistance.” <i>This is old language and will need to be revised.</i>
This criterion seems to refer mostly to cost information. Include some information about cost of recommendations, or cost saving of implementing the recommendations.
4. The guideline presents monitoring or auditing criteria.
Where found: p. 7 --“If use during the acute phase...does not lead to improvements in pain and function of at least 30%, or to pain interference levels of 4 or less..” Prescriber-patient agreement included in appendix. Dosing threshold for pain consultant. Interpreting results of UDT.
This criterion is not strongly relevant for this guideline, where most recommendations have ranges, and require clinical judgment.
DOMAIN 6: EDITORIAL INDEPENDENCE
1. The views of the funding body have not influenced the content of the guideline.
Where found: Need to add
Recommendations: Include statement, “The views or interests of the funding body have not influenced the final recommendations”. Also “No explicit funding was provided for this guideline, and no funds came from outside the state government”.
2. Competing interest of the guideline development group members have been recorded and addressed.
Where found: Need to add
Recommendations: Include detailed list of participants and whether or not they declared conflicts of interest.

Acknowledgements

The Washington State Agency Medical Directors’ Group wishes to acknowledge the many individuals and groups from both the private and public sectors who provided crucial consultation and input to this guideline. Their clinical, scientific, and technical expertise helped ensure that this guideline would be relevant, accurate, and of practical use to prescribers. Every effort was made to create a guideline as evidence-based as possible. Where scientific evidence was insufficient or unavailable, the best clinical opinions and consensus of the advisory group were used.

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References

1. Hegmann KT, Weiss MS, Bowden K, et al. ACOEM practice guidelines: opioids for treatment of acute, subacute, chronic, and postoperative pain. *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine* 2014;56:e143-59.
2. Bates C, Laciak R, Southwick A, Bishoff J. Overprescription of postoperative narcotics: a look at postoperative pain medication delivery, consumption and disposal in urological practice. *The Journal of urology* 2011;185:551-5.
3. Binswanger IA, Glanz JM. Pharmaceutical opioids in the home and youth: implications for adult medical practice. *Substance abuse : official publication of the Association for Medical Education and Research in Substance Abuse* 2015:0.
4. Siegler A, Tuazon E, Bradley O'Brien D, Paone D. Unintentional opioid overdose deaths in New York City, 2005-2010: a place-based approach to reduce risk. *The International journal on drug policy* 2014;25:569-74.
5. Franklin G, Sabel J, Jones CM, et al. A comprehensive approach to address the prescription opioid epidemic in Washington State: milestones and lessons learned. *American journal of public health* 2015;105:463-9.
6. Deyo RA, Dworkin SF, Amtmann D, et al. Report of the NIH Task Force on Research Standards for Chronic Low Back Pain. *The spine journal : official journal of the North American Spine Society* 2014;14:1375-91.
7. Henschke N, Kuijpers T, Rubinstein SM, et al. Trends over time in the size and quality of randomised controlled trials of interventions for chronic low-back pain. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2012;21:375-81.
8. Chou R, Huffman LH. Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Annals of internal medicine* 2007;147:492-504.
9. Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Annals of internal medicine* 2007;147:478-91.
10. Furlan AD, Yazdi F, Tsertsvadze A, et al. A systematic review and meta-analysis of efficacy, cost-effectiveness, and safety of selected complementary

- and alternative medicine for neck and low-back pain. Evidence-based complementary and alternative medicine : eCAM 2012;2012:953139.
11. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. Cochrane database of systematic reviews (Online) 2010:Cd006605.
 12. Agency for Healthcare Research and Quality R, MD. The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. <http://www.ahrq.gov/research/findings/evidence-based-reports/opoidstp.html>2014.
 13. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2006;174:1589-94.
 14. Katz N, Mazer NA. The impact of opioids on the endocrine system. The Clinical journal of pain 2009;25:170-5.
 15. Vallejo R, de Leon-Casasola O, Benyamin R. Opioid therapy and immunosuppression: a review. American journal of therapeutics 2004;11:354-65.
 16. Saunders KW, Dunn KM, Merrill JO, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. Journal of general internal medicine 2010;25:310-5.
 17. Creanga AA, Sabel JC, Ko JY, et al. Maternal drug use and its effect on neonates: a population-based study in Washington State. Obstetrics and gynecology 2012;119:924-33.
 18. Katz DF, Albright K, Krantz MJ. An ECG-based cardiac safety initiative is well received by opioid treatment program staff: results from a qualitative assessment. Journal of addictive diseases 2013;32:387-92.
 19. Walker JM, Farney RJ, Rhondeau SM, et al. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 2007;3:455-61.
 20. Ballantyne JC. Opioid analgesia: perspectives on right use and utility. Pain physician 2007;10:479-91.
 21. Coben JH, Davis SM, Furbee PM, Sikora RD, Tillotson RD, Bossarte RM. Hospitalizations for poisoning by prescription opioids, sedatives, and tranquilizers. American journal of preventive medicine 2010;38:517-24.
 22. Braden JB, Russo J, Fan MY, et al. Emergency department visits among recipients of chronic opioid therapy. Archives of internal medicine 2010;170:1425-32.

23. Paulozzi LJ, Annest JL. US data show sharply rising drug-induced death rates. *Injury prevention : journal of the International Society for Child and Adolescent Injury Prevention* 2007;13:130-2.
24. Association AP. *Diagnostic and statistical manual of mental health*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
25. Juurlink DN, Dhalla IA. Dependence and addiction during chronic opioid therapy. *Journal of medical toxicology : official journal of the American College of Medical Toxicology* 2012;8:393-9.
26. Edlund MJ, Martin BC, Russo JE, DeVries A, Braden JB, Sullivan MD. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. *The Clinical journal of pain* 2014;30:557-64.
27. van Tulder M, Becker A, Bekkering T, et al. Chapter 3. European guidelines for the management of acute nonspecific low back pain in primary care. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2006;15 Suppl 2:S169-91.
28. Dembe A, Wickizer T, Sieck C, Partridge J, Balchick R. Opioid use and dosing in the workers' compensation setting. A comparative review and new data from Ohio. *American journal of industrial medicine* 2012;55:313-24.
29. Franklin GM, Rahman EA, Turner JA, Daniell WE, Fulton-Kehoe D. Opioid use for chronic low back pain: A prospective, population-based study among injured workers in Washington state, 2002-2005. *The Clinical journal of pain* 2009;25:743-51.
30. Franklin GM, Stover BD, Turner JA, Fulton-Kehoe D, Wickizer TM. Early opioid prescription and subsequent disability among workers with back injuries: the Disability Risk Identification Study Cohort. *Spine* 2008;33:199-204.
31. Martin BC, Fan MY, Edlund MJ, Devries A, Braden JB, Sullivan MD. Long-term chronic opioid therapy discontinuation rates from the TROUP study. *Journal of general internal medicine* 2011;26:1450-7.
32. Bree Collaborative: Spine/Low Back Pain Topic. Foundation for Health Care Quality, Health Care Authority, 2013. (Accessed March 9th 2015, at http://www.breecollaborative.org/wp-content/uploads/spine_lbp.pdf)
33. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA : the journal of the American Medical Association* 2013;310:591-608.

34. Franklin GM, Wickizer TM, Coe NB, Fulton-Kehoe D. Workers' compensation: poor quality health care and the growing disability problem in the United States. *American journal of industrial medicine* 2015;58:245-51.
35. Krebs EE, Lorenz KA, Bair MJ, et al. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. *Journal of general internal medicine* 2009;24:733-8.
36. Turk DC, Melzack R. *Handbook of Pain Assessment, Third Edition*: Guilford Publications; 2011.
37. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2003;106:337-45.
38. Turk DC, Dworkin RH, McDermott MP, et al. Analyzing multiple endpoints in clinical trials of pain treatments: IMMPACT recommendations. *Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials*. *Pain* 2008;139:485-93.
39. Carreon LY, Glassman SD, Campbell MJ, Anderson PA. Neck Disability Index, short form-36 physical component summary, and pain scales for neck and arm pain: the minimum clinically important difference and substantial clinical benefit after cervical spine fusion. *The spine journal : official journal of the North American Spine Society* 2010;10:469-74.
40. Carragee EJ, Cheng I. Minimum acceptable outcomes after lumbar spinal fusion. *The spine journal : official journal of the North American Spine Society* 2010;10:313-20.
41. Ostelo RW, Deyo RA, Stratford P, et al. Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change. *Spine* 2008;33:90-4.
42. Gatchel RJ, Mayer TG, Choi Y, Chou R. Validation of a consensus-based minimal clinically important difference (MCID) threshold using an objective functional external anchor. *The spine journal : official journal of the North American Spine Society* 2013;13:889-93.
43. Cepeda MS, Africano JM, Polo R, Alcalá R, Carr DB. What decline in pain intensity is meaningful to patients with acute pain? *Pain* 2003;105:151-7.
44. ten Klooster PM, Drossaers-Bakker KW, Taal E, van de Laar MA. Patient-perceived satisfactory improvement (PPSI): interpreting meaningful change in pain from the patient's perspective. *Pain* 2006;121:151-7.
45. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared with placebo or other treatments for chronic low back pain: an update of the Cochrane Review. *Spine* 2014;39:556-63.

46. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Annals of internal medicine* 2010;152:85-92.
47. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA : the journal of the American Medical Association* 2011;305:1315-21.
48. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Archives of internal medicine* 2011;171:686-91.
49. Zedler B, Xie L, Wang L, et al. Risk Factors for Serious Prescription Opioid-Related Toxicity or Overdose among Veterans Health Administration Patients. *Pain medicine (Malden, Mass)* 2014;15:1911-29.
50. CDC grand rounds: prescription drug overdoses - a U.S. epidemic. *MMWR Morbidity and mortality weekly report* 2012;61:10-3.
51. Fulton-Kehoe D, Garg RK, Turner JA, et al. Opioid poisonings and opioid adverse effects in workers in Washington state. *American journal of industrial medicine* 2013;56:1452-62.
52. Fulton-Kehoe D, Sullivan M, Turner J, et al. Opioid poisonings in Washington State Medicaid: Trends, dosing, and guidelines. *Medical Care* 2015 (*in press*).
53. Gomes T, Redelmeier DA, Juurlink DN, Dhalla IA, Camacho X, Mamdani MM. Opioid dose and risk of road trauma in Canada: a population-based study. *JAMA internal medicine* 2013;173:196-201.
54. White JM. Pleasure into pain: the consequences of long-term opioid use. *Addictive behaviors* 2004;29:1311-24.
55. King T, Gardell LR, Wang R, et al. Role of NK-1 neurotransmission in opioid-induced hyperalgesia. *Pain* 2005;116:276-88.
56. Mao J, Sung B, Ji RR, Lim G. Chronic morphine induces downregulation of spinal glutamate transporters: implications in morphine tolerance and abnormal pain sensitivity. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 2002;22:8312-23.
57. Ossipov MH, Porreca F. Challenges in the development of novel treatment strategies for neuropathic pain. *NeuroRx : the journal of the American Society for Experimental NeuroTherapeutics* 2005;2:650-61.
58. King NB, Fraser V, Boikos C, Richardson R, Harper S. Determinants of increased opioid-related mortality in the United States and Canada, 1990-2013: a systematic review. *American journal of public health* 2014;104:e32-42.

59. Frank JW, Brooker AS, DeMaio SE, et al. Disability resulting from occupational low back pain. Part II: What do we know about secondary prevention? A review of the scientific evidence on prevention after disability begins. *Spine* 1996;21:2918-29.
60. Jarvik JG, Gold LS, Comstock BA, et al. Association of early imaging for back pain with clinical outcomes in older adults. *JAMA : the journal of the American Medical Association* 2015;313:1143-53.
61. Schandelmaier S, Ebrahim S, Burkhardt SC, et al. Return to work coordination programmes for work disability: a meta-analysis of randomised controlled trials. *PloS one* 2012;7:e49760.
62. Malmivaara A, Hakkinen U, Aro T, et al. The treatment of acute low back pain--bed rest, exercises, or ordinary activity? *The New England journal of medicine* 1995;332:351-5.
63. Hagen KB, Jamtvedt G, Hilde G, Winnem MF. The updated cochrane review of bed rest for low back pain and sciatica. *Spine* 2005;30:542-6.
64. Roddy E, Zhang W, Doherty M. Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. *Annals of the rheumatic diseases* 2005;64:544-8.
65. Wang SY, Olson-Kellogg B, Shamliyan TA, Choi JY, Ramakrishnan R, Kane RL. Physical therapy interventions for knee pain secondary to osteoarthritis: a systematic review. *Annals of internal medicine* 2012;157:632-44.
66. Hayden JA, van Tulder MW, Malmivaara A, Koes BW. Exercise therapy for treatment of non-specific low back pain. *Cochrane database of systematic reviews (Online)* 2005:Cd000335.
67. Busch AJ, Webber SC, Richards RS, et al. Resistance exercise training for fibromyalgia. *Cochrane database of systematic reviews (Online)* 2013;12:CD010884.
68. Beinart NA, Goodchild CE, Weinman JA, Ayis S, Godfrey EL. Individual and intervention-related factors associated with adherence to home exercise in chronic low back pain: a systematic review. *The spine journal : official journal of the North American Spine Society* 2013;13:1940-50.
69. Wertli MM, Rasmussen-Barr E, Weiser S, Bachmann LM, Brunner F. The role of fear avoidance beliefs as a prognostic factor for outcome in patients with nonspecific low back pain: a systematic review. *The spine journal : official journal of the North American Spine Society* 2014;14:816-36 e4.
70. Chou R, Shekelle P. Will this patient develop persistent disabling low back pain? *JAMA : the journal of the American Medical Association* 2010;303:1295-302.

71. Turner JA, Franklin G, Fulton-Kehoe D, et al. ISSLS prize winner: early predictors of chronic work disability: a prospective, population-based study of workers with back injuries. *Spine* 2008;33:2809-18.
72. Darlow B, Fullen BM, Dean S, Hurley DA, Baxter GD, Dowell A. The association between health care professional attitudes and beliefs and the attitudes and beliefs, clinical management, and outcomes of patients with low back pain: a systematic review. *European journal of pain (London, England)* 2012;16:3-17.
73. Integration of behavioral and relaxation approaches into the treatment of chronic pain and insomnia. NIH Technology Assessment Panel on Integration of Behavioral and Relaxation Approaches into the Treatment of Chronic Pain and Insomnia. *JAMA : the journal of the American Medical Association* 1996;276:313-8.
74. Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain* 1999;80:1-13.
75. Eccleston C, Morley SJ, Williams AC. Psychological approaches to chronic pain management: evidence and challenges. *British journal of anaesthesia* 2013;111:59-63.
76. Ehde DM, Dillworth TM, Turner JA. Cognitive-behavioral therapy for individuals with chronic pain: efficacy, innovations, and directions for research. *The American psychologist* 2014;69:153-66.
77. Eccleston C, Palermo TM, Williams AC, et al. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. *Cochrane database of systematic reviews (Online)* 2014;5:CD003968.
78. Clauw DJ. Fibromyalgia: a clinical review. *JAMA : the journal of the American Medical Association* 2014;311:1547-55.
79. Bernardy K, Klose P, Busch AJ, Choy EH, Hauser W. Cognitive behavioural therapies for fibromyalgia. *Cochrane database of systematic reviews (Online)* 2013;9:CD009796.
80. Makris UE, Abrams RC, Gurland B, Reid MC. Management of persistent pain in the older patient: a clinical review. *JAMA : the journal of the American Medical Association* 2014;312:825-36.
81. Ford AC, Quigley EM, Lacy BE, et al. Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis. *The American journal of gastroenterology* 2014;109:1350-65; quiz 66.

82. Aggarwal VR, Lovell K, Peters S, Javidi H, Joughin A, Goldthorpe J. Psychosocial interventions for the management of chronic orofacial pain. Cochrane database of systematic reviews (Online) 2011:Cd008456.
83. Lin EH, Katon W, Von Korff M, et al. Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. *JAMA : the journal of the American Medical Association* 2003;290:2428-9.
84. Mann EG, Lefort S, Vandenberg EG. Self-management interventions for chronic pain. *Pain management* 2013;3:211-22.
85. LeFort SM, Gray-Donald K, Rowat KM, Jeans ME. Randomized controlled trial of a community-based psychoeducation program for the self-management of chronic pain. *Pain* 1998;74:297-306.
86. Ory MG, Ahn S, Jiang L, et al. Successes of a national study of the Chronic Disease Self-Management Program: meeting the triple aim of health care reform. *Medical care* 2013;51:992-8.
87. Standaert CJ, Friedly J, Erwin MW, et al. Comparative effectiveness of exercise, acupuncture, and spinal manipulation for low back pain. *Spine* 2011;36:S120-30.
88. Furlan AD, Yazdi F, Tsertsvadze A, et al. Complementary and alternative therapies for back pain II. Evidence report/technology assessment 2010:1-764.
89. French SD, Cameron M, Walker BF, Reggars JW, Esterman AJ. A Cochrane review of superficial heat or cold for low back pain. *Spine* 2006;31:998-1006.
90. WA Health Technology Assessment. Electrical Nerve Stimulation For The Treatment of Pain. In: Authority WSHC, ed.2009.
91. Turk DC. Clinical effectiveness and cost-effectiveness of treatments for patients with chronic pain. *The Clinical journal of pain* 2002;18:355-65.
92. Gatchel RJ, Okifuji A. Evidence-based scientific data documenting the treatment and cost-effectiveness of comprehensive pain programs for chronic nonmalignant pain. *The journal of pain : official journal of the American Pain Society* 2006;7:779-93.
93. Kamper SJ, Apeldoorn AT, Chiarotto A, et al. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain. Cochrane database of systematic reviews (Online) 2014;9:CD000963.
94. Hill JC, Whitehurst DG, Lewis M, et al. Comparison of stratified primary care management for low back pain with current best practice (STarT Back): a randomised controlled trial. *Lancet* 2011;378:1560-71.

95. Fulton-Kehoe D, Stover BD, Turner JA, et al. Development of a brief questionnaire to predict long-term disability. *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine* 2008;50:1042-52.
96. Davies KA, Macfarlane GJ, Nicholl BI, et al. Restorative sleep predicts the resolution of chronic widespread pain: results from the EPIFUND study. *Rheumatology (Oxford, England)* 2008;47:1809-13.
97. Roehrs T, Hyde M, Blaisdell B, Greenwald M, Roth T. Sleep loss and REM sleep loss are hyperalgesic. *Sleep* 2006;29:145-51.
98. Laudon M, Frydman-Marom A. Therapeutic effects of melatonin receptor agonists on sleep and comorbid disorders. *International journal of molecular sciences* 2014;15:15924-50.
99. Smith MT, Perlis ML, Park A, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *The American journal of psychiatry* 2002;159:5-11.
100. Morin CM, Benca R. Chronic insomnia. *Lancet* 2012;379:1129-41.
101. Veehof MM, Oskam MJ, Schreurs KM, Bohlmeijer ET. Acceptance-based interventions for the treatment of chronic pain: a systematic review and meta-analysis. *Pain* 2011;152:533-42.
102. Chiesa A, Serretti A. Mindfulness-based interventions for chronic pain: a systematic review of the evidence. *Journal of alternative and complementary medicine (New York, NY)* 2011;17:83-93.
103. Cramer H, Haller H, Lauche R, Dobos G. Mindfulness-based stress reduction for low back pain. A systematic review. *BMC complementary and alternative medicine* 2012;12:162.
104. Reiner K, Tibi L, Lipsitz JD. Do mindfulness-based interventions reduce pain intensity? A critical review of the literature. *Pain medicine (Malden, Mass)* 2013;14:230-42.
105. Zeidan F, Grant JA, Brown CA, McHaffie JG, Coghill RC. Mindfulness meditation-related pain relief: evidence for unique brain mechanisms in the regulation of pain. *Neuroscience letters* 2012;520:165-73.
106. Carette S, Oakson G, Guimont C, Steriade M. Sleep electroencephalography and the clinical response to amitriptyline in patients with fibromyalgia. *Arthritis and rheumatism* 1995;38:1211-7.
107. Tauben D. Non-Opioid Medications for Pain. *Physical Medicine and Rehabilitation. Clinics of North America* 2015 Elsevier Press (*in press*).
108. Yang C, White DP, Winkelman JW. Antidepressants and periodic leg movements of sleep. *Biological psychiatry* 2005;58:510-4.

109. Schweitzer P. Drugs that disturb sleep and wakefulness. Philadelphia: Elsevier Saunders; 2005.
110. Pigeon WR, Bishop TM, Marcus JA. Advances in the management of insomnia. *F1000prime reports* 2014;6:48.
111. Buysse DJ. Insomnia. *JAMA : the journal of the American Medical Association* 2013;309:706-16.
112. Derry CJ, Derry S, Moore RA. Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain. *Cochrane database of systematic reviews (Online)* 2013;6:Cd010210.
113. FDA Center for Drug Evaluation and Research. Acetaminophen Overdose and Liver Injury. (Accessed March 9th 2015, at <http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm165107.htm>)
114. Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW. Non-steroidal anti-inflammatory drugs for low back pain. *Cochrane database of systematic reviews (Online)* 2008:CD000396.
115. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 2007;132:237-51.
116. Kuijpers T, van Middelkoop M, Rubinstein SM, et al. A systematic review on the effectiveness of pharmacological interventions for chronic non-specific low-back pain. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2011;20:40-50.
117. Gaskell H, Derry S, Moore RA, McQuay HJ. Single dose oral oxycodone and oxycodone plus paracetamol (acetaminophen) for acute postoperative pain in adults. *Cochrane database of systematic reviews (Online)* 2009:Cd002763.
118. Moore PA, Hersh EV. Combining ibuprofen and acetaminophen for acute pain management after third-molar extractions: translating clinical research to dental practice. *Journal of the American Dental Association (1939)* 2013;144:898-908.
119. Oxford league table of analgesics in acute pain. 2007. (Accessed April 8th 2015, at <http://www.medicine.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesic/Leagtab.html>.)
120. Moulin D, Boulanger A, Clark AJ, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain research & management : the journal of the Canadian Pain*

Society = journal de la société canadienne pour le traitement de la douleur 2014;19:328-35.

121. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *European journal of neurology : the official journal of the European Federation of Neurological Societies* 2010;17:1113-e88.

122. Boyle J, Eriksson ME, Gribble L, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. *Diabetes care* 2012;35:2451-8.

123. Mercier A, Auger-Aubin I, Lebeau JP, et al. Evidence of prescription of antidepressants for non-psychiatric conditions in primary care: an analysis of guidelines and systematic reviews. *BMC family practice* 2013;14:55.

124. Centre for Clinical Practice at N. National Institute for Health and Clinical Excellence: Guidance. *Neuropathic Pain: The Pharmacological Management of Neuropathic Pain in Adults in Non-specialist Settings*. London: National Institute for Health and Care Excellence, (UK)

National Institute for Health and Care Excellence; 2013.

125. Federal Drug Administration - CYMBALTA prescribing information. 2009. at

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021427s037s0421bl.pdf.)

126. Chou R, Norris SL, Carson S, Chan BKS. Drug Class Reviews. Drug Class Review on Drugs for Neuropathic Pain: Final Report. Portland (OR): Oregon Health & Science University

Oregon Health & Science University, Portland, Oregon; 2007.

127. Uceyler N, Sommer C, Walitt B, Hauser W. Anticonvulsants for fibromyalgia. *Cochrane database of systematic reviews (Online)* 2013;10:CD010782.

128. Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. *Diabetes care* 2008;31:1448-54.

129. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clinic proceedings* 2010;85:S3-14.

130. Vaillancourt PD, Langevin HM. Painful peripheral neuropathies. *The Medical clinics of North America* 1999;83:627-42, vi.
131. van Tulder MW, Touray T, Furlan AD, Solway S, Bouter LM. Muscle relaxants for non-specific low back pain. *Cochrane database of systematic reviews (Online)* 2003:Cd004252.
132. Langer-Gould AM, Anderson WE, Armstrong MJ, et al. The American Academy of Neurology's top five choosing wisely recommendations. *Neurology* 2013;81:1004-11.
133. Bendtsen L, Evers S, Linde M, Mitsikostas DD, Sandrini G, Schoenen J. EFNS guideline on the treatment of tension-type headache - report of an EFNS task force. *European journal of neurology : the official journal of the European Federation of Neurological Societies* 2010;17:1318-25.
134. Franklin GM. Opioids for chronic noncancer pain: a position paper of the American Academy of Neurology. *Neurology* 2014;83:1277-84.
135. Fitzcharles MA, Ste-Marie PA, Gamsa A, Ware MA, Shir Y. Opioid use, misuse, and abuse in patients labeled as fibromyalgia. *The American journal of medicine* 2011;124:955-60.
136. Kroenke K, Krebs EE, Bair MJ. Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews. *General hospital psychiatry* 2009;31:206-19.
137. Brummett CM, Janda AM, Schueller CM, et al. Survey criteria for fibromyalgia independently predict increased postoperative opioid consumption after lower-extremity joint arthroplasty: a prospective, observational cohort study. *Anesthesiology* 2013;119:1434-43.
138. Painter JT, Crofford LJ. Chronic opioid use in fibromyalgia syndrome: a clinical review. *Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases* 2013;19:72-7.
139. Ngian GS, Guymer EK, Littlejohn GO. The use of opioids in fibromyalgia. *International journal of rheumatic diseases* 2011;14:6-11.
140. Pengel HM, Maher CG, Refshauge KM. Systematic review of conservative interventions for subacute low back pain. *Clinical rehabilitation* 2002;16:811-20.
141. Edlund MJ, Martin BC, Devries A, Fan MY, Braden JB, Sullivan MD. Trends in use of opioids for chronic noncancer pain among individuals with mental health and substance use disorders: the TROUP study. *The Clinical journal of pain* 2010;26:1-8.
142. Braden JB, Sullivan MD, Ray GT, et al. Trends in long-term opioid therapy for noncancer pain among persons with a history of depression. *General hospital psychiatry* 2009;31:564-70.

143. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain* 2007;129:355-62.
144. Sullivan MD, Edlund MJ, Zhang L, Unutzer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. *Archives of internal medicine* 2006;166:2087-93.
145. Cicero TJ, Wong G, Tian Y, Lynskey M, Todorov A, Isenberg K. Co-morbidity and utilization of medical services by pain patients receiving opioid medications: data from an insurance claims database. *Pain* 2009;144:20-7.
146. Liao P, Yegneswaran B, Vairavanathan S, Zilberman P, Chung F. Postoperative complications in patients with obstructive sleep apnea: a retrospective matched cohort study. *Canadian journal of anaesthesia = Journal canadien d'anesthesie* 2009;56:819-28.
147. Chidambaran V, Olbrecht V, Hossain M, Sadhasivam S, Rose J, Meyer MJ. Risk predictors of opioid-induced critical respiratory events in children: naloxone use as a quality measure of opioid safety. *Pain medicine (Malden, Mass)* 2014;15:2139-49.
148. Pergolizzi J, Boger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain practice : the official journal of World Institute of Pain* 2008;8:287-313.
149. Jungquist CR, Karan S, Perlis ML. Risk factors for opioid-induced excessive respiratory depression. *Pain management nursing : official journal of the American Society of Pain Management Nurses* 2011;12:180-7.
150. Funk RD, Hilliard P, Ramachandran SK. Perioperative opioid usage: avoiding adverse effects. *Plastic and reconstructive surgery* 2014;134:32s-9s.
151. Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA : the journal of the American Medical Association* 2008;300:2613-20.
152. Gudin JA, Mogali S, Jones JD, Comer SD. Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. *Postgraduate medicine* 2013;125:115-30.
153. Lee LA, Caplan RA, Stephens LS, et al. Postoperative Opioid-induced Respiratory Depression: A Closed Claims Analysis. *Anesthesiology* 2015;122:659-65.
154. Jarzyna D, Jungquist CR, Pasero C, et al. American Society for Pain Management Nursing guidelines on monitoring for opioid-induced sedation

- and respiratory depression. *Pain management nursing : official journal of the American Society of Pain Management Nurses* 2011;12:118-45.e10.
155. Dahan A, Overdyk F, Smith T, Aarts L, Niesters M. Pharmacovigilance: a review of opioid-induced respiratory depression in chronic pain patients. *Pain physician* 2013;16:E85-94.
156. Sommer M, de Rijke JM, van Kleef M, et al. Predictors of acute postoperative pain after elective surgery. *The Clinical journal of pain* 2010;26:87-94.
157. Rapp SE, Ready LB, Nessly ML. Acute pain management in patients with prior opioid consumption: a case-controlled retrospective review. *Pain* 1995;61:195-201.
158. Rozen D, DeGaetano NP. Perioperative management of opioid-tolerant chronic pain patients. *Journal of opioid management* 2006;2:353-63.
159. Patanwala AE, Jarzyna DL, Miller MD, Erstad BL. Comparison of opioid requirements and analgesic response in opioid-tolerant versus opioid-naive patients after total knee arthroplasty. *Pharmacotherapy* 2008;28:1453-60.
160. Huxtable CA, Roberts LJ, Somogyi AA, MacIntyre PE. Acute pain management in opioid-tolerant patients: a growing challenge. *Anaesthesia and intensive care* 2011;39:804-23.
161. McCormick Z, Chu SK, Chang-Chien GC, Joseph P. Acute pain control challenges with buprenorphine/naloxone therapy in a patient with compartment syndrome secondary to McArdle's disease: a case report and review. *Pain medicine (Malden, Mass)* 2013;14:1187-91.
162. Caumo W, Schmidt AP, Schneider CN, et al. Preoperative predictors of moderate to intense acute postoperative pain in patients undergoing abdominal surgery. *Acta anaesthesiologica Scandinavica* 2002;46:1265-71.
163. Hadi I, Morley-Forster PK, Dain S, Horrill K, Moulin DE. Brief review: perioperative management of the patient with chronic non-cancer pain. *Canadian journal of anaesthesia = Journal canadien d'anesthesie* 2006;53:1190-9.
164. Jitpakdee T, Mandee S. Strategies for preventing side effects of systemic opioid in postoperative pediatric patients. *Paediatric anaesthesia* 2014;24:561-8.
165. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology* 2012;116:248-73.
166. Sinatra R. Causes and consequences of inadequate management of acute pain. *Pain medicine (Malden, Mass)* 2010;11:1859-71.

167. Levy AS, Marmar E. The role of cold compression dressings in the postoperative treatment of total knee arthroplasty. *Clinical orthopaedics and related research* 1993;174-8.
168. Schroder D, Passler HH. Combination of cold and compression after knee surgery. A prospective randomized study. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA* 1994;2:158-65.
169. Haase O, Schwenk W, Hermann C, Muller JM. Guided imagery and relaxation in conventional colorectal resections: a randomized, controlled, partially blinded trial. *Diseases of the colon and rectum* 2005;48:1955-63.
170. Tusek D, Church JM, Fazio VW. Guided imagery as a coping strategy for perioperative patients. *AORN journal* 1997;66:644-9.
171. Seers K, Crichton N, Tutton L, Smith L, Saunders T. Effectiveness of relaxation for postoperative pain and anxiety: randomized controlled trial. *Journal of advanced nursing* 2008;62:681-8.
172. Ashton C, Jr., Whitworth GC, Seldomridge JA, et al. Self-hypnosis reduces anxiety following coronary artery bypass surgery. A prospective, randomized trial. *The Journal of cardiovascular surgery* 1997;38:69-75.
173. Nilsson U, Rawal N, Enqvist B, Unosson M. Analgesia following music and therapeutic suggestions in the PACU in ambulatory surgery; a randomized controlled trial. *Acta anaesthesiologica Scandinavica* 2003;47:278-83.
174. Simcock XC, Yoon RS, Chalmers P, Geller JA, Kiernan HA, Macaulay W. Intraoperative music reduces perceived pain after total knee arthroplasty: a blinded, prospective, randomized, placebo-controlled clinical trial. *The journal of knee surgery* 2008;21:275-8.
175. Tramer MR, Williams JE, Carroll D, Wiffen PJ, Moore RA, McQuay HJ. Comparing analgesic efficacy of non-steroidal anti-inflammatory drugs given by different routes in acute and chronic pain: a qualitative systematic review. *Acta anaesthesiologica Scandinavica* 1998;42:71-9.
176. DeAndrade JR, Maslanka M, Reines HD, et al. Ketorolac versus meperidine for pain relief after orthopaedic surgery. *Clinical orthopaedics and related research* 1996:301-12.
177. Gimbel JS, Brugger A, Zhao W, Verburg KM, Geis GS. Efficacy and tolerability of celecoxib versus hydrocodone/acetaminophen in the treatment of pain after ambulatory orthopedic surgery in adults. *Clinical therapeutics* 2001;23:228-41.
178. Ong CK, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. *Anesthesia and analgesia* 2010;110:1170-9.

179. American Pain Society. Management of Postoperative Pain: Clinical Guidelines 2015 (*in press*).
180. Egbert LD, Battit GE, Welch CE, Bartlett MK. REDUCTION OF POSTOPERATIVE PAIN BY ENCOURAGEMENT AND INSTRUCTION OF PATIENTS. A STUDY OF DOCTOR-PATIENT RAPPORT. The New England journal of medicine 1964;270:825-7.
181. Reynolds MA. Postoperative pain management discharge teaching in a rural population. Pain management nursing : official journal of the American Society of Pain Management Nurses 2009;10:76-84.
182. Holman JE, Stoddard GJ, Horwitz DS, Higgins TF. The effect of preoperative counseling on duration of postoperative opiate use in orthopaedic trauma surgery: a surgeon-based comparative cohort study. Journal of orthopaedic trauma 2014;28:502-6.
183. Butler GS, Hurley CA, Buchanan KL, Smith-VanHorne J. Prehospital education: effectiveness with total hip replacement surgery patients. Patient education and counseling 1996;29:189-97.
184. Wilson JF. Behavioral preparation for surgery: benefit or harm? Journal of behavioral medicine 1981;4:79-102.
185. Elia N, Lysakowski C, Tramer MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. Anesthesiology 2005;103:1296-304.
186. Hernandez-Palazon J, Tortosa JA, Martinez-Lage JF, Perez-Flores D. Intravenous administration of propacetamol reduces morphine consumption after spinal fusion surgery. Anesthesia and analgesia 2001;92:1473-6.
187. Straube S, Derry S, Moore RA, Wiffen PJ, McQuay HJ. Single dose oral gabapentin for established acute postoperative pain in adults. Cochrane database of systematic reviews (Online) 2010:Cd008183.
188. Marret E, Rolin M, Beaussier M, Bonnet F. Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. The British journal of surgery 2008;95:1331-8.
189. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane database of systematic reviews (Online) 2006:Cd004603.
190. Joshi GP, Bonnet F, Shah R, et al. A systematic review of randomized trials evaluating regional techniques for postthoracotomy analgesia. Anesthesia and analgesia 2008;107:1026-40.

191. Wang H, Akbar M, Weinsheimer N, Gantz S, Schiltenswolf M. Longitudinal observation of changes in pain sensitivity during opioid tapering in patients with chronic low-back pain. *Pain medicine (Malden, Mass)* 2011;12:1720-6.
192. Gershman JA, Gershman JA, Fass AD, Popovici I. Evaluation of Florida physicians' knowledge and attitudes toward accessing the state prescription drug monitoring program as a prescribing tool. *Pain medicine (Malden, Mass)* 2014;15:2013-9.
193. Irvine JM, Hallvik SE, Hildebran C, Marino M, Beran T, Deyo RA. Who uses a prescription drug monitoring program and how? Insights from a statewide survey of Oregon clinicians. *The journal of pain : official journal of the American Pain Society* 2014;15:747-55.
194. Macintyre PE, Huxtable CA, Flint SL, Dobbin MD. Costs and consequences: a review of discharge opioid prescribing for ongoing management of acute pain. *Anaesthesia and intensive care* 2014;42:558-74.
195. Pedersen T, Nicholson A, Hovhannisyanyan K, Moller AM, Smith AF, Lewis SR. Pulse oximetry for perioperative monitoring. *Cochrane database of systematic reviews (Online)* 2014;3:Cd002013.
196. Kobelt P, Burke K, Renker P. Evaluation of a standardized sedation assessment for opioid administration in the post anesthesia care unit. *Pain management nursing : official journal of the American Society of Pain Management Nurses* 2014;15:672-81.
197. Nisbet AT, Mooney-Cotter F. Comparison of selected sedation scales for reporting opioid-induced sedation assessment. *Pain management nursing : official journal of the American Society of Pain Management Nurses* 2009;10:154-64.
198. Tweddell JS, Ghanayem NS, Hoffman GM. All this monitoring...what's necessary, what's not? *Seminars in thoracic and cardiovascular surgery Pediatric cardiac surgery annual* 2014;17:81-90.
199. Dahan A, Aarts L, Smith TW. Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression. *Anesthesiology* 2010;112:226-38.
200. Momeni M, Crucitti M, De Kock M. Patient-controlled analgesia in the management of postoperative pain. *Drugs* 2006;66:2321-37.
201. George JA, Lin EE, Hanna MN, et al. The effect of intravenous opioid patient-controlled analgesia with and without background infusion on respiratory depression: a meta-analysis. *Journal of opioid management* 2010;6:47-54.
202. Viscusi ER. Patient-controlled drug delivery for acute postoperative pain management: a review of current and emerging technologies. *Regional anesthesia and pain medicine* 2008;33:146-58.

203. Ruetzler K, Blome CJ, Nabecker S, et al. A randomised trial of oral versus intravenous opioids for treatment of pain after cardiac surgery. *Journal of anesthesia* 2014;28:580-6.
204. Gordon DB, Dahl J, Phillips P, et al. The use of "as-needed" range orders for opioid analgesics in the management of acute pain: a consensus statement of the American Society for Pain Management Nursing and the American Pain Society. *Pain management nursing : official journal of the American Society of Pain Management Nurses* 2004;5:53-8.
205. Dorn S, Lembo A, Cremonini F. Opioid-Induced Bowel Dysfunction: Epidemiology, Pathophysiology, Diagnosis, and Initial Therapeutic Approach. *The American journal of gastroenterology* 2014;2:31-7.
206. Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. *American journal of surgery* 2001;182:11s-8s.
207. Naliboff BD, Wu SM, Schieffer B, et al. A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. *The journal of pain : official journal of the American Pain Society* 2011;12:288-96.
208. Miller M, Barber CW, Leatherman S, et al. Prescription Opioid Duration of Action and the Risk of Unintentional Overdose Among Patients Receiving Opioid Therapy. *JAMA internal medicine* 2015.
209. Degenhardt L, Bruno R, Lintzeris N, et al. Agreement between definitions of pharmaceutical opioid use disorders and dependence in people taking opioids for chronic non-cancer pain (POINT): a cohort study. *The Lancet Psychiatry* 2015;2:314-22.
210. Katz EC, Schwartz RP, King S, et al. Brief vs. extended buprenorphine detoxification in a community treatment program: engagement and short-term outcomes. *The American journal of drug and alcohol abuse* 2009;35:63-7.
211. Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Eng J Med* 2003;349:1943-53.
212. Chang G, Chen L, Mao J. Opioid tolerance and hyperalgesia. *Med Clin N Am* 2007;91:199-211.
213. Mao J. Opioid-induced abnormal pain sensitivity: implications in clinical opioid therapy. *Pain* 2002;10:213-7.
214. Jensen MP, Turner JA, Romano JM. Changes in beliefs, catastrophizing, and coping are associated with improvement in multidisciplinary pain treatment. *Journal of consulting and clinical psychology* 2001;69:655-62.
215. Gold MS, Pottash AL, Extein I. Clonidine: inpatient studies from 1978 to 1981. *The Journal of clinical psychiatry* 1982;43:35-8.

216. Jasinski DR, Johnson RE, Kocher TR. Clonidine in morphine withdrawal. Differential effects on signs and symptoms. *Archives of general psychiatry* 1985;42:1063-6.
217. Derry S, Wiffen PJ, Aldington D, Moore RA. Nortriptyline for neuropathic pain in adults. *Cochrane database of systematic reviews* (Online) 2015;1:Cd011209.
218. Edelsberg JS, Lord C, Oster G. Systematic review and meta-analysis of efficacy, safety, and tolerability data from randomized controlled trials of drugs used to treat postherpetic neuralgia. *The Annals of pharmacotherapy* 2011;45:1483-90.
219. Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. *Lancet* 2009;374:1252-61.
220. Orbai AM, Meyerhoff JO. The effectiveness of tricyclic antidepressants on lumbar spinal stenosis. *Bulletin of the NYU hospital for joint diseases* 2010;68:22-4.
221. Kitahara M, Kojima KK, Ohmura A. Efficacy of interdisciplinary treatment for chronic nonmalignant pain patients in Japan. *The Clinical journal of pain* 2006;22:647-55.
222. Turk DC SK. Efficacy and cost-effectiveness treatment for chronic pain: an analysis and evidence-based synthesis. . New York: Informa Healthcare; 2007.
223. Stanos S. Focused review of interdisciplinary pain rehabilitation programs for chronic pain management. *Current pain and headache reports* 2012;16:147-52.
224. Gatchel RJ, McGeary DD, McGeary CA, Lippe B. Interdisciplinary chronic pain management: past, present, and future. *The American psychologist* 2014;69:119-30.
225. Guzman J, Esmail R, Karjalainen K, Malmivaara A, Irvin E, Bombardier C. Multidisciplinary bio-psycho-social rehabilitation for chronic low back pain. *The cochrane database of systematic reviews* 2002:CD000963.
226. Collins ED, Kleber HD, Whittington RA, Heitler NE. Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. *JAMA : the journal of the American Medical Association* 2005;294:903-13.
227. Passik SD, Kirsh KL, Donaghy KB, Poretnoy RK. Pain and aberrant drug-related behaviors in medically ill patients with and without histories of substance abuse. *Clin J Pain* 2006;22:173-81.

228. Ives TJ, Chelminski PR, Hammet-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res* 2006;6.
229. Braden J, Sullivan MD. Suicidal thoughts and behavior among adults with self-reported pain: conditions in the national comorbidity survey replication. *J Pain* 2008;9:1106-15.
230. Orman JS, Keating GM. Buprenorphine/naloxone: a review of its use in the treatment of opioid dependence. *Drugs* 2009;69:577-607.
231. Ballantyne JC. Assessing the prevalence of opioid misuse, abuse, and addiction in chronic pain. *Pain* 2015;156:567-8.
232. Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. *Lancet* 2003;361:662-8.
233. Gunne LM, Gronbladh L. The Swedish methadone maintenance program: a controlled study. *Drug and alcohol dependence* 1981;7:249-56.
234. O'Connor PG, Carroll KM, Shi JM, Schottenfeld RS, Kosten TR, Rounsaville BJ. Three methods of opioid detoxification in a primary care setting. A randomized trial. *Annals of internal medicine* 1997;127:526-30.
235. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane database of systematic reviews (Online)* 2009:CD002209.
236. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane database of systematic reviews (Online)* 2014;2:CD002207.
237. Fullerton CA, Kim M, Thomas CP, et al. Medication-assisted treatment with methadone: assessing the evidence. *Psychiatric services (Washington, DC)* 2014;65:146-57.
238. Thomas CP, Fullerton CA, Kim M, et al. Medication-assisted treatment with buprenorphine: assessing the evidence. *Psychiatric services (Washington, DC)* 2014;65:158-70.
239. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane database of systematic reviews (Online)* 2011:CD001333.
240. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. *JAMA : the journal of the American Medical Association* 2012;307:1934-40.

241. Antonucci R, Zaffanello M, Puxeddu E, et al. Use of non-steroidal anti-inflammatory drugs in pregnancy: impact on the fetus and newborn. *Current drug metabolism* 2012;13:474-90.
242. Koren G, Florescu A, Costei AM, Boskovic R, Moretti ME. Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. *The Annals of pharmacotherapy* 2006;40:824-9.
243. Pritham UA, McKay L. Safe management of chronic pain in pregnancy in an era of opioid misuse and abuse. *Journal of obstetric, gynecologic, and neonatal nursing : JOGNN / NAACOG* 2014;43:554-67.
244. Ailes EC, Dawson AL, Lind JN, et al. Opioid prescription claims among women of reproductive age--United States, 2008-2012. *MMWR Morbidity and mortality weekly report* 2015;64:37-41.
245. Desai RJ, Hernandez-Diaz S, Bateman BT, Huybrechts KF. Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. *Obstetrics and gynecology* 2014;123:997-1002.
246. Bateman BT, Hernandez-Diaz S, Rathmell JP, et al. Patterns of opioid utilization in pregnancy in a large cohort of commercial insurance beneficiaries in the United States. *Anesthesiology* 2014;120:1216-24.
247. de Castro A, Jones HE, Johnson RE, Gray TR, Shakleya DM, Huestis MA. Methadone, cocaine, opiates, and metabolite disposition in umbilical cord and correlations to maternal methadone dose and neonatal outcomes. *Therapeutic drug monitoring* 2011;33:443-52.
248. Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. Periconceptional use of opioids and the risk of neural tube defects. *Obstetrics and gynecology* 2013;122:838-44.
249. Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. *American journal of obstetrics and gynecology* 2011;204:314 e1-11.
250. Whiteman VE, Salemi JL, Mogos MF, Cain MA, Aliyu MH, Salihu HM. Maternal opioid drug use during pregnancy and its impact on perinatal morbidity, mortality, and the costs of medical care in the United States. *Journal of pregnancy* 2014;2014:906723.
251. Zuspan FP, Gumpel JA, Mejia-Zelaya A, Madden J, Davis R. Fetal stress from methadone withdrawal. *American journal of obstetrics and gynecology* 1975;122:43-6.
252. Rementeria JL, Nunag NN. Narcotic withdrawal in pregnancy: stillbirth incidence with a case report. *American journal of obstetrics and gynecology* 1973;116:1152-6.

253. Steven G Gabbe JRN, Henry L Galan, Eric R. M. Jauniaux, Mark B Landon, Joe Leigh Simpson, Deborah A Driscoll. *Obstetrics: Normal and Problem Pregnancies*. 6th ed. Philadelphia PA: Elsevier Saunders; 2012.
254. Dashe JS, Sheffield JS, Olscher DA, Todd SJ, Jackson GL, Wendel GD. Relationship between maternal methadone dosage and neonatal withdrawal. *Obstetrics and gynecology* 2002;100:1244-9.
255. Luty J, Nikolaou V, Bearn J. Is opiate detoxification unsafe in pregnancy? *Journal of substance abuse treatment* 2003;24:363-7.
256. Stewart RD, Nelson DB, Adhikari EH, et al. The obstetrical and neonatal impact of maternal opioid detoxification in pregnancy. *American journal of obstetrics and gynecology* 2013;209:267 e1-5.
257. Brogly SB, Saia KA, Walley AY, Du HM, Sebastiani P. Prenatal buprenorphine versus methadone exposure and neonatal outcomes: systematic review and meta-analysis. *American journal of epidemiology* 2014;180:673-86.
258. Breastfeeding and the use of human milk. *Pediatrics* 2012;129:e827-41.
259. Hudak ML, Tan RC. Neonatal drug withdrawal. *Pediatrics* 2012;129:e540-60.
260. Finnegan LP, Connaughton JF, Jr., Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. *Addictive diseases* 1975;2:141-58.
261. Seligman NS, Almario CV, Hayes EJ, Dysart KC, Berghella V, Baxter JK. Relationship between maternal methadone dose at delivery and neonatal abstinence syndrome. *The Journal of pediatrics* 2010;157:428-33, 33 e1.
262. Shah SS, Hall M, Goodman DM, et al. Off-label drug use in hospitalized children. *Archives of pediatrics & adolescent medicine* 2007;161:282-90.
263. Food and Drug Administration - Drug Research and Children at <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143565.htm>.)
264. Berde CB, Walco GA, Krane EJ, et al. Pediatric analgesic clinical trial designs, measures, and extrapolation: report of an FDA scientific workshop. *Pediatrics* 2012;129:354-64.
265. GJ. H. *Developmental pharmacology of opioids*. Oxford UK: Oxford University Press; 2013.
266. The assessment and management of acute pain in infants, children, and adolescents. *Pediatrics* 2001;108:793-7.
267. Ishizaki Y, Yasujima H, Takenaka Y, et al. Japanese clinical guidelines for chronic pain in children and adolescents. *Pediatrics international : official journal of the Japan Pediatric Society* 2012;54:1-7.

268. Stevens BJ ZW. Prevalence and distribution of pain in children. Oxford Textbook of Paediatric Pain. Oxford, UK: Oxford University Press; 2013:12-9.
269. Walco GA, Dworkin RH, Krane EJ, LeBel AA, Treede RD. Neuropathic pain in children: Special considerations. Mayo Clinic proceedings 2010;85:S33-41.
270. Stemland CJ, Witte J, Colquhoun DA, et al. The pharmacokinetics of methadone in adolescents undergoing posterior spinal fusion. Paediatric anaesthesia 2013;23:51-7.
271. Pace F, Zuin G, Di Giacomo S, et al. Family history of irritable bowel syndrome is the major determinant of persistent abdominal complaints in young adults with a history of pediatric recurrent abdominal pain. World journal of gastroenterology : WJG 2006;12:3874-7.
272. Shelby GD, Shirkey KC, Sherman AL, et al. Functional abdominal pain in childhood and long-term vulnerability to anxiety disorders. Pediatrics 2013;132:475-82.
273. Walker LS, Sherman AL, Bruehl S, Garber J, Smith CA. Functional abdominal pain patient subtypes in childhood predict functional gastrointestinal disorders with chronic pain and psychiatric comorbidities in adolescence and adulthood. Pain 2012;153:1798-806.
274. Walker LS, Dengler-Crish CM, Rippel S, Bruehl S. Functional abdominal pain in childhood and adolescence increases risk for chronic pain in adulthood. Pain 2010;150:568-72.
275. Dengler-Crish CM, Horst SN, Walker LS. Somatic complaints in childhood functional abdominal pain are associated with functional gastrointestinal disorders in adolescence and adulthood. Journal of pediatric gastroenterology and nutrition 2011;52:162-5.
276. Fearon P, Hotopf M. Relation between headache in childhood and physical and psychiatric symptoms in adulthood: national birth cohort study. BMJ (Clinical research ed) 2001;322:1145.
277. Waldie KE. Childhood headache, stress in adolescence, and primary headache in young adulthood: a longitudinal cohort study. Headache 2001;41:1-10.
278. Hestbaek L, Leboeuf-Yde C, Kyvik KO. Is comorbidity in adolescence a predictor for adult low back pain? A prospective study of a young population. BMC musculoskeletal disorders 2006;7:29.
279. Mustard CA, Kalcevich C, Frank JW, Boyle M. Childhood and early adult predictors of risk of incident back pain: Ontario Child Health Study 2001 follow-up. American journal of epidemiology 2005;162:779-86.

280. Mirovsky Y, Jakim I, Halperin N, Lev L. Non-specific back pain in children and adolescents: a prospective study until maturity. *Journal of pediatric orthopedics Part B* 2002;11:275-8.
281. Pharmacological management of persistent pain in older persons. *Journal of the American Geriatrics Society* 2009;57:1331-46.
282. Patel KV, Guralnik JM, Dansie EJ, Turk DC. Prevalence and impact of pain among older adults in the United States: findings from the 2011 National Health and Aging Trends Study. *Pain* 2013;154:2649-57.
283. Riskowski JL. Associations of socioeconomic position and pain prevalence in the United States: findings from the National Health and Nutrition Examination Survey. *Pain medicine (Malden, Mass)* 2014;15:1508-21.
284. Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. *Journal of pain and symptom management* 2006;31:58-69.
285. Centers for Disease Control and Prevention. Fast Facts: Inpatient Surgery. 2014. at <http://www.cdc.gov/nchs/fastats/inpatient-surgery.htm>)
286. Manchikanti L, Helm S, 2nd, Fellows B, et al. Opioid epidemic in the United States. *Pain physician* 2012;15:ES9-38.
287. Park J, Lavin R. Risk factors associated with opioid medication misuse in community-dwelling older adults with chronic pain. *The Clinical journal of pain* 2010;26:647-55.
288. Won A, Lapane KL, Vallow S, Schein J, Morris JN, Lipsitz LA. Long-term effects of analgesics in a population of elderly nursing home residents with persistent nonmalignant pain. *The journals of gerontology Series A, Biological sciences and medical sciences* 2006;61:165-9.
289. Ensrud KE, Blackwell T, Mangione CM, et al. Central nervous system active medications and risk for fractures in older women. *Archives of internal medicine* 2003;163:949-57.
290. Aparasu RR, Chatterjee S. Use of narcotic analgesics associated with increased falls and fractures in elderly patients with osteoarthritis. *Evidence-based medicine* 2014;19:37-8.
291. Kessler ER, Shah M, Gruschus SK, Raju A. Cost and quality implications of opioid-based postsurgical pain control using administrative claims data from a large health system: opioid-related adverse events and their impact on clinical and economic outcomes. *Pharmacotherapy* 2013;33:383-91.

292. Fong HK, Sands LP, Leung JM. The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. *Anesthesia and analgesia* 2006;102:1255-66.
293. Gosch M, Nicholas JA. Pharmacologic prevention of postoperative delirium. *Zeitschrift fur Gerontologie und Geriatrie* 2014;47:105-9.
294. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society* 2012;60:616-31.
295. Davies PS. Chronic pain management in the cancer survivor: tips for primary care providers. *The Nurse practitioner* 2013;38:28-38; quiz -9.
296. DeSantis CE, Lin CC, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2014. *CA: a cancer journal for clinicians* 2014;64:252-71.
297. Denlinger CS, Ligibel JA, Are M, et al. Survivorship: fatigue, version 1.2014. *Journal of the National Comprehensive Cancer Network : JNCCN* 2014;12:876-87.
298. Denlinger CS, Ligibel JA, Are M, et al. Survivorship: sleep disorders, version 1.2014. *Journal of the National Comprehensive Cancer Network : JNCCN* 2014;12:630-42.
299. Denlinger CS, Ligibel JA, Are M, et al. Survivorship: cognitive function, version 1.2014. *Journal of the National Comprehensive Cancer Network : JNCCN* 2014;12:976-86.
300. van den Beuken-van Everdingen M. Chronic pain in cancer survivors: a growing issue. *Journal of pain & palliative care pharmacotherapy* 2012;26:385-7.
301. Glare PA, Davies PS, Finlay E, et al. Pain in cancer survivors. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2014;32:1739-47.
302. Mao JJ, Armstrong K, Bowman MA, Xie SX, Kadakia R, Farrar JT. Symptom burden among cancer survivors: impact of age and comorbidity. *Journal of the American Board of Family Medicine : JABFM* 2007;20:434-43.
303. Lu Q, Krull KR, Leisenring W, et al. Pain in long-term adult survivors of childhood cancers and their siblings: a report from the Childhood Cancer Survivor Study. *Pain* 2011;152:2616-24.
304. Zucca AC, Boyes AW, Linden W, Girgis A. All's well that ends well? Quality of life and physical symptom clusters in long-term cancer survivors across cancer types. *Journal of pain and symptom management* 2012;43:720-31.

305. Fathers E, Thrush D, Huson SM, Norman A. Radiation-induced brachial plexopathy in women treated for carcinoma of the breast. *Clinical rehabilitation* 2002;16:160-5.
306. Kenyon M, Mayer DK, Owens AK. Late and long-term effects of breast cancer treatment and surveillance management for the general practitioner. *Journal of obstetric, gynecologic, and neonatal nursing : JOGNN / NAACOG* 2014;43:382-98.
307. Partridge AH, LaFountain A, Mayer E, Taylor BS, Winer E, Asnis-Alibozek A. Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2008;26:556-62.
308. Harrington CB, Hansen JA, Moskowitz M, Todd BL, Feuerstein M. It's not over when it's over: long-term symptoms in cancer survivors--a systematic review. *International journal of psychiatry in medicine* 2010;40:163-81.
309. National Cancer Institute. Follow up care after cancer treatment. . 2010. (Accessed March 1st 2015, at <http://www.cancer.gov/cancertopics/coping/after-treatment/follow-up-care/follow-up-fact-sheet>.)
310. Institute of Medicine. Implementing Cancer Survivorship Care Planning: Workshop Summary (2006). (Accessed March 1st, 2015, at <https://www.iom.edu/Reports/2006/Implementing-Cancer-Survivorship-Care-Planning-Workshop-Summary.aspx>.)
311. American Cancer Society. Survivorship Care Plan. . 2015. (Accessed March 1st, 2015, at <http://www.cancer.org/treatment/survivorshipduringandaftertreatment/survivorshipcareplans/index>.)
312. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the opioid risk tool. *AAPM* 2005;6:432-42.
313. Brown RL, Rounds LA. Conjoint screening questionnaires for alcohol and other drug abuse: criterion validity in a primary care practice. *Wis Med J* 1995;94:135-40.
314. Couwenbergh C, Gaag RJVD, Koeter M, Ruitter CD, Brink WVD. Screening for substance abuse among adolescents validity of the CAGE-AID in youth mental health care. *Substance Use & Misuse* 2009;44:823-34.
315. Leonardson GR, Kemper E, Ness FK, Koplun BA, Daniels MC, Leonardson GA. Validity and reliability of the AUDIT and CAGE-AID in northern plains American Indians. *Psychological Reports* 2005;97:161-6.

316. Thomas CP, Kim M, Nikitin RV, Kreiner P, Clark TW, Carrow GM. Prescriber response to unsolicited prescription drug monitoring program reports in Massachusetts. *Pharmacoepidemiology and drug safety* 2014;23:950-7.
317. Reisman RM, Shenoy PJ, Atherly AJ, Flowers CR. Prescription opioid usage and abuse relationships: an evaluation of state prescription drug monitoring program efficacy. *Substance abuse : research and treatment* 2009;3:41-51.
318. Reifler LM, Droz D, Bailey JE, et al. Do prescription monitoring programs impact state trends in opioid abuse/misuse? *Pain medicine (Malden, Mass)* 2012;13:434-42.
319. Worley J. Prescription drug monitoring programs, a response to doctor shopping: purpose, effectiveness, and directions for future research. *Issues in mental health nursing* 2012;33:319-28.
320. Paulozzi LJ, Kilbourne EM, Desai HA. Prescription drug monitoring programs and death rates from drug overdose. *Pain medicine (Malden, Mass)* 2011;12:747-54.
321. Heltsley R, Zichterman A, Black DA, et al. Urine drug testing of chronic pain patients II: prevalence patterns of prescription opiates and metabolites. *J of Analytical Toxicology* 2010;34:32-8.
322. Moeller KE, Lee KC, Kissack JC. Urine drug screening: practical guide for clinicians. *Mayo Clin Proc* 2008;83:66-76.
323. Standridge JB, Adams SM, Zotos AP. Urine drug screening: a valuable office procedure. *Am Academy of Fam Phys* 2010;81:635-40.