Report to

The California Department of Industrial Relations and
The California Commission on Health and Safety and Workers' Compensation

"Identifying Risky Opioid Prescribing Practices"

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Background

In California and nationally, policymakers and individual physicians are striving to attain an elusive goal: balancing adequate pain control with minimizing the risks associated with prescription pain medications. Overdoses due to prescription opioid medications are leading to an increasing number of emergency department visits, hospitalizations, and deaths. According to the Centers for Disease Control and Prevention, fatalities associated with prescription opioids rose from 4,000 to nearly 14,000 annually between 1999 and 2006 (1). Now there are nearly as many accidental deaths due to use of opioids as due to motor vehicle accidents (2).

Many patients do not use medications as prescribed, for a variety of reasons. This is particularly hazardous with opioid medications due to the risk of accidental overdose, which often occurs when patients take opioids in combination with other sedatives such as sleeping medication or even alcohol. Over longer periods of time, using opioids puts patients at increasing risk for tolerance (requiring increasing doses to obtain an effect), dependence (causing withdrawal symptoms upon cessation of use), or the development of a substance abuse disorder (involving impaired control over use)(3, 4). Further, unused medications in the home are a common source of the substances abused by teenagers and young adults (5). Finally, a small proportion of patients seek medical care to obtain and use opioids for non-medical purposes or to provide the drugs to others. Sometimes these individuals may go from physician to physician ("doctor shopping") to obtain prescriptions (6).

Several factors may be contributing to this epidemic of prescription drug abuse and accidental overdoses. One is that the public mistakenly perceives prescription drugs as being safer than street drugs; while abuse of prescription drugs has risen, use of street drugs has dropped (2). Secondly, over the past two to three decades, there has been a dramatic change in the standard of care for pain management, with an increasing emphasis on adequately controlling pain. The provider community had a history of under-treating pain, with physicians failing to provide adequate (or sometimes even any) pain medication to patients with objective sources of pain such as advanced cancer and long bone fractures. Specialty societies, guidelines, and regulatory bodies established new standards of care and helped to draw attention to improving pain control (7-9). For example, the Joint Commission established pain control as a priority in the hospital accreditation process (10). Physicians are often taught that there is no objective measure of pain so providers should be responsive to patients' subjective complaints (3, 8). In California, since 2001, each physician has been required to take 12 units of continuing medical education training in pain management (11). In combination with the perceived safety of long-term opioid use in the vast majority of patients with chronic pain, the principle of "no ceiling dose" when titrating opioids for pain relief, and the development of long-acting formulations of opioids, the more recent emphasis and teachings about pain control may have encouraged lax prescribing practices, and limited concerns about when opioids are appropriate. Conversely, some recently published guidelines argue that opioids have limited efficacy in treating certain conditions, such as musculoskeletal disorders like back pain (9, 12). Nonetheless, the overall result has been a dramatic increase in the number of patients receiving opiates, particularly for non-cancer pain, and a rise in the total doses prescribed and used (6, 7). The increase in the prescribing of opioids has been for both appropriate and inappropriate indications, though defining inappropriate use can be challenging (7, 9).

Epidemiologic studies support the hypothesis that physicians' prescribing practices play a major role in permitting this epidemic of prescription opioid overuse and misuse to grow. In a national survey on drug use and health from 2006 to 2008, users of prescription opiates for non-health-related purposes revealed that they obtained their drugs from a physician 31% of the time (13). Another study found that

while 40% of prescription drug overdoses involved individuals seeing multiple doctors and typically involved diversion another 40% involved patients seeing one doctor and being prescribed higher doses of opioids. In addition, the remaining 20% of overdoses involved patients seeing one doctor and being prescribed low doses of opioids (6). Recent studies indicate that the risk of overdose increases with the dose of opioid dispensed (14), and the risk of death due to overdose rises with the prescribed daily dose (15). The risks of overdose is four to twelve-fold higher when the dose exceeds the equivalent of 100 mg of morphine per day (14, 15). About half of fatal overdoses occur in situations in which opioids are used in combination with other drugs, most frequently benzodiazepines (1).

In workers' compensation settings, opioid prescribing issues take on unique implications due to the responsibility that employers bear for disability costs; the association between chronic pain and workplace factors such as job satisfaction, disputed disability claims, or receipt of disability payments; and the fact that similar injuries tend to have worse outcomes in workers' compensation settings than otherwise (16). In addition, opioid use may be associated with poorer outcomes in workers' compensation settings. One study by a large workers' compensation insurer found that individuals with back problems who were prescribed opioids at doses above 140 mg of morphine equivalents over the first 15 days of their claim had longer disability and higher medical care costs. The authors attempted to control for injury severity using ICD-9 codes; nevertheless, these findings could reflect an association between unmeasured injury severity and opiate use, or an association between opiate use and worse outcomes (9). Other studies have made similar observations about the relationship between receiving opioids and disability duration or cost, including a study in California (17, 18).

In the California workers' compensation system, a recent study suggests potential issues with particular opioids and that a small number of physicians represent outliers with high-risk prescribing practices. One percent of physicians who prescribed opioids within the California workers' compensation system were the source of 33% of all opioid prescriptions. Of all opioid prescriptions, many are for medications with high risk profiles, including fentanyl immediate release preparations, fentanyl patches, and methadone: 3%, 17%, and 10%, respectively (19). Immediate release fentantyl is only approved by the Food and Drug Administration for use in patients with cancer, but has been prescribed for non-cancer pain, possibly due in part to illegal promotion for this indication. In 2008 the manufacturer of Actiq settled a criminal lawsuit for promoting the drug for the treatment of patients with injuries and other types of non-cancer pain (20). Fentanyl patches have Public Health Advisory warnings from the Food and Drug Administration due to inadvertent overdoses even when used properly (21). Methadone represents only 2% of the opioids prescribed for pain nationally but is associated with a third of deaths related to the use of prescription pain medications (22). Methadone overdoses also represent a 30% of opioid-related emergency department visits (23). Forty-five percent of prescriptions in the California workers' compensation system were for oxycodone, which is one of the more frequently abused opioids. In 2007, Purdue Pharma L.P. agreed to pay $19.5 million dollars in a settlement over off-label marketing of Oxycontin (24).

Research Objective

Given the pressing need to reduce the risk of opioid overdose and misuse among injured workers in California, the California Department of Industrial Relations and the California Commission on Health and Safety and Workers' Compensation are currently working to develop criteria that can be used to screen for higher risk prescribing practices within the workers' compensation system. The objective of the current study was to search for information on opioid prescribing that can be used to inform the development of such "screening criteria for assessing opioid prescribing risk."

Higher risk prescribing practices could be defined as practices that warrant scrutiny because they are thought to be associated with an increased risk of suboptimal patient outcomes. The screening criteria for assessing opioid prescribing risk are, therefore, analogous to a screening test for cancer in which a positive test is not diagnostic but rather needs to be followed by a second test that can be used to confirm or rule out the diagnosis. The screening criteria for assessing opioid prescribing risk would generally not represent absolute rules but rather aspects of care where providers should venture only with specialized expertise and/or considerable caution. One potential strategy would be for prescriptions flagged by the screening criteria to undergo review by a third party, and, if the third party feels that the treatment plan is unsafe or not in accordance with widely accepted standards of care, some intervention could be undertaken to mitigate the situation.

When considering how to define higher risk prescribing practices, it is essential to consider the types of data that will be available to a future monitoring system. Such a system would, in all likelihood, rely on patients' medical care claims data, including claims from multiple dates over time. The system will be less burdensome to implement if it relies on prescription claims rather than complete medical claims. The information contained in prescription claims may include, at a minimum: medication name and formulation, route of administration, dose per unit of medication, and number dispensed. Over time, the number and frequency of refills would be available.

This suggests that the following specific elements of prescribing would be feasible for monitoring:

1. Types of opioid medications, formulations, and routes of administration;
2. Daily doses of opioid medications, in morphine equivalents;
3. Issues relating to medications and time, such as speed of dose titration;
4. Drug-drug interactions: Other medications prescribed with the opioid that the increase risk of adverse and overdose events.

If the system for identifying risky prescribing practices includes additional information from the patient's medical claims, particularly diagnosis codes, it may be possible to identify other characteristics about the patient's situation that define it as high risk. For example, patients who have sleep apnea are at particularly high risk of opioid overdoses (23).

The research questions this project set out to address focused, therefore, on the four above elements of prescribing and their relationship to patient outcomes. The study sought to understand how specific types of medications, formulations, routes, doses, durations of therapy, and drug-drug interactions affected outcomes such as pain control, functional status, and adverse events including the risk of overdose, addiction, and mortality.

To answer these questions, we focused our search for information on medical treatment guidelines, systematic literature reviews, meta-analyses, and information on individual medications released by the Food and Drug Administration. We restricted our search to information published since 2007, since studies have shown that new studies can render guidelines out of date as quickly as three years after publication (25).

When identifying guideline recommendations or topic areas as potential screening criteria for assessing opioid prescribing risk, we did so on the basis of the following criteria:

1. The potential screening criterion was believed to be associated with one or more adverse patient outcomes, such as overdose, addiction, substance misuse, mortality, or another adverse outcome;
2. The association was supported by one of the following types of evidence:
    a. Supported by strong, high-quality research evidence (such as randomized controlled trials or well-executed observational studies);
    b. Recommended by multiple guidelines, contradicted by few guidelines, and not contradicted by strong, high quality research evidence; or
    c. Included in Food and Drug Administration (FDA) prescribing information;
    d. Recommended by one or more guidelines, contradicted by no other guidelines, not contradicted by research evidence, and believed to pose a substantial risk to specific populations (e.g., specific drug-drug interactions).
3. Applying the screening criterion appeared potentially feasible using billing data;

In addition to affecting the types of medications and doses prescribed, other strategies may also reduce risks associated with opioid use. Consequently, secondary objectives included considering practices that may affect the risks associated with prescribing opioids, such as strategies for minimizing prescription opioid use when appropriate, screening for substance abuse with a medical history, assessing patients' individual risks of misuse, performing urinary drug tests, and entering into written treatment agreements with patients.

Methods

Part I: Search for Relevant Guidelines, Systematic Reviews and Other Information Sources

Inclusion and Exclusion Criteria

We searched for guidelines and systematic reviews addressing chronic pain, acute/subacute pain, and neuropathic pain; however, our exclusion criteria (see below) meant that our search emphasized chronic pain. Chronic pain was defined as pain that lasts longer than the expended time of tissue healing, generally longer than three to six months. All searches were conducted between March 20 and May 15, 2012.

We included documents that addressed opioid prescribing for pain, the effectiveness of other medications vs. opioids, the concurrent use of other medications and opioids, or adverse events related to opioid prescribing. We restricted our evaluation to documents published within the past five years because, as mentioned previously, most published guidelines become out of date within three years (25). We required documents to be published in English.

We excluded documents addressing cancer pain, pain at the end of life, post-operative pain, pain associated with labor and delivery, and pain related to specific diseases or parts of the body rather than addressing pain in general (e.g., guidelines addressing low back pain, carpal tunnel syndrome, or osteoarthritis pain). Although these exclusion criteria would seem to eliminate many guidelines of potential relevance to treating patients with occupational injuries, we were interested in more general questions about the appropriate use of opioids in the management of chronic pain. Documents also needed to address opioid therapy specifically rather than solely other treatments used in the management of pain, such as interventional techniques used for back pain.

For guidelines, we excluded documents that did not meet the definition of a guideline. A commonly used definition is, "Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" (26).

For systematic reviews, we excluded documents that were publications of previously or concurrently published guidelines, animal studies, studies of children only and systematic reviews that did not address chronic pain control. We also excluded non-systematic reviews that did not clearly describe how studies were identified, selected, and synthesized (27).

Searching for Guidelines

To search for guidelines, we used the information sources listed below.

1. National Guidelines Clearinghouse, searched using the terms "opioid," "opiate," and "narcotic" (28);
2. Websites of specialty societies that are listed on the American Medical Association Website and whose members treat acute and chronic pain, including (29):
    a. American Academy of Family Physicians
    b. American Academy of Pain Medicine
    c. American Academy of Physical Medicine & Rehabilitation
    d. American College of Occupational and Environmental Medicine

e. American College of Physicians
f. American Geriatrics Society
g. American Society of Addiction Medicine
h. American Society of Anesthesiologists
i. American Society of Interventional Pain Physicians
j. Association of Military Surgeons of the United States
k. National Medical Association
l. Society of Medical Consultants to the Armed Forces

3. Guidelines listed on state workers' compensation websites for states known to have their own guidelines:
   a. California
   b. Washington State
   c. Colorado
4. PubMed (search terms listed below)
5. Recommendations of experts

Table of PubMed Search Terms for Guideline Search

	Concept	Terms
	Search PubMed for Opioids: (#1)	
1	Analgesics, opioid	"analgesics, opioid"[MeSH] OR "opioid"[tiab] OR "opioids"[tiab] OR "opioid analgesic"[tiab] OR "opioid analgesics"[tiab] OR "opiate"[tiab] OR "opiates"[tiab]
	Search PubMed for Guidelines: (#2)	
2	Guidelines	"guideline"[Publication Type] OR "guideline*"[tiab] OR "position statement*"[tiab] OR "practice parameter*"[tiab] OR "position paper*"[tiab] OR "consensus statement*"[tiab]
	Identify Articles Published after 2007: (#3)	
3	Recent articles	"2007/01/01"[PDAT] : "3000"[PDAT]
	Identify Articles Published in English: (#4)	
4	English Language	English[lang]
	Exclude Irrelevant Articles Based on Title Words: NOT (#5)	
5	Irrelevant Title Words	"gene"[ti] OR "genome"[ti] OR "genomics"[ti] OR "genomic"[ti] OR "genetic"[ti] OR "in vitro"[ti] OR "in vivo"[ti] OR "proteomics"[ti] OR "mouse"[ti] OR "mice"[ti] OR "rat"[ti] OR "methadone maintenance"[ti] OR "methadone treatment"[ti] OR "neonate*"[ti] OR "pediatric*"[ti] OR "child"[ti] OR "children"[ti] OR "pregnan*"[ti] OR "cancer"[ti] OR "malignant"[ti] OR "malignancy"[ti] OR "cancer-related"[ti] OR "palliative"[ti] OR "ovarian"[ti] OR "dogs"[ti] OR "bronchoscopy"[ti] OR "procedure"[ti] OR "procedural"[ti] OR "surgery"[ti] OR "surgical"[ti] OR "postoperative"[ti] OR "intensive care"[ti] OR "ICU"[ti] OR "post-operative"[ti] OR "cough"[ti] OR "restless legs"[ti] OR "headache"[ti] OR "migraine"[ti] OR "hospital"[ti] OR "mental health"[ti] OR "irritable bowel"[ti] OR "critical illness"[ti] OR "pregnancy"[tiab] OR "lactation"[tiab] OR "ileus"[ti] OR "perioperative"[ti] OR "peri-operative"[ti] OR "illicit substance*"[ti] OR "peptide*"[ti] OR "protein*"[ti]

Searching for Systematic Reviews

We performed searched for systematic reviews using the following data sources:

1. AHRQ website: http://www.ahrq.gov/
2. Information Service Center for Reviews and Dissemination at the University of York: www.york.ac.uk/inst/crd/econ.htm
    a. DARE,
    b. National Health Service EDD,
    c. HTA
3. Evidence for Policy and Practice Information and Coordinating Center (EPPI-Centre), University of London. http://eppi.ioe.ac.uk/cms/
4. Campbell Collaboration. http://www.campbellcollaboration.org/library.php
5. Health Systems Evidence, McMaster University. www.healthsystemsevidence.org
6. Cochrane Reviews. http://www.cochrane.org/cochrane-reviews
7. PubMed (search terms listed below)
8. Recommendations of Experts

Table of PubMed Search Terms for Systematic Reviews

	Concept	Terms
	Search More Likely to Identify Relevant Articles: (#1) AND (#3) AND (#4) AND (#5) NOT (#6)	
1	Analgesics, opioid	"analgesics, opioid"[MeSH] OR "opioid"[tiab] OR "opioids"[tiab] OR "opioid analgesic"[tiab] OR "opioid analgesics"[tiab] OR "opiate"[tiab] OR "opiates"[tiab]
	Search Less Likely to Identify Relevant Articles: (#2) AND (#3) AND (#4) AND (#5) NOT (#6)	
2	Opioid-Related Disorders	"opioid-related disorders "[mesh] OR "Disorder, Opioid-Related" OR "Opiate Dependence" OR "Dependence, Opiate" OR "Opiate Addiction" OR "Addiction, Opiate" OR "Narcotic Abuse" OR "Abuse, Narcotic" OR "Abuses, Narcotic" OR "Narcotic Abuses" OR "Narcotic Dependence" OR "Dependence, Narcotic" OR "Narcotic Addiction" OR "Addiction, Narcotic"
	Search PubMed for Systematic Reviews	
3	Reviews	"review"[ti] OR "systematic review*"[tiab] OR "health technology assessment"[tiab] OR "metaanalysis"[tiab] OR "meta-analysis"[tiab]
	Identify Articles Published after 2007	
4	Recent articles	"2007/01/01"[PDAT] : "3000"[PDAT]
	Identify Articles Published in English	
5	English Language	English[language]
	Exclude Irrelevant Articles Based on Title Words	
6	Irrelevant Title Words	"gene"[ti] OR "genome"[ti] OR "genomics"[ti] OR "genomic"[ti] OR "genetic"[ti] OR "in vitro"[ti] OR "in vivo"[ti] OR "proteomics"[ti] OR "mouse"[ti] OR "mice"[ti] OR "rat"[ti] OR "methadone maintenance"[ti] OR "methadone treatment"[ti] OR "newborn*"[ti] OR "neonate*"[ti] OR "pediatric*"[ti] OR "child"[ti] OR "children"[ti] OR "pregnan*"[ti] OR "cancer"[ti] OR "malignant"[ti] OR "malignancy"[ti] OR "cancer-related"[ti] OR "palliative"[ti] OR "ovarian"[ti] OR "dogs"[ti] OR "bronchoscopy"[ti] OR "procedure"[ti] OR "procedural"[ti] OR "surgery"[ti] OR "surgical"[ti] OR "postoperative"[ti] OR "intensive care"[ti] OR "ICU"[ti] OR "post-operative"[ti] OR "cough"[ti] OR "restless legs"[ti] OR "headache"[ti] OR "migraine"[ti] OR

		"hospital"[ti] OR "mental health"[ti] OR "irritable bowel"[ti] OR "critical illness"[ti] OR "pregnancy"[tiab] OR "lactation"[tiab] OR "ileus"[ti] OR "perioperative"[ti] OR "peri-operative"[ti] OR "illicit substance*"[ti] OR "peptide*"[ti] OR "protein*"

Identifying Recent Publications

To identify recent publications, we hand-searched major medical journals, reviewed reference lists, and obtained recommendations from experts. We also reviewed relevant statements, websites and reports by governmental and other bodies, such as the White House, Food and Drug Administration, Centers for Disease Control and Prevention, and the Institute of Medicine.

Part II: Evaluating Guidelines and Systematic Reviews

The quality of the literature review is a fundamental dimension of both systematic review and guideline development. We used the AMSTAR Instrument to rate the quality of the literature searches that were the basis for the guidelines, as well as the quality of the systematic reviews. The AMSTAR Instrument has been shown to have good reliability, construct validity, and to be easy to apply (30). This approach provided consistency between our evaluation of the guidelines and systematic reviews. We did not use an instrument such as AGREE II to evaluate the guideline development process since it could not be applied to systematic reviews; it addresses issues not as germane to understanding the underlying evidence (such as composition of the guideline panel, plans for updating, and management of conflicts), and the available timeframe for this project (31).

The AMSTAR Instrument involves answering the following questions (determining how to answer them requires additional specifications available with the instrument itself):

1. Was an 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest stated? Required for both the guideline/literature search itself and for the component studies.

One health services research physician rated each guideline or systematic review. Questions of interpretation were discussed as a group when an individual rater felt it was necessary.

The instrument can be used to generate a summary score of 1 to 11. We report the number of affirmative responses, which is the score on a scale of 1 to 11. Responses can be coded as "not available;" therefore, we also created scores that were percentages of the highest possible score excluding non-applicable questions.

This approach has limitations, however, in that it weights each question equally when there is no empiric basis for assuming that each question should carry equal weight. A more nuanced approach is to examine the responses to individual questions within the AMSTAR Instrument. This report includes results for individual questions in appendices and reports the summary scores in the text of the report. Nonetheless, the developers of the AMSTAR Instrument used summary scores when assessing the reliability and validity of the instrument (30).

Part III: Extracting Key Information from Guidelines

Based on the study objectives, we developed a list of the domains pertinent to the research questions and specific information that we wanted to extract from each guideline. Fundamentally, we were interested in the relationship between patient outcomes (both favorable and unfavorable) and several topic areas.

Patient outcomes of interest included:

1. Pain control (including self-reported pain and other)
2. Functional status (including self-reported functional status, ability to work, and other), and
3. Adverse events (including overdose, substance misuse/abuse, death, and other adverse events)

The core topic areas included:

1. Maximum daily dose
2. Drug type, route of administration, or formulation and association with outcomes (association can be stated or implied in document)
3. Maximum cumulative dose
4. Duration of opioid therapy
5. Concomitant use of other medications that increase the risk for adverse events (i.e., drug-drug interactions involving opioids and other medications)
6. Use of opioids vs. NSAIDS (non-steroidal anti-inflammatory drugs)
7. Use of opioids vs. acetaminophen
8. Usefulness of written treatment agreements (providing patient with written information about plan for managing his or her pain, including expectations for patient behavior and adherence and potential consequences of non-adherence)
9. Usefulness of urinary drug testing
10. Usefulness of screening for substance abuse by taking medical history
11. Other domains that the guideline recommends or that affects patient outcomes

We developed a structured abstraction form to standardize the extraction of the pertinent information. We extracted key details relative to the core topics, including the opioids studied, if specified. For topics relating to written treatment agreements, urinary drug testing, and screening for substance abuse, we extracted information on the recommended timing of the interventions. We also extracted information on the details of the guideline recommendations and on the nature and strength of the research data underlying the recommendations. The document used to abstract the information from the guidelines is shown in **Appendix 1**.

In this report, we use a simplified scheme for rating the strength of evidence:

- Blank: If no comment is made regarding strength of evidence, this information was unavailable.
- Level A Evidence: Data from randomized controlled trials. It was not possible to assess the quality of the randomized controlled trials as part of our review.

- Level B Evidence: Data from other studies, such as epidemiological studies or treatment studies without randomization.
- Level C Evidence: Recommendations based on expert consensus.

Part IV: Extracting Information from Systematic Reviews

We looked for the same types of information in the systematic reviews. However, these documents tended to be much more focused so we did not use the same abstraction instrument. Rather, a health services research trained physician extracted the relevant information and summarized it in tabular form.

Part V: Food and Drug Administration (FDA) Warnings for Specific Opioid Types and Formulations

We checked the Food and Drug Administration website for specific warnings regarding individual opioid medication. The information sources used included FDA Drug Approval Reports and FDA Drug Safety Alerts. We reviewed Drug Safety Alerts from 2009 to 2012. These medications included in the search were:

a. Morphine (MS Contin, Kadian, Avinza, Roxanol, Oramorph SR, MSIR, DepoDur)
b. Oxycodone (Roxicodone, OxyContin, Percolone, OxyIR, OxyFAST)
c. Fentanyl
d. HydroMORPHONE (Dilaudid, Exalgo)
e. Meperedine (Demerol, pethidine)
f. Methadone (Diskets, Dolophine, Methadose)
g. Codeine
h. Oxymorphone (Opana, Opana ER)
i. Medications only available in combination form
    i. Hydrocodone
        i. Hydrocodone/acetaminophen (Vicodin, Lorcet, Lortab, Maxidone, Norco, Xodol, Zydone)
        ii. Hydrocodone/ibuprofen (Vicoprofen, Ibudone)
        iii. Hydrocodone/acetaminophen (Lorcet)
    ii. Pentazocine/acetaminophen (Talcen)
    iii. Propoxyphene/acetaminophen (Wygesic)
    i. Dihydrocodeine/ASA/caffeine (Synalgos-DC)
j. Medications that are related to opioids
    i. Tramadol (Ultram)
    ii. Tapentadol

Part VI: Identifying Possible Screening Criteria for Assessing Opioid Prescribing Risk

We proposed guideline recommendations or topic areas as potential screening criteria for assessing opioid prescribing risk on the basis of the following criteria:

1. The potential screening criterion is believed to be associated with one or more adverse patient outcome, such as overdose, addiction, substance misuse, mortality, or another adverse outcome;
2. The association was supported by one of the following types of evidence:
    a. If possible, supported by strong, high-quality research evidence (such as randomized controlled trials or well-executed observational studies) (such data are rare);

   b. Recommended by multiple guidelines, contradicted by few guidelines, and not contradicted by strong, high quality research evidence; or
   c. Included in Food and Drug Administration (FDA) prescribing information;
   d. Recommended by one or more guidelines, contradicted by no other guidelines, not contradicted by research evidence, and believed to pose a substantial risk to specific populations (e.g., specific drug-drug interactions).
3. Applying the screening criterion appeared potentially feasible using billing data;

However, our goal was not to identify all of the possible screening criteria that could be extracted from the many guideline recommendations listed in this report. It was only to identify the most basic ones. In addition, we consider the potential screening criteria to be preliminary and subject to modification based on future research.

Results

Part I: Search Results

Searching for Guidelines

Appendix 2 lists the documents identified by the searches of databases and websites, and reasons for exclusions.

Results of Search for Guidelines: Numbers of Guidelines Identified

	Identified by Initial Search	Selected for Examination Based on Title and Year	Guidelines Included in Review
National Guidelines Clearinghouse	"opioid" 91, "opiate" 22, "narcotic" 27	10	9 (one proprietary guideline unavailable)
Websites of specialty societies	26	7	5 (3 unique)
PubMed	96	10	5 (4 unique)
State workers' compensation websites	3	3	3
Recommendations of experts	2	2	1
		Total Unique Guidelines	20

After obtaining available documents we excluded articles that were not guidelines and duplicate or updated guidelines; and identified supporting documents for each guideline, including systematic reviews. We included the following guidelines:

1. National Guidelines Clearinghouse: The guidelines are generally available through the National Guidelines Clearinghouse website.
    a. **"VA":** "VA/DoD clinical practice guideline for management of opioid therapy for chronic pain." 2003 Mar (revised 2010 May). Department of Defense; Department of Veterans Affairs; Veterans Health Administration (32).
    b. **"ASA":** "Practice Guidelines for Chronic Pain Management, An Updated Report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine," 2010. (33).
    c. **"NICE Neuro":** "Neuropathic pain: The pharmacological management of neuropathic pain in adults in non-specialist settings," United Kingdom National Institute for Health and Clinical Excellence (NICE), March 2010 (34).
    d. **"APS-AAPM":** "Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain." American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Opioid Treatment Guidelines (35).
        i. "Guideline for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain, Evidence Review," American Pain Society, 2009. (36).

e. **"WA State Interagency":** "Interagency guideline on opioid dosing for chronic non-cancer pain: an educational aid to improve care and safety with opioid therapy." 2007 Mar (revised 2010 Jun). Washington State Agency Medical Directors' Group. (37).

f. **"ICSI":** "Assessment and management of chronic pain." 2005 Nov (revised 2011). Institute for Clinical Systems Improvement - Nonprofit Organization. Fifth Edition. (38).

g. **"U of M":** "Managing chronic non-terminal pain in adults including prescribing controlled substances." 2009 Mar (republished 2011 Jan). University of Michigan Health System. (39).

h. **"EFNS":** "EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision." 2006 Nov (revised 2010 Sep). (40).

i. **"WLDI":** Pain (chronic). 2003 (revised 13 May 2011). Work Loss Data Institute.

2. Specialty Websites

   a. **"ACOEM":** "Guidelines for Chronic Use of Opioids," American College of Occupational and Environmental Medicine, 2011 (12).

   b. **"ASIPP":** "American Society of Interventional Pain Physicians, ASIPP Opioid Guidelines: Opioid Guidelines in the Management of Chronic Non-Cancer Pain." 2008 (41).

   c. **"AGS":** "Pharmacological Management of Persistent Pain in Older Persons, American Geriatrics Society." 2009. (42). Refers to 2002 guideline as still being current.

      i. American Geriatrics Society 2002 (42).

3. PubMed

   a. **"Canada":** "Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain, McMaster University." (43).

      i. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 1: general population. (44).

      ii. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 2: special populations. (45).

      iii. Opioids for chronic noncancer pain: a new Canadian practice guideline. (46).

   b. **"Utah":** "Utah clinical guidelines on prescribing opioids for treatment of pain". (47).

   c. **"Fine":** Establishing "best practices" for opioid rotation: conclusions of an expert panel. (48).

   d. **"CPS":** Pharmacological management of chronic neuropathic pain - consensus statement and guidelines from the Canadian Pain Society. Canadian Pain Society. (49).

4. State Guidelines:

   a. California Medical Treatment Utilization Schedule (MTUS) http://www.dir.ca.gov/dwc/mtus/mtus_regulationsguidelines.html (50)

   b. Colorado http://www.colorado.gov/cs/Satellite/CDLE-WorkComp/CDLE/1248095316931 (51)

c. Washington State
http://www.lni.wa.gov/claimsins/providers/treatingpatients/treatguide/ (52)

i. WA State - "Outpatient Prescription of Oral Opioids for Injured Workers with Chronic, Noncancer Pain" (53)

ii. WA State – "WA State Controlled Substances Guideline" (54)

5. Documents known to research team

a. "ACP PIER & AHFS DI, Essentials, Pain," American College of Physicians, updated February 7, 2012 (55).

All of the guidelines we reviewed addressed the management of patients with chronic non-cancer pain. Chronic pain has been defined as, "pain that persists beyond normal tissue healing time, which is assumed to be three months" (35). Some other sources define the time period as three to six months (32). Most of the guidelines addressed the treatment of chronic pain, covering issues relating to the long-term use of opioids. One definition of long-term use is use for three to six months or longer. (In one study, a more precise definition of long-term opioid use was episodes of use lasting longer than 90 days and associated with either a supply of at least 120 days or ten or more filled opioid prescriptions (56).

Three guidelines focus exclusively on neuropathic pain (34, 40, 49) while others included some mention of neuropathic pain within their scope. Two guidelines addressed both acute and chronic pain, but contained less detail related to the core topics of interest (42, 55).

We included the ACP PIER document in this analysis and extracted key elements from it, but later the group concluded that it was not truly a guideline.

Searching for Systematic Reviews

Results of Search for Systematic Reviews: Numbers of Reviews Identified

	Identified by Initial Search	Selected for Examination Based on Title and Year	Included in Review
AHRQ #1	3	0	0
AHRQ #2	0	0	0
University of York #1	43	1	0
University of York #2	5	0	0
University of London	0	0	0
Campbell Collaboration #1	10	0	0
Campbell Collaboration #2	0	0	0
McMaster University #1	0	0	0
McMaster University #2	0	0	0
Cochrane Reviews #1	33	0	0
Cochrane Reviews #2	828	7	1
PubMed #1	422	63	6
PubMed #2	83	3	0

Known to Research Team			2
Total Unique Systematic Reviews			9

These nine systematic reviews include:

1. **"Noble 2008":** Long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and safety. Noble, M., S. J. Tregear, et al. (2008). J Pain Symptom Manage 35(2): 214-228.
2. **"Noble 2010":** Long-term opioid management for chronic noncancer pain. Noble, M., J. R. Treadwell, et al. (2010). Cochrane Database Syst Rev(1). (This appears to be an updated version of the systematic review above).
3. **"Dembe":** Opioid use and dosing in the workers' compensation setting. A comparative review and new data from Ohio. Dembe, A., T. Wickizer, et al. (2012). Am J Ind Med 55(4): 313-324.
4. **"Papaleontiou ":** Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: a systematic review and meta-analysis. Papaleontiou, M., C. R. Henderson, Jr., et al. (2010). J Am Geriatr Soc 58(7): 1353-1369.
5. **"Turk":** Predicting opioid misuse by chronic pain patients: a systematic review and literature synthesis. Turk, D. C., K. S. Swanson, et al. (2008). Clin J Pain 24(6): 497-508.
6. **"Starrels":** Systematic review: treatment agreements and urine drug testing to reduce opioid misuse in patients with chronic pain. Starrels, J. L., W. C. Becker, et al. (2010). Ann Intern Med 152(11): 712-720.
7. **"Fishbain ":** What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. Fishbain, D. A., B. Cole, et al. (2008). Pain Med 9(4): 444-459.

In addition to the above, two systematic reviews were recommended to us by experts. Some of these did not meet our very strict cut-off of being published in the last five years; however, the experts felt that they had not been rendered out of date by recent publications.

1. **"Kalso":** Opioids in chronic non-cancer pain: a systematic review of efficacy and safety. Kalso E, JE Edwards, RA Moore, HJ McQuay (2004) Pain 112: 372-380.
2. **"Furlan 2006":** Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. Furlan AD, JA Sandoval, A Mailis-Gagnon, E Tunks. (2006). CMAJ, 174 (11): 1589-94

Five of these systematic reviews addressed the broader question of how effective opioids are for the management of chronic non-cancer pain, considering outcomes including pain control, functional status, and adverse effects (57-61). One of the four studies focused on older adults (58).

Two reviews addressed ways of predicting which patients are at greater risk of substance misuse (62, 63). One of the systematic reviews addressed the utility of urinary drug testing and written treatment agreements (64). One review addressed issues in the Ohio workers' compensation system (65).

Identifying Recent Publications

Our experts identified the following recent publications of interest on opioid prescribing:

1. Krebs EE, Becker WC, Zerzan J, Bair MJ, McCoy K, Hui S. Comparative mortality among Department of Veterans Affairs patients prescribed methadone or long-acting morphine for chronic pain. Pain. 2011 Aug;152(8):1789-95. Epub 2011 Apr (66).
2. Andrea D Furlan, Luis E Chaparro, Emma Irvin, Angela Mailis-Gagnon. A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. Pain Res Manag. 2011 Sep-Oct; 16(5): 337–351. (This article is not available in PubMed Central until September 2012).

Part II: Quality of Literature Searches

Evaluating Guidelines

Of 20 guidelines meeting inclusion criteria, we found evidence summaries that enabled us to evaluate the literature reviews for 14. The AMSTAR ratings for the guidelines revealed that the two highest performing general pain guidelines were the APS-AAPM guideline and the Canadian guideline, which had scores of 6 (55%) and 5 (50%), respectively. Two guidelines for the treatment of neuropathic pain, the NICE guideline and the EFNS guideline, had scores of 5 (50%) and 6 (55%), respectively. The remaining guidelines all had scores of 4 or lower (below 40%). See **Appendix 3**.

Evaluating Systematic Reviews

The AMSTAR ratings for the systematic reviews were generally higher than those for the guidelines, likely because many guidelines do not convey the full details of their literature searches that they perform. These ratings ranged from 3 (27%) to 11 (100%). Seven of the nine reviews had AMSTAR ratings of 6 (55%) or above. See **Appendix 4**.

Part III: Potential Screening Criteria for Assessing Opioid Prescribing Risk

Type of Opioids, Formulation, and Route of Exposure

The tables in the pages below focus on the risks of overdose, mortality, and substance misuse, addiction, and diversion. In addition, risks unique to specific types of drugs or routes are also listed. To summarize major observations shared by multiple sources, three types of medications/formulations are associated with substantially increased risk of overdose, death, substance misuse, or other adverse events when prescribed for acute or chronic pain. These include: immediate release fentanyl preparations, methadone, and meperidine. A monitoring system targeting specific opioids for greater scrutiny could select these three as potential screening criteria for assessing opioid prescribing risk based on the information presented below.

- Meperidine is associated with risks of seizures and central nervous system toxicity. However, it has poor oral absorption so it is probably seldom, if ever, used in outpatient settings.
- Immediate release transmucosal fentanyl is only approved by the Food and Drug Administration (FDA) for the treatment of cancer pain due to its extremely high addiction and overdose risk. Data do exist for non-cancer populations; short-term studies have found it to be substantially more effective than placebo for the treatment of chronic back and neuropathic pain) (35).
- Methadone is challenging to dose correctly due its long and variable half-life, so most guidelines recommend restricting its use to providers with specific training or experience, with low starting doses and slow dose titration.

Most of the guidelines include recommendations restricting the use of methadone to qualified providers due to its risks (see Table below). Several guidelines comment on the high mortality rates associated with methadone. The study by Krebs et al. (2011) attempted to determine whether mortality rates are higher in Veterans Affairs (VA) patients prescribed methadone compared with long-acting morphine through an analysis that controlled for the likelihood of being prescribed methadone (propensity score analysis). Exclusion criteria included metastatic cancer, receiving palliative care, or receiving opioid addiction treatment. They found that 1.2% of patients placed on methadone and 3.7% of patients placed on morphine died from any cause within 30 days of starting the drug, representing most of the mortality risks observed during the study period. Propensity-score-adjusted mortality was lower among patients on methadone vs. morphine (hazard ratio = 0.56, 95% confidence interval = 0.51, 0.62). Excluding patients on 180 mg of morphine equivalents or more per day did not change results (66). The VA guideline on managing chronic pain endorses the use of methadone but is among the many that recommend restricting its use to qualified providers (32). Using methadone may, therefore, appear "safer" than long-acting morphine in this analysis because it is prescribed more cautiously or by more knowledgeable clinicians, not necessarily because methadone is an inherently safer drug (the technical term for this is confounding by indication). The article does not describe, however, whether providers or opioid prescribing practices differed between patients who received methadone vs. morphine.

Nevertheless, the difficulties of safely prescribing methadone are well established and there is widespread consensus that only specially qualified providers should undertake the task. The purpose of having a screening criterion for methadone should not necessarily be to restrict the use of methadone but rather to provide a means of checking to ensure that patients on methadone are, indeed, being seen by providers with additional experience or qualifications in prescribing this medication. This implies that a minimum level of acceptable qualifications would need to be defined, and creating such a definition

may not be easy. The FDA has announced plans to extend its Risk Evaluation and Mitigation Strategy program to long-acting agents including methadone, but this change has yet to be implemented (see information in Appendix 5). Once it is, participation in this program could be one definition, albeit a minimum standard. Another approach would be to observe whether patients who are started on methadone receive an initial dosing titration schedule that is safe.

Another potential screening criterion based on overdose risk is the fentanyl patch. The FDA has received many reports of fatal overdoses, which have often been due to patients engaging in routine activities such as exercise or being exposed to heat that can result in increased absorption. Other potentially fatal mistakes can include heating the patch and putting on a new patch but forgetting to take off the old one, among others. This medication is more commonly prescribed than the three above, so selecting it as a screening criterion would result in many prescriptions being scrutinized. It is listed as a second-line agent in one of the higher quality guidelines, for example (43). Listing the fentanyl patch as a screening criterion might alert providers to the fact that the patch is associated with potential unique risks associated with its transdermal route of administration. An alternative approach to scrutinizing transdermal fentanyl prescriptions to ensure that they are appropriate could be to insure that providers sufficiently educate patients about how to use the patch safely.

Another means of identifying potential screening criteria is via assessments of the risk of substance misuse or diversion associated with specific medications. Some guidelines identified oxycodone, hydromorphone, and hydrocodone as being associated with high rates of abuse and diversion. However, the evidence that these medications are more addictive than other opioids is limited. Hydrocodone and oxycodone, for example, are the two most commonly prescribed opioids so the high rates of abuse and diversion may simply reflect availability (23). In addition, the frequency with which these medications are prescribed means an extremely high number of potential screening criteria would need to undergo scrutiny.

The systematic reviews we examined provide estimates of the prevalence of substance abuse and addiction among patients with chronic pain who use opioids long term. Fishbain et al. (2008) reported that chronic opioid use will lead to abuse or addiction in 3.27% of patients but 11.5% of patients will engage in aberrant drug related behaviors or illicit use (63). Noble et al. (2008) reported in two different systematic reviews that, among users of opioids for chronic non-cancer pain, addiction affected 0.042% and abuse rate 0.43% (57, 61). Caveats on these highly variable estimates include the fact that studies have used different definitions of aberrant-drug related behaviors, abuse, and addiction; studies do not always measure them well; and the prevalence varies depending on the population being studied.

Other systematic reviews we identified offered information on the side effects associated with opioid therapy. According to one review, one third of patients taking opioids for chronic non-cancer pain stop their oral medications due to adverse effects (61). One of the guidelines reported that up to 50% of patients discontinue opioids due to adverse effects (35). Kalso et al. (2004) reported that, among users of opioids for chronic non-cancer pain, most experience adverse effects, including vomiting, constipation, nausea, somnolence/sedation, dizziness, itching, dry mouth, and headache (60). Furlan et al. (2006) reported the six most frequent adverse effects were: constipation, nausea, dizziness or vertigo, somnolence or drowsiness, vomiting, dry skin or pruritus (59). In a 2008 review, Noble et al. observed a slightly different spectrum of adverse effects: gastrointestinal complaints (constipation, nausea and dyspepsia); headache, fatigue/lethargy/ somnolence and urinary complaints (retention, hesitancy, disturbance) (61). A subsequent systematic review by the same lead author documented the same types of adverse effects as well as sedation, hypoventilation/bradypnea, hallucinations, and

abdominal pain (57). Papaleontiou et al. (2010) described the frequencies of adverse effects among older adults who take opioids to treat chronic pain. The adverse effects reported by older adults were the same as in the general population: nausea, dizziness, somnolence, constipation, pruritus, nervousness, vomiting, diarrhea, headache, dry mouth, fatigue (58).

Risks in General Population Associated with Type, Formulation, or Route of Opioid Medication

Opioid	Formulation or Route	Risks	Rationale or Recommendation	Level of Evidence*	Source
Any	Parenteral (intravenous, intramuscular)	Substance Misuse, Addiction, Infection	Avoid parenteral route for chronic non-cancer pain due to increased risk of substance misuse, addiction, and infection.	Level C Evidence	Canadian Guideline (43)
Any	Combined with acetaminophen	Hepatic Toxicity	Limit acetaminophen dose to 3.2 g per day in healthy adults		Canadian Guideline (43)
Fentanyl	Any	Overdose, Mortality	Risk of overdose is high		ASIPP Guideline (41)
	Any	Overdose	Fentanyl metabolism varies across patients. Limit to opioid tolerant patients (on equivalent of 60-90 mg of morphine /day for $\geq$ 2 weeks)		Canadian Guideline (43)
	Immediate Release	Overdose, Substance Misuse	Due to very high risks of overdose and misuse, prescribing is limited to providers certified through the "Risk Evaluation and Mitigation Strategy" Access program		FDA Warnings, see Appendix 5
		Overdose	Limit to opioid tolerant patients		FDA Warnings, See Appendix 5; VA Guideline (32)
		Overdose	High risk of respiratory suppression and death among users.		ASIPP Guideline (41)
		Substance Misuse, Addiction	Only FDA approved for patients with cancer due to high addiction potential		FDA Warnings, See Appendix 5
		Substance Misuse, Addiction	Should not be used to treat chronic musculoskeletal pain		California MTUS (50)
		Substance Misuse	Avoid as supplemental therapy unless the time course of pain matches the onset of the drug because safety of this formulation has not been established for non-cancer pain	Level C Evidence (Consensus)	VA Guideline (32)

	Patch	Overdose, Mortality	Has Issued Public Health Advisory: Many fatalities have occurred. Risk of overdose increased by routine activities such as exposure to heat, changing patch too often		FDA Warnings, See Appendix 5
		Overdose, Mortality, Substance Misuse, Diversion	All drugs with long-acting formulations will soon be subject to "Risk Evaluation and Mitigation Strategy" policy. Includes fentanyl.		FDA Warnings, See Appendix 5
		Overdose, Mortality	Limit to opioid tolerant patients		FDA Warnings, See Appendix 5; VA Guideline (32)
		Overdose	Risk of overdose increased by routine activities such as exercise and exposure to heat		Canadian Guideline (43)
		Overdose	Due to high potency, limit to patients who need continuous analgesia		California MTUS (50)
		Overdose	Absorption can be variable, leading to unpredictable dosing		U. of Michigan (39)
		Substance Misuse	Can be abused by cutting open patch and ingesting		U. of Michigan (39)
Methadone	n/a	Overdose, Mortality	Public Health Advisory due to high number of fatalities. Respiratory depression is a major hazard and risk is increased when dose is titrated too quickly		FDA Warnings, See Appendix 5
		Overdose, Mortality, Substance Misuse, Diversion	All drugs with long-acting formulations will soon be subject to "Risk Evaluation and Mitigation Strategy" policy. Includes methadone.		FDA Warnings, See Appendix 5 (20)
		Overdose, Mortality	The analgesic half-life is 6-12 hrs but the pharmacological half-life is >100 hrs for some patients, creating risk of accumulation.		ACOEM Guideline (12)
		Overdose, Mortality	Due to risks, special caution and prescribers should engage in a mentoring program.		WA State Opioid Dosing Guideline (37)

		Overdose, Mortality	Methadone should be initiated and titrated only by clinicians familiar with its use and risks		VA Guideline (32); Utah Guideline (47); ICSI Guideline (38); ACP PIER Guideline (55); California MTUS (50)AGS Guideline (42)
		Overdose, Mortality	Titration is hazardous due to long half-life and risk of bioaccumulation. Physicians need a specific exemption to use methadone in Canada.	Level B Evidence	Canadian Guideline (43)
		Cardiac Arrhythmias (QT ↑, Torsades)	Most cases of Torsades involve people taking large, multiple daily doses.		FDA Warnings, See Appendix 5; APS-ASPM Guideline (35)
		Cardiac Arrhythmias (QT ↑, Torsades)	Methadone prolongs the QT interval on the EKG. Check an EKG before initiating methadone to prevent Torsades.	Level B Evidence	VA Guideline (32); ACP PIER Guideline (55); California MTUS (50)
Codeine	Any	Overdose	Up to 10% of population rapidly converts codeine to morphine, producing very high levels after taking usual dose		FDA Warnings, See Appendix 5
		Substance Misuse	Codeine has lower rate of abuse than other opioids based on large U.S. study.	Level B evidence	Canadian Guideline (43)
		Unknown	Avoid use of codeine for chronic pain management. No rationale given.		ACP Pier Given (55)
	Combined with acetaminophen	Substance Misuse, Diversion	Preferred over hydrocodone due to lower rates of abuse.		U of Michigan (39)
Morphine	Long Acting	Overdose, Mortality, Substance Misuse, Diversion	All drugs with long-acting formulations will soon be subject to “Risk Evaluation and Mitigation Strategy” policy.		FDA Warnings, See Appendix 5

Oxycodone	Any	Substance Misuse	Oxycodone ranked as among most desirable among abusers on validated attractiveness scale, and law enforcement and poison control centers rank oxycodone as most among commonly abused.		Canadian Guideline (43)
		Substance Misuse, Diversion	High substance misuse and diversion potential due to short half life.		U. of Michigan (39)
	Long Acting	Overdose, Mortality, Substance Misuse, Diversion	All drugs with long-acting formulations will soon be subject to "Risk Evaluation and Mitigation Strategy" policy.		FDA Warnings, See Appendix 5
		Substance Misuse	Outer layer of OxyContin is an immediate release formulation, increasing the risk of abuse given the drug can be released if someone bites the pill.		Canadian Guideline (43)
Hydro-morphone	Any	Substance Misuse	Hydromorphone ranked as among most desirable among abusers on validated attractiveness scale		Canadian Guideline (43)
	Long Acting	Overdose, Mortality, Substance Misuse, Diversion	All drugs with long-acting formulations will soon be subject to "Risk Evaluation and Mitigation Strategy" policy.		FDA Warnings, See Appendix 5
Hydro-codone	Any	Substance Misuse, Diversion	Law enforcement and poison control centers rank hydrocodone as most among commonly abused.		Canadian Guideline (43)
	Combined with acetaminophen	Substance Misuse, Diversion	Avoid these combination pills due to risk of substance misuse.		U of Michigan (39)
Meperidine	Any	Central Nervous System Toxicity, Seizure	Active metabolite accumulates after 48 hours of use and in older patients, leading to seizures. This medication should not be used to treat chronic pain.		ACP Pier (55)
		Not Stated, (Central Nervous System Toxicity, Seizure)	Do not use meperidine to treat chronic pain		WA State - "Outpatient Prescription of Oral Opioids for Injured Workers with Chronic, Noncancer Pain" (53)

		Central Nervous System Toxicity, Seizure	Meperedine has poor bioavailability. Can accumulate and lead to seizures.		Canadian guideline (43)
		Cardiac Arrhythmia	Can trigger supraventricular tachycardia		FDA Warnings, See Appendix 5
Tramadol	Any	Serotonin Syndrome	Tramadol is associated with Serotonin Syndrome. Risk is increased when used with other serotonergic medications (see Drug-Drug Interactions section)		FDA Warnings, See Appendix 5
		Seizure	Tramadol increases the risk of seizure		ACOEM Guideline (12); Canadian Guideline (43); Canadian Pain Society Neuropathic Pain Guideline (49)
		Substance Misuse, Addiction	Tramadol has a lower addiction potential than other opioids but can be addictive. Recommended as first line for mild to moderate pain.		ACOEM Guideline (12); Canadian Guideline (43)

* Scheme for rating the strength of evidence:

- Blank: If no comment is made regarding strength of evidence, this information was unavailable.
- Level A Evidence: Data from randomized controlled trials. It was not possible to assess the quality of the randomized controlled trials as part of our review.
- Level B Evidence: Data from other studies in humans, such as epidemiological studies or treatment studies without randomization.
- Level C Evidence: Recommendations based on expert consensus.

Risks in Special Populations Associated with Type, Formulation, or Route of Opioid Medication

Opioid	Formulation or Route	Population	Risks	Rationale or Recommendation	Source
At Risk for Substance Misuse					
Any	Combined with acetaminophen	Heavy alcohol drinkers	Hepatic toxicity	Use "extra caution" with acetaminophen in heavy drinkers.	Canadian Guideline (43)
Fentanyl	Immediate Release	At Risk for Substance Misuse	Substance Misuse, Overdose	Do not prescribe immediate release formulations of fentanyl due to high addictive potential.	VA Guideline (32)
Special Populations or Medical Issues					
Fentanyl	Any	HIV/AIDS	Overdose, Mortality	Protease inhibitors are cytochrome P450 3A4 inhibitors that inhibit metabolism of fentanyl	FDA Warnings, See Appendix 5
Codeine	Oral	Breast Feeding Women	Overdose, Mortality in Infant	In a small percentage of women, codeine is rapidly converted to morphine, putting the infant at risk of morphine overdose.	Canadian Guideline (43)
Morphine	Any	Renal Impairment	Overdose	M-6 glucoronide metabolite of morphine accumulates to toxic levels in patients with renal impairment, leading to overdose. Degree of accumulation is proportionate to degree of renal impairment.	Canadian Guideline (43)
Fentanyl	Patch	Advanced Age	Overdose	Increased risk of overdose	University of Michigan (39)
Tramadol	Any	Seizure Disorder or Disease of Central Nervous System	Seizure	Tramadol lowers seizure threshold within the recommended dosing range	FDA Warnings, See Appendix 5
		Suicidal or At Risk for Addiction	Suicide	FDA warns of suicide risk in these populations	FDA Warnings, See Appendix 5

Meperidine	Any	Seizure Disorder or Disease of Central Nervous System	Seizure	Meperidine increases the risk of seizure due to the accumulation of toxic metabolites	FDA Warnings, See Appendix 5; ACP PIER Guideline (55)

Maximum Daily Dose

According to the systematic review by Dembe et al. (2012) the mean dose of opioids used was 58 mg of morphine equivalents per day in the Ohio workers' compensation system, 48 mg in other state workers' compensation systems, and 42 mg among patients treated for chronic non-cancer pain outside of workers' compensation settings (65).

There are two types of outcomes related to limits on the daily dose of opioids, the effectiveness of opioids at controlling pain and improving function and the adverse effects associated with opioids. With regard to the former type of outcome, randomized controlled trials did not evaluate doses above 180 to 200 mg of morphine equivalents per day and most focused on much lower doses. Numerous studies have examined the effectiveness of opioids at different doses and in different patient populations. A smaller number of studies, which were generally not randomized controlled trials, have examined major adverse effects, such as overdose, functional decline, medication misuse, and other problems.

Several guidelines suggest limits on the dose of opioids that patients are prescribed (see the Tables below). If such doses fail to relieve a patient's pain, the guidelines generally recommend careful risk assessment for substance misuse issues, potential re-evaluation of the patient's original diagnosis, and referral to a pain management expert if higher dose opioids are to be considered further. Thus, these opioid dosing limits do not tend to be hard and fast rules but rather establish standards for closer evaluation and monitoring.

Three tables below pertain to information on dosing limits. The first table (p. 31) lists guideline recommendations regarding dosing limits when those limits are based on risks of adverse effects. The second table (p. 33) lists recent studies that have not yet been incorporated into many guidelines that provide new evidence about doses and the risk of overdose and overdose-related mortality. The last table (p. 36) presents guideline recommendations relating to dosing limits when those limits are based on evidence of efficacy.

As is evident from the tables, the dosing limits recommended by the guidelines vary. However, several guidelines recommend dosing limits in the range of 100 to 200 mg of morphine equivalents per day. Recommendations that were based on perceived risks of overdose tended to be lower. In contrast, recommendations that were based on the maximum doses that had been studied in randomized controlled trials were higher, 200 mg of morphine equivalents per day (35, 43).

Three recent studies show increased risks of overdose and overdose-related deaths, and there are three important observations to make based on these studies. First, there is a dose-response relationship observed in two of the studies (Figures 1 and 2), with higher doses being associated with greater risks. Second, even low doses are associated with increased risk; one of the studies detected an increased risk of fatal overdose with a dose as low as 50 mg per day (67). Third, all three studies show elevations in risk at doses above 100 mg of morphine per day, with approximately a 20% to 200% increased risk of a fatal overdose and an 1100% increased risk of serious or fatal overdose (14, 15, 67).

Shortcomings of these studies include the potential for residual confounding and evaluation of broad dosing categories (e.g., including all doses above 100 mg of morphine equivalents together, as done in one study) (67). The studies were not designed to evaluate how risk mitigation strategies might affect overdose risk. No study has evaluated pain control, overdose, and other outcomes in persons who

reach a threshold dose of opioids and are titrated to higher doses of opioids, compared with stable doses, dose reductions, or other strategies (68).

For the California workers' compensation system, the guidelines and data suggest that, based on both the risk of overdose and efficacy, it would be reasonable to select a dosing limit somewhere between 100 mg and 200 mg of morphine equivalents per day as a screening criterion for higher risk opioid prescribing practice.

Risks in General Population Associated with Daily Dose of Opioid Medication

Opioid	Dose per Day	Risks	Rationale or Recommendation	Level of Evidence*	Source
Any	Any	Decline in Functional Status	Increasing opioid doses are associated with worse functional and disability outcomes	Level B Evidence	Canadian Guideline (43)
	Any	Hypogonadism	Increasing opioid doses are associated with reduced reproductive hormone levels	Level B Evidence	Canadian Guideline (43)
	Any	Hyperalgesia	Increasing opioid doses are associated with increased sensitivity to pain	Level B Evidence	Canadian Guideline (43)
	200 mg Morphine Equivalents	Substance Misuse, Decline in Functional Status	Prescribing doses >200 mg morphine equivalents per day requires careful reassessment of the pain, of risk for misuse, and frequent monitoring with evidence of improved patient outcomes.	Level A and B Evidence	Canadian Guideline (43)
	Lower doses	Overdose	For geriatric patients, use lower starting doses, slower titration, longer dosing interval, and more frequent monitoring. Elderly patients are at higher risk for overdose due to differences in pharmacokinetics as well as greater sensitivity to psychoactive and respiratory effects. A high percentage of elderly patients are also on benzodiazepines and other psychotropic medications.	Level C Evidence	Canadian Guideline (43)
	120 mg Morphine Equivalents	Not Stated, (? Substance Misuse, Decline in Functional Status)	For patients with neuropathic pain, opioid dose should not exceed 120 mg morphine equivalents per day		California MTUS Guideline (50)
	120 mg Morphine Equivalents	Substance Misuse, Decline in Functional Status	Guideline recommendations include limiting dose to 120 mg unless patient demonstrates improvement in function OR first obtaining consultation from pain management physician		Washington State Opioid Dosing Guideline (37)
	100 mg Morphine Equivalents	Overdose	More than 100 morphine equivalents a day associated with 9-fold increased risk of overdose	Level B Evidence	Washington State Opioid Dosing Guideline (37)

	100-150 mg Morphine Equivalents	Not Stated, (? Substance Misuse, Decline in Functional Status)	Obtain consultation if dose > 100-150 mg morphine equivalent		WA State Oral Opioids Chronic, Non-cancer Pain (53)
	200 mg	Hyperalgesia, Substance Misuse	At doses exceeding 200 mg for non-cancer pain, one needs to consider whether pain is inadequately controlled OR there is actual misuse of opioids, OR pain is actually due to opioid-induced hyperalgesia (which is rare and typically occurs at higher cumulative doses)		ICSI Guideline (38)

* Scheme for rating the strength of evidence:

- Blank: If no comment is made regarding strength of evidence, this information was unavailable.
- Level A Evidence: Data from randomized controlled trials. It was not possible to assess the quality of the randomized controlled trials as part of our review.
- Level B Evidence: Data from other studies in humans, such as epidemiological studies or treatment studies without randomization.
- Level C Evidence: Recommendations based on expert consensus.

Recent Publications Addressing Daily Doses of Opioids and Risks of Adverse Outcomes: Level B Evidence

Author	Setting	Population	Daily Doses Compared*	Outcome Studied	Subgroup	Relationship between Dose and Outcome	Citation
Bohnert 2011	Veterans Health Administration	VHA patients treated with opioids in 2004-2005, excluding those with palliative/hospice care evaluations	≥ 100 mg vs. No opioids	Fatal overdose	Acute pain	Hazard Ratio 1.53 (1.04-2.17) †	(15)
			≥ 100 mg vs. No opioids	Fatal overdose	Chronic non-cancer pain	Hazard Ratio 1.24 (1.04-1.48)	
			≥ 100 mg vs. No opioids	Fatal overdose	Substance abuse disorder diagnosis	Hazard Ratio 2.61 (1.81-3.65)	
Dunn 2010	Health Maintenance Organization	Adults with a new onset use of opioids (3 or more prescriptions) for non-cancer pain between 1997 and2005	≥ 100 mg vs. 1- 19 mg	Serious non-fatal or fatal overdose	n/a	Hazard Ratio 11.18 (4.80–26.03)	(14)
			50-99 mg vs. 1- 19 mg	Serious non-fatal or fatal overdose		Hazard Ratio 3.11 (1.01–9.51)	
			20-49 mg vs. 1- 19 mg	Serious non-fatal or fatal overdose		Hazard Ratio 1.19 (0.40–3.60)	
Gomes 2011	Ontario, Canada	Residents ages 15-64 with an opioid prescription for non-cancer pain	≥200 mg vs. 1- 19 mg	Opioid-related death per Coroner report		Odds Ratio 2.88 (1.79-4.63) ‡	(67)
			100-199 mg vs. 1- 19 mg	Opioid-related death per Coroner report		Odds Ratio 2.04 (1.28-3.24)	

			50-99 mg vs. 1- 19 mg	Opioid-related death per Coroner report		Odds Ratio 1.92 (1.30-2.85)	
			20-49 mg vs. 1- 19 mg	Opioid-related death per Coroner report		Odds Ratio 1.32 (0.94-1.84)	

* mg of morphine equivalents/day

† Hazard ratio: A measure of how often a particular event happens in one group compared to how often it happens in another group, over time. A hazard ratio of greater than one means that the exposure may increase the risk of the outcome, and a ratio of less than one means that the exposure may reduce the risk of the outcome (69).

‡ Odds ratio: A measure of the odds of an event happening in one group compared to the odds of the same event happening in another group. An odds ratio of greater than one means that the exposure may increase the risk of the outcome, and a ratio of less than one means that the exposure may reduce the risk of the outcome (70).

Figure 1: Dose-Response Relationship in Dunn 2011: Overdose

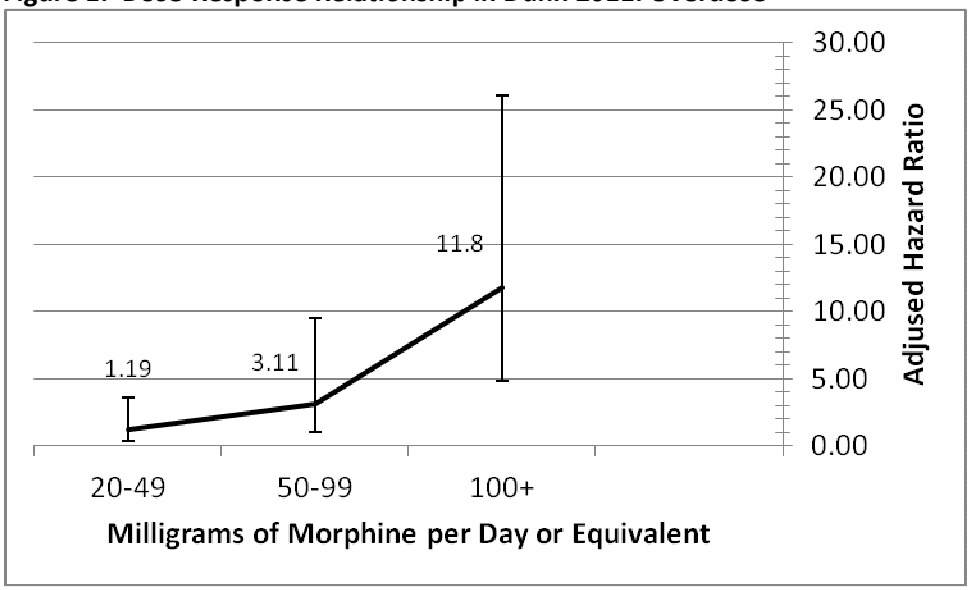
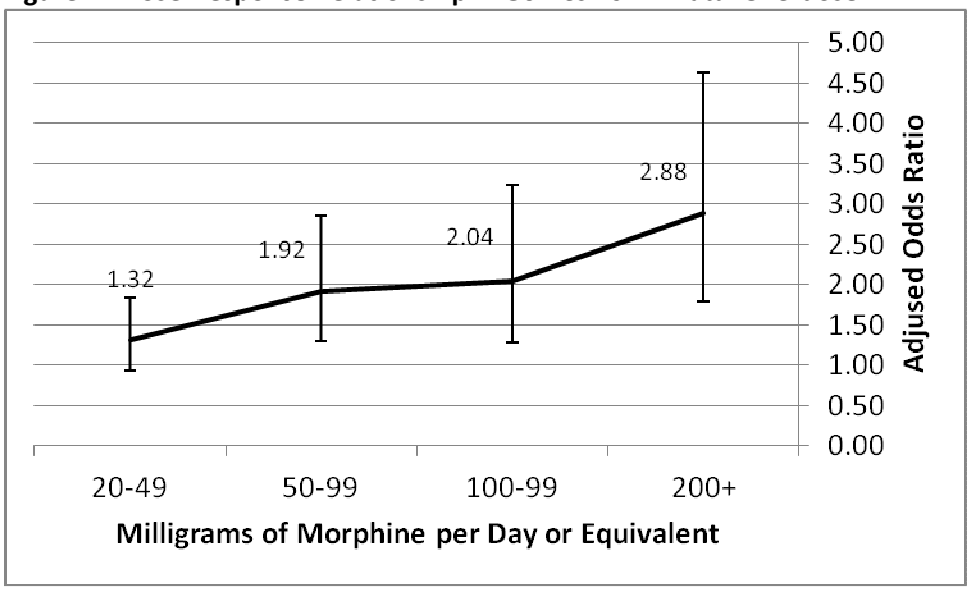


Figure 2: Dose-Response Relationship in Gomes 2011: Fatal Overdose



Effectiveness in General Population Associated with Daily Dose of Opioid Medication

Opioid	Dose per Day	Outcome	Rationale or Recommendation	Level of Evidence*	Source
Any	200 mg Morphine Equivalents	Pain Control	Chronic non-cancer pain can be managed effectively in most patients with dosages at or below 200 mg/day of morphine or equivalent. In 62 randomized controlled trials on titrating opioid doses, most patients' pain was controlled on under 100 mg morphine equivalents per day, and most of the studies used dosing limits under 200 mg per day.	Level A Evidence	Canadian Guideline (43)
	120 mg Morphine Equivalents	Pain Control	Guideline recommendations include limiting dose to 120 mg morphine equivalent unless patient demonstrates improvement in function OR first obtaining consultation from pain management physician. Rationale is that this was the highest maximum dose considered in the trials included in a 2006 systematic review by Furlan et al.	Level A Evidence	Washington State Opioid Dosing Guideline (37)
	120-200 mg Morphine Equivalents	Pain Control	Limit opioid doses to a maximum within this range because these were the highest doses used in most randomized controlled trials.	Level A Evidence	Colorado Guideline (51)
Tramadol	400 mg Tramadol	Pain Control	For neuropathic pain, titrate up to this dose based on randomized controlled trials assessing dosing limits.	Level A Evidence	NICE Neuropathic Pain Guideline (34)
Tramadol	400 mg Tramadol	Pain Control	Titrate up to this dose based on randomized controlled trials assessing dosing limits.	Level A Evidence	VA Guideline (32)
Codeine	400 mg Codeine	Pain Control	Titrate up to this dose based on randomized controlled trials assessing dosing limits.	Level A Evidence	VA Guideline (32)
Fentanyl	100 micrograms/hr Fentanyl	Pain Control	Titrate up to this dose based on randomized controlled trials assessing dosing limits.	Level A Evidence	VA Guideline (32)
	75 micrograms/hr Fentanyl (not daily dose)		When using the fentanyl patch, the maximum recommended dose is up to 75 micrograms/hr		U of Michigan (39)

Morphine	70-300 mg Morphine	Pain Control	Titrate up to this dose based on randomized controlled trials assessing dosing limits.	Level A Evidence	VA Guideline (32)
	180 mg Morphine Equivalents		The maximum recommended dose of opioids per day is up to 180 mg of morphine or the equivalent		U of Michigan (39)
Oxycodone	60-400 mg Oxycodone	Pain Control	Titrate up to this dose based on randomized controlled trials assessing dosing limits.	Level A Evidence	VA Guideline (32)
	120 mg Oxycodone		When using oxycodone for chronic pain, the maximum recommended dose is up to 120 mg total per day		U of Michigan (39)
Methadone	40 mg Methadone		When using methadone for chronic pain, the maximum recommended dose is up to 40 mg per day		U of Michigan (39)
Hydro-morphone	6 mg Hydro-morphone as needed every 4 hours (not daily dose)		When using hydromorphone for breakthrough pain, the maximum recommended dose is up to 6 mg as needed every four hours		U of Michigan (39)
	No Ceiling Dose		Be aware that most opioids do not have an analgesic efficacy ceiling and can be titrated upward as needed until limiting side effects appear, except for codeine, buprenorphine, meperidine, tapentadol, and tramadol, which all have a maximum dose.		ACP Pier Guideline (55)

* Scheme for rating the strength of evidence:

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- Level B Evidence: Data from other studies in humans, such as epidemiological studies or treatment studies without randomization.
- Level C Evidence: Recommendations based on expert consensus.

Drug-Drug Interactions

Opioid medications are affected by numerous drug-drug interactions. Some interactions affect all opioid medications, while others are specific to certain agents. All opioids interact with alcohol, benzodiazepines, barbiturates, and other sedatives such as muscle relaxants by producing excessive sedation. Eighty percent of people who die from opioid-related overdoses have other substances, such as alcohol or sedatives, present in their blood at the time of death. Alcohol is the most common, followed by benzodiazepines (23). Methadone and tramadol are notable for having numerous interactions, several of which are dangerous or life threatening.

Each drug-drug interaction potentially associated with decreased pain efficacy or increased adverse events can be identified as a potential screening criterion. Identifying these potential screening criteria would be most useful if the problem can be caught as soon as possible after the medication is ordered or prescribed. E-prescribing systems with computerized decision support can be programmed to intercept these sorts of drug-drug interactions, notifying providers of the problem as they are writing the prescription. The federal government is paying primary care physicians incentives to adopt electronic medication ordering systems for Medicare and Medicaid patients for just this situation. If it is not possible to intercept these problems real time, then the next best thing would be to notify the patient as soon as the system detects the issue.

Risks in General Population of Drug-Drug Interactions

Opioid	Formulation or Route	Risks	Drugs and Rationale or Recommendation	Level of Evidence*	Source
Any	Any	Not Stated, (Excessive Sedation, Mortality)	Patients with chronic pain (up to six months duration) should not receive opioids in combination with scheduled sedatives for longer than six weeks. (Examples of commonly prescribed scheduled sedatives include ***benzodiazepines*** and some ***barbiturates***).		WA State - Controlled Substances Guideline (54)
		Not Stated, (Excessive Sedation, Mortality)	When prescribing opioids to patients with chronic pain, avoid ***barbiturates*** and ***benzodiazepines***.		WA State - "Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain" (37)
		Not Stated, (Excessive Sedation, Mortality)	Do not combine opioids with sedative hyponotics, such as ***benzodiazepines*** and ***barbiturates***, except when treating seizure disorders.		WA State - "Outpatient Prescription of Oral Opioids for Injured Workers with Chronic, Noncancer Pain" (53)
		Overdose, Mortality	Benzodiazepines increase risk of opioid overdose, especially in elderly patients. Before starting patients with chronic non-cancer pain on long-term opioids, consider mitigating risk by tapering ***benzodiazepines*** down or off. Tapering may not be indicated for patients with severe anxiety/panic, seizures, or spasticity.	Level B Evidence	Canadian Guideline (43)
		Overdose, Mortality	When starting elderly patients with chronic pain on long-term opioids, taper off any ***benzodiazepines***, if possible.	Level C Evidence	Canadian Guideline (43)

		Overdose, Mortality	For patients with chronic non-cancer pain starting on long-term opioids, if tapering ***benzodiazepines*** is unsuccessful, titrate opioids up slowly and use lower doses.	Level C Evidence	Canadian Guideline (43)
		Motor Vehicle Accidents	When assessing safety to drive in patients on long-term opioid therapy, consider factors that could impair cognition and psychomotor ability, such as concomitant medications that increase sedation. Examples listed include ***benzodiazepines*** and ***anticholinergics, tricyclic antidepressants, anticonvulsants, antihistamines***, and ***opioids*** used for breakthrough pain.	Level C Evidence	Canadian Guideline (43)
Any	Any	Overdose	Erythromycin leads to increased opioid effects		ASIPP Guideline (41)
Any	Any	Uncontrolled Pain	Do not combine opioid agonists with partial agonist/antagonists (butorphanol, dezocine, nalbuphine, and pentazocine)		WA State - "Outpatient Prescription of Oral Opioids for Injured Workers with Chronic, Noncancer Pain" (53)
Morphine, Oxycodone, Hydro-morphone, Oxy-morphone	Controlled Release Formulations	Overdose	Metoclopramide leads to faster absorption of opioids with controlled release formulations and, therefore, may lead to overdose		ASIPP Guideline (41)
Morphine	Any	Overdose	Tricyclic antidepressants lead to increased blood levels		ASIPP Guideline (41)
Fentanyl	Any	Overdose, Mortality	***Macrolide antibiotics*** are cytochrome P450 3A4 inhibitors that inhibit metabolism of fentanyl		FDA Warnings, See Appendix 5
Fentanyl	Any	Overdose, Mortality	Protease inhibitors are cytochrome P450 3A4 inhibitors that inhibit metabolism of fentanyl		FDA Warnings, See Appendix 5

Methadone	Any	Cardiac Arrhythmias (QT prolongation, Torsades)	Methadone interacts with other ***drugs that prolong QT***.		VA Guideline (32)
	Any	Overdose, Mortality	***Many drugs*** can slow the elimination of methadone (see long list in Appendix E of VA Guideline)		VA Guideline (32)
		Overdose, Uncontrolled Pain	***Many drugs*** can slow and other speed the elimination of methadone		ASIPP Guideline (41)
Codeine	Any	Overdose, Uncontrolled Pain	***P-450 enzyme inducers or inhibitors*** interfere with codeine metabolism (long list of drugs and some foods)		FDA Warnings, See Appendix 5
Tramadol	Any	Seizures	***Selective serotonin re-uptake inhibitors, tricyclic antidepressants*** and other ***tricyclic compounds*** (e.g., cyclobenzaprine, promethazine), other ***opioids***, ***MAO inhibitors, neuroleptics***, or ***any other drugs that reduce seizure threshold***		FDA Warnings, See Appendix 5; Canadian Guideline (43)
		Serotonin Syndrome	Other ***drugs with serotonergic properties*** (examples: selective serotonergic reuptake inhibitors, MAO inhibitors, triptans, and many other medications)		FDA Warnings, See Appendix 5
		Overdose	Do not combine tramadol with other ***opioids***		WA State - "Outpatient Prescription of Oral Opioids for Injured Workers with Chronic, Noncancer Pain" (53)
		Overdose	Certain inducers and substrates of liver enzymes that metabolize tramadol can lead to elevated blood levels		ASIPP Guideline (41)
Meperidine	Any	Serotonin Syndome	Other ***drugs with serotonergic properties*** (examples: selective serotonergic reuptake inhibitors, MAO inhibitors, triptans, and many other medications)		ACP PIER Guideline (55)

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Opioid-Disease Interactions

There are specific diseases and conditions for which the risks of opioid therapy may be increased. These are discussed in the table below.

The evidence for some of these associations is limited. Identifying certain categories of patients with a screening criterion puts them at risk for under-treatment of their pain. Providers naturally want to avoid scrutiny of their care practices as would be triggered by a system of potential screening criteria. Thus, establishing potential screening criteria for opioid-disease interactions may inadvertently create incentives for discriminatory treatment practices. For example, patients diagnosed with "cognitive disorders," heart failure, renal impairment, and chronic obstructive pulmonary disease may find their pain is undertreated, even if their diagnoses are incorrect, resolved, or exceedingly mild. Consequently, it would be prudent to designate opioid-disease interactions as potential screening criteria only in specific circumstances. The evidence for the association should be quite robust. In addition, the disease, condition, or situation that confers the increased risk should be able to be very precisely defined.

Creating potential screening criteria that relate to opioid-disease interactions would require two types of data sources: pharmaceutical data, and medical billing claims diagnoses. In workers' compensation settings, payers use data sets containing medical diagnoses but they do not consistently use ICD-9 or ICD-10 codes. Some sort of coded data would greatly facilitate the identification of the diseases for which opioids may pose greater risk.

Risks in General Population Relating to Opioid-Disease Interactions

Opioid	Disease or Condition	Risks	Rationale or Recommendation	Level of Evidence*	Source
Any	Sleep Apnea	Overdose	Patients are at increased risk of overdose	Level B Evidence	Canadian Guideline (43)
Any except hydro-morphone	Renal Impairment	Overdose	Patients are at increased risk of overdose	Level B Evidence	Canadian Guideline (43)
Any	Chronic Obstructive Pulmonary Disease	Overdose	Patients are at increased risk of overdose	Level B Evidence	Canadian Guideline (43)
Any	Cognitive Disorders	Overdose	The risk of overdose is particularly increased among patients with cognitive disorders who live alone	Level B Evidence	Canadian Guideline (43)
Any	Sleep Disorders	Overdose	Patients are at increased risk of overdose	Level B Evidence	Canadian Guideline (43)
Any	Substance abuse disorders, including alcohol	Substance Misuse, (presumed)	Relative contraindication to prescribing controlled substances		WA State – Opioid Dosing Guideline (37)
Any	Borderline Personality Disorder	Substance Misuse, (presumed)	Relative contraindication to prescribing controlled substances		WA State – Opioid Dosing Guideline (37)
Any	Depression	Substance Misuse, (presumed)	Relative contraindication to prescribing controlled substances		WA State – Opioid Dosing Guideline (37)

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- Level C Evidence: Recommendations based on expert consensus.

Opioids and Treatment Issues Relating to Time

One of the questions we attempted to address was whether there are risks associated with opioid therapy that vary over time, as time-based events would be another way of identifying potential screening criteria for assessing opioid prescribing risk. The table below summarizes information from the guidelines relating to these issues.

Unfortunately, none of the recommendations seem to easily lend themselves to defining specific prescribing practices as particularly risky. Some of the relevant guideline content pertains to using caution when titrating opioids up over time, which would be hard, if not impossible, to turn into clearly identifiable screening criterion. Other recommendations refer to limiting opioid prescriptions for acute pain and for exacerbations of chronic pain, but these, too, are not concrete enough to enable potential screening criteria to be defined. However, it may be feasible to review claims for methadone and determine whether patients who are started on methadone receive doses that are low enough and whether the initial titration is slow enough to be safe.

Additional questions that have been asked are how long patients with chronic non-cancer pain should be treated with opioids or at what point weaning them off would be appropriate. Unfortunately, the studies that have demonstrated opioids can be effective in treating chronic non-cancer pain generally last no longer than six months (43). There has been limited research to answer this question.

In workers' compensation, some states have determined that opioids should not be paid for indefinitely, which effectively forces patients to be weaned off of them or to obtain them outside of the workers' compensation system. In Washington State, injured workers with chronic pain are generally able to receive financial coverage for opioids for only six months, with specific exceptions. Patients who experience improvement in function and attain maximum medical stability no longer have their opioids covered. Patients who do not experience improvement in function are weaned off opioids. By inference, only a few patients can continue to receive opioids and have them covered under the workers' compensation system after six months: the patients must continue to show improvement without reaching maximum medical stability, and improvement cannot go on indefinitely.

Roger Chou, one of our co-authors, lead author of the ASP-AAPM Guideline, and an active investigator in the field, has observed that limited attention has been paid to treating patients after they are weaned off opioids (68). Patients generally remain in pain after coming off of opioids. However, patients may not have access to other non-medication-based modalities for controlling pain, such as physical therapy or cognitive behavioral therapy (a form of psychotherapy). In California, physical therapy visits are capped at 24 total per claim (71). Payers may be unlikely to authorize psychological therapies for a musculoskeletal injury.

Risks in General Population and Treatment Issues Relating to Time

Opioid	Formulation or Route	Risks	Rationale or Recommendation	Level of Evidence*	Source
Any	Any	Overdose	When conducting a trial of opioid therapy, start with a low dosage, increase dosage gradually and monitor opioid effectiveness until optimal dose is attained.	Level C Evidence	Canadian Guideline (43)
Any	Any	Adverse Effects	"There is no evidence regarding the frequency of medical complications, the relationship between length of time on opioids and occurrence of medical complications, or whether the complications are permanent or transient." (page 19)	Level B Evidence	Canadian Guideline (43)
Any	Non-controlled Release Formulations	Substance Misuse, (presumed)	Most exacerbations of chronic pain do not require opioids. If opioids are necessary for an exacerbation, do not prescribe for more than two weeks.		ICSI Guideline (38)
Any	Non-controlled Release Formulations	Substance Misuse, (presumed)	For acute pain, only use opioids for severe pain and after determining that non-opioids will not provide adequate relief. Only prescribe limited amounts of non-controlled release opioids, enough to suffice for the anticipated duration of the episode		Utah Guideline (47)
Any	Any	Withdrawal	If discontinuation is necessary, tapering is recommended (25-50% reduction per week over 2-4 weeks)		University of Michigan (39)
Morphine, Oxycodone, Hydro-morphone, Oxy-morphone	Controlled Release Formulations	Overdose, Substance Misuse	When using controlled release formulations, titrate with caution to avoid overdose and misuse.	Level A Evidence	Canadian Guideline (43)

Any	Any		After six months, assess for improvement in function. If the patient has not improved, wean opioids. If the patient has improved and has reach maximum medical stability, the Washington State Workers' compensation system will no longer pay for opioids.		WA State - "Outpatient Prescription of Oral Opioids for Injured Workers with Chronic, Noncancer Pain" (53)
Fentanyl	Patch	Overdose, Substance Misuse	When using controlled release formulations, including fentanyl patch, titrate with caution to avoid overdose and misuse.	Level A Evidence	Canadian Guideline (43)
		Overdose	Do not titrate dose more rapidly than every six days		Canadian Guideline (43)
Oxycodone	Any	Substance Misuse, (presumed)	No evidence supports the long-term use of this medication		ASIPP Guideline (41)
Hydro-codone	Combined with acetaminophen or ibuprofen	Substance Misuse, (presumed)	No evidence supports the long-term use of these medications		ASIPP Guideline (41)

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Switching from One Opioid to Another

Switching from one opioid to another is commonly called "rotation." Indications for rotating opioids include: intolerable adverse effects, poor analgesic efficacy despite aggressive dose titration, drug-drug interactions, need for a different route of administration, clinical concerns (abuse, tolerance), financial concerns, and drug availability (e.g., some unusual medications may not be available at local pharmacies) (48). According to the APS-AAPM guideline, there is insufficient evidence to recommend rotation as a routine practice to enhance opioid effectiveness in the treatment of pain (35).

Opioid rotation can entail risks because patients may have developed a tolerance for the old opioid that they will not have for the new one due to differences in how the opioids are metabolized. As a result, opioid rotation can result in inadvertent overdoses. "Equianalgesic dosing tables" attempt to list doses of opioids that are believed to have similar effects in the body. These tables were developed about 40 years ago and they are widely used, but have different equianalgesic doses and were often based on small, single dose studies. Advances in the understanding of how opioids are metabolized suggest that the tables are not very accurate. Most importantly, they do not account for the very high degrees of variability that can occur across patients due to genetic differences. A dosing conversion that may be safe for one person may be life threatening in another (48, 72). Dosing errors during opioid rotation are leading to preventable fatalities (73). Other guidelines also suggest moderate dose reductions when opioids are rotated (35).

Nevertheless, it may be potentially feasible to develop potential screening criteria for opioid rotation. If a patient is on an opioid long term for chronic pain and they are switched to a different opioid medication, it would be feasible to determine whether the new dose is a certain pre-specified percentage lower than the original dose. When switching to methadone, the percentages selected would need to be much lower than for other medications because of incomplete cross-tolerance and other technical issues. Switching to fentanyl patches would require specific rules to be extracted from the packaging information for individual brands. One last step would be required to enable this screening criterion to be feasible and that would be to decide whether the limits apply to the total daily dose, or only to any long-acting agents.

Risks in General Population of Changing from One Opioid to Another

From Opioid	To Opioid	Risks	Recommendation	Level of Evidence*	Source
Any	Any except Methadone or Fentanyl	Overdose	Apply automatic dose reduction of 25-50% when rotating from one opioid to another	Level C Evidence	Fine Opioid Rotation Guideline (48)
Any	Any except Methadone or Fentanyl	Overdose	Pain control and psychosocial factors aside, use closer to a 50% reduction if the patient is receiving a relatively high dose of the current opioid, is not Caucasian, or is elderly or medically frail.	Level C Evidence	Fine Opioid Rotation Guideline (48)
Any	Any except Methadone or Fentanyl	Overdose	Pain control and psychosocial factors aside, use closer to a 25% reduction if the patient does not have above characteristics, or if the change is to the same drug via a different route.	Level C Evidence	Fine Opioid Rotation Guideline (48)
Any	Any except Methadone or Fentanyl	Overdose	Do a second assessment of pain severity, medical and psychosocial factors to determine whether an additional dose increase or decrease of 15% to 30% of the initial dose will be effective at controlling pain and minimizing risk of overdose.	Level C Evidence	Fine Opioid Rotation Guideline (48)
Any	Methadone	Overdose	Apply automatic dose reduction of 75%-90% when rotating from one opioid to methadone	Level C Evidence	Fine Opioid Rotation Guideline (48)
Any	Fentanyl	Overdose	When rotating from one opioid to fentanyl, follow directions on package insert as conversion varies	Level C Evidence	Fine Opioid Rotation Guideline (48)
Any	Fentanyl	Overdose	Frequently assess response and titrate the dose of the new opioid regimen to optimize outcomes.	Level C Evidence	Fine Opioid Rotation Guideline (48)
Any	Any	Overdose	To allow for incomplete cross-tolerance, in most cases, the starting conversion dose should be 50% to 67% of the calculated equianalgesic dose		VA Guideline (32)
Fentanyl	Any	Overdose	Do not switch from codeine to fentanyl because some people do not develop tolerance to codeine		Canadian Guideline (43)

Methadone	Any	Overdose	Methadone has little cross-tolerance with other opioids so it should be started at much lower doses		VA Guideline (32)

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Other Issues Related to Reducing the Risks of Opioid Prescribing in Workers' Compensation Settings

The guidelines and systematic reviews offered much useful information on how to reduce the risks of overdose, substance misuse, and mortality attributable to prescription opioid therapy that went beyond the details of the prescriptions themselves. We have summarized some of this the information below.

Minimizing The Use of Opioids When Not Appropriate or Necessary

The guidelines offered several principles for minimizing the use of opioids:

- Control pain with lowest dose of opioids necessary (55);
- Before patients with chronic pain are started on long-term opioid therapy, they should have tried and failed NSAIDs and/or acetaminophen, unless there are contraindications (37, 51, 55, 74);
    - Some guidelines require that the patients also have decreased function due to pain (12), have failed non-pharmacological therapy (32, 37), or have demonstrated functional improvement on a trial of opioids (37); and
- One guideline suggests that patients on long-term opioid therapy can also take NSAIDS and/or acetaminophen to reduce the dose of opioid needed to control pain (55).

However, among elderly individuals with moderate to severe pain, two guidelines consider opioids to be safer than NSAIDs (Level B Evidence) (42, 43). Safety is relative: both opioids and NSAIDs involve risks as well as benefits, and the risks of both therapies are increased in this population.

Assessing the Risk of Misuse before Starting Long-Term Opioid Therapy for Chronic Pain

The patients who are at greatest risk for misusing opioids or experiencing overdoses have certain recognizable characteristics. One of the systematic reviews, by Turk et al. (2008), determined that no one procedure can predict opioid misuse but strong predictors include a personal history of illicit drug or alcohol abuse. Other predictors include a history of legal or psychiatric issues, and being an adolescent (43, 62).

Many of the guidelines include a recommendation to conduct an informal or formal assessment of risk before initiating long-term opioid therapy (12, 32, 33, 37, 39, 41, 43, 47, 55). Some guidelines include suggestions for tools that are intended to facilitate the assessment of the risk of misuse and addiction (32, 35, 37, 43). The APS-AAPM Guideline offers a strong recommendation that such risk assessment is advisable based on low-quality evidence and expert consensus; however, the guideline notes there is insufficient evidence to determine the diagnostic accuracy of the individual screening instruments (35).

Some guidelines suggest asking about a family history of substance abuse (32, 43), and a peer history (32). One guideline recommends screening for substance misuse at each follow-up visit after opioids are initiated (38).

Once patients at increased risk of misuse have been identified, the question arises as to how to manage their pain; i.e., whether prescribing opioids is appropriate or not. Some guidelines consider prescribing opioids to be acceptable in certain higher risk patients so long as providers monitor closely for aberrant drug-seeking behaviors (43). Others suggest this as well as referral to specialists, such as experts in pain management and/or substance abuse disorders (32). Another guideline takes a different approach,

considering factors such as the use of alcohol or smoking cigarettes as relative contraindications to prescribing opioids (37). A related guideline from the same state-government based development group recommends proceeding only with "extreme caution" in the presence of relative contraindications to opioid therapy (53).

Performing Urinary Drug Tests

Most of the guidelines we reviewed advise considering urinary drug testing if patients are prescribed opioids over the long-term for the treatment of chronic non-cancer pain (12, 32, 35, 37-39, 43, 47, 51, 55). Specific nuances in these recommendations are discussed below. The overall rationale is the relatively high rate of substance misuse among patients who take long-term opioids for chronic pain. According to one of the systematic reviews, 3.3% of patients using opioids chronically for pain control will develop addiction and 12% will develop problems such as aberrant drug-related behaviors or illicit use (63), although these estimates are based on studies with methodological limitations, as discussed previously. Urinary testing before starting patients on chronic opioid therapy can reveal information when patients have not been forthcoming during medical history taking, such as the use of prescription opioids or benzodiazepines other than those on the patients' medication list, and illicit drugs. Random testing during long-term therapy can identify similar unexpected findings, as well as unexpectedly negative test results.

Two systematic reviews concluded that urinary drug testing is useful in detecting substance abuse issues. A review by Turk et al. (2008) observed that these tests should not be relied upon as the only means of detecting substance abuse – in other words, obtaining a medical history from the patient and observing the patient's behavior over time remain important. The Canadian guideline, which had a particularly high quality systematic review, identified two low-quality studies that reported lower rates of illicit substance use and abuse of prescribed opioids when urinary drug testing is used (in one study, it was in combination with treatment agreements, pill counts, and patient education)(43). However, the APS-AAPM guideline, which also had particularly high quality systematic reviews, concluded that, overall, there is limited evidence that urinary drug testing improves outcomes (35).

Of note, urinary drug testing has several technical and logistical issues that make it challenging to interpret results. The more that providers test low risk patients, the greater the chance that an unexpected result is due to technical and logistical issues rather than substance misuse or diversion. The Canadian guideline provides a nuanced discussion of testing issues (43).

- There are several different types of tests. Some don't detect all commonly prescribed opioids, particularly oxycodone, one of the most frequently abused opioids. Certain tests are unable to distinguish between certain types of opioids;
- Patients engaged in unsanctioned activities may try to tamper with test results;
- A positive test result for a non-prescribed medication can be due to:
    - A false positive test (e.g., laboratory error);
    - Patient acquiring medication from another provider;
    - Patient acquiring medication via diversion;
    - Use of illegal substances;
- Negative test result can be due to:

- A false negative test (e.g., due to technical issues noted above);
- Patient has not taken medication recently, such as due to side effects, fear of addiction, or lack of understanding about how to take the medication including language barriers or low health literacy (12);
- Patient may not be taking medication and may be engaging in diversion.

Given the limitations to the literature on urinary drug testing, any guideline recommendations are generally based on Level C evidence (i.e. consensus among experts).

- Some guidelines recommend periodic testing in all patients at high risk for misuse, and consider testing optional in lower risk populations (35). This approach is likely to be more cost-effective because confirming the results found on positive urinary screening tests can be quite costly.
- A guideline designed for the workers' compensation population recommends testing all patients and making the receipt of opioids conditional on agreeing to urinary drug testing (12).
- Another workers' compensation guideline provides a suggested testing frequency (no evidence was provided to support these recommendations): once per year in low risk patients, twice per year in medium risk patients, three times per year in high risk patients and those on doses greater than 120 mg of morphine equivalents per day, and immediate testing when misuse is suspected (37).

Guidelines also vary greatly in how providers should respond to positive urinary drug tests:

- Wean off the opioids immediately (12, 37).
- Set a policy that is zero tolerance or, take a more forgiving approach and give patients up to three "chances" (41).
- Refer patients to experts in the treatment of chronic pain and/or substance misuse issues (32, 37).
- Consider the possibility that the test could have been a false positive (e.g., laboratory error) among other possibilities (43).

Issues to consider in responding to abnormal urinary drug tests that some guidelines neglect to discuss in a nuanced fashion is that not all transgressions are equal. Having a negative urinary screen because medication side effects prompted a patient to stop taking a drug is not the same as diversion. Honestly forgetting to mention the sleeping medication prescribed by one's primary care physician is not the same as injecting heroin.

<u>Entering into Written Treatment Agreements with Patients</u>

Many guidelines recommend that providers enter into written treatment agreements when they start patients on long-term opioid therapy, continue therapy beyond 90 days, or take over such therapy from another provider (12, 32, 37-39, 43, 47, 50, 51, 54). The written treatment agreement is often described as a patient education tool and part of the informed consent process as well as a set of expectations of patient behavior. Several offer detailed suggestions as to how to structure such treatment agreements, and how providers might consider responding if patients violate the agreements (12). The Canadian Guideline, which had a more rigorous literature search, found one small study showing that written

treatment agreements improve patients' adherence to prescribed medications (43). Written treatment agreements are subject to the same caveats as urinary drug tests, however. There are no studies showing that agreements improve outcomes, or that identify the essential components of an agreement.

Summary and Conclusions

Chronic pain, defined as pain lasting at least three months longer than the expected period of healing, is unfortunately very common. Opioids can be an appropriate means of treating patients with chronic pain, particularly those with moderate to severe pain. Four of the systematic reviews we identified found that oral opioids are significantly more effective than placebo in treating chronic pain, with declines in pain in the range of 30-50%. Use of opioids for chronic pain has also been associated with significant improvements in measures of functional status (such as on SF-36) (57-60). According to two of these studies, opioids are also more effective at improving pain and functional status than NSAIDs (59, 60). Nevertheless, the increasing use of opioids has been accompanied by real risks of substance misuse, addiction, diversion, overdose, and death. The Institute of Medicine Report, *Relieving Pain in America*, summarizes the ongoing challenges involved in balancing effective treatment of pain against the known risks associated with opioid therapy and provides specific recommendations for national and other policy audiences (26).

The risks of overdose, substance misuse, and mortality may be higher in workers' compensation settings than elsewhere, based on a systematic review published this year that documents opioid prescribing practices in workers' compensation and other settings. In workers' compensation settings, opioids are used more often in the treatment of chronic non-cancer pain and the doses used tend to be higher. Dembe et al. reported that 8.8% to 52% of injured workers (mean 32%) were reported as using opioids across nine studies. In seven studies of patients with chronic non-cancer pain from outside of workers' compensation settings, use ranged from 8% to 30% (mean 18%) among those with chronic pain. Among users of opioids in workers' compensation settings, average daily doses ranged from 7.8 mg to 110 mg morphine equivalents (mean 48 mg). Outside of workers' compensation settings, doses ranged from 13 mg to 128 mg morphine equivalents (mean 42 mg) daily (65).

Workers' compensation settings have an additional unique issue as well: the value of ensuring that the patients being prescribed opioids return to their baseline functional status as quickly as possible. Observational studies, including one in California, found use of higher dose opioids associated with longer disability and higher workers' compensation claim costs (9, 18).

The objective of the current study, commissioned by the California Department of Industrial Relations and the California Commission on Health and Safety and Workers' Compensation, was to perform a systematic literature search for information that can be used to identify higher risk prescribing practices within the workers' compensation system.

Higher risk practices are those that are thought to be associated with suboptimal patient outcomes. The potential screening criteria for identifying them focus on areas of practice where providers should proceed with caution or not at all. Those prescriptions flagged as positive for the screening criteria could undergo review by a third party, and, if the third party feels that the treatment plan is unsafe or not in accordance with widely accepted standards of care, some intervention could be undertaken to mitigate the situation. Most likely, any criteria implemented as a state policy or by workers' compensation payers would be applied to pharmaceutical claims (billing) data so the criteria should be able to identify high risk practices based on medication name and formulation, route of administration, dose per unit of medication, number dispensed, and patterns of refills over time.

The research questions this project set out to address focused, therefore, on how specific types of medications, formulations, routes, doses, durations of therapy, and drug-drug interactions affected outcomes such as pain control, functional status, and adverse events including the risk of overdose, addiction, and mortality. To answer these questions, we focused our search for information on medical treatment guidelines, systematic literature reviews, meta-analyses, and information on individual medications released by the Food and Drug Administration. We restricted our search to information published since 2007, since studies have shown that new studies can render guidelines out of date as quickly as three years after publication (25).

We identified 20 recent guidelines that appeared relevant. Of these, two had particularly high quality literature reviews and addressed a range of topics relevant to patients with chronic pain. We extracted a great deal of information from all of the guidelines relating to the risks of adverse events. Selecting a variety of potential screening criteria based on this work appears quite feasible.

The guidelines and other information sources identified two individual medications as posing particularly high risks of overdose, substance misuse, or toxicity: immediate release fentanyl preparations, and meperidine. Methadone can also be included as a screening criterion to ensure that patients are started on the drug in a safe manner. These three are clear candidates for consideration as potential screening criteria, meaning that particularly close scrutiny is warranted (the first two) or the drug should not be prescribed to outpatients (meperidine).

In terms of selecting a dose of each opioid to use as a screening criterion for inappropriate prescribing, this too appears feasible. Most guidelines agreed that doses above 200 mg of morphine equivalents per day warranted additional scrutiny because many patients achieve pain control with doses about half that level. Risks of overdose rise, according to three recent studies, around 100 mg, if not at lower doses. That said, it is hard to determine the dosing levels at which the optimal balance is achieved between effectiveness and an acceptably low risk of overdose. We do not have a recommendation for the specific dose at which a screening criterion dosing limit should be set, other than suggesting it should be between 100 mg and 200 mg. Pilot work implementing the potential screening criteria could help to sort out the limit that would identify a number of claims that would be feasible to review.

In terms of drug-drug interactions, one potential screening criterion is benzodiazepines. Please refer to the tables above for others as there are too many potential screening criteria to summarize them here. Indeed, even the tables above primarily list drug classes. Take “MAO inhibitors,” for example. These include not only an old fashioned type of anti-depressant but also a new and increasingly common antibiotic, linezolid. In the actual implementation of an opioid prescribing safety program, each potential interaction should be cataloged according to the individual drugs involved.

This report also identifies, based on the guidelines we reviewed, potential screening criteria for when patients are switched from one opioid to another. These transitions are fraught with risks of overdose due to the characteristics of the different drugs as well as variability across individual patients in how they metabolize different opioids. Doses calculated using the old standby equianalgesic dosing tables must be adjusted downward by 25-50% for most drugs to

allow for the possibility that patients may not be nearly as tolerant to the new medication; other adjustments are required for fentanyl and methadone, as explained in the section above.

As a window into how many patients might have care that will be flagged by such potential screening criteria, Swedlow et al. have provided detailed relevant information on opioid claims in the California workers' compensation system. With regard to type of medication and formulation, rates as a percentage of prescriptions from 1993 to 2009 were as follows: oxycodone 45%, fentanyl immediate release preparations 2.9%, fentanyl patch 17%, methadone 10%, morphine 17%, oxymorphone 2.4%, hydromorphone 4.3%, meperidine 0.%, levorphanol 0.3% (no longer available) (19).

The Swedlow study did not provide information on dose or drug-drug interactions. However, a study by Dembe et al. based on opioid claims in the Ohio workers' compensation system did provide that information. With regard to dose, that varied greatly. Twenty percent had average daily doses above 72 mg, 9.2% had doses above 120 mg, and 0.2% had doses above 1,000 mg of morphine equivalents per day. Regarding potential drug-drug interactions, 31% of those prescribed opioids also received skeletal muscle relaxants, 14% received benzodiazepines, and 13% received sedative-hypnotics (65).

If prescribing practices in California are similar to those in Ohio, the potential screening criteria suggested by the various guideline recommendations will identify quite a number of medical claims warranting review. Thus, it would be helpful to test how a system of claims-based screening criteria that identify risky opioid prescribing practices would actually work. The guidelines and other documents we reviewed suggest possible screening criteria. The next step would be to identify the various types of data sources that could be available for examining prescribing practices. The potential screening criteria need to be reviewed and the ones most in line with policy objectives selected. These preliminary screening criteria need to be compared with the relevant data elements in the various data sources to determine the exact nature of the information available, whether relevant patients can be identified, and whether data pertaining to screening criteria can be identified. For each data element, it will be essential to understand how frequently it is missing or miscoded. The individuals who routinely work with the data sets can probably provide a general sense of these issues. Rules will need to be devised for calculating the incidence or prevalence of each screening criterion in a population. Then basic incidence or prevalence rates for each screening criterion should be determined for an actual population over a particular time period, giving a sense of how many claims are affected by the proposed rules. If the proposed screening criteria identify more claims than would be feasible to review, it may be necessary to down-prioritize certain flags or redefine them to focus on only the highest risk patients. Re-estimating the frequency statistics after such changes will confirm that the new screening criteria appear more feasible.

Finally, it would be advisable to conduct a formal analysis of the screening criteria by conducting a receiver-operator curve analysis. Receiver-operator curve analyses test the sensitivity, specificity, and overall performance of a new diagnostic test against a gold standard. In this case, the screening criteria would be the "new diagnostic test" and the gold standard would be outcomes of interest, which could be defined as overdoses, substance misuse, mortality, time on disability, or some other endpoint. In assessing the "new diagnostic test," overall performance is measured by an area-under-the-receiver-operating-characteristic curve statistic. A perfect test has a statistic of 1.0, while a test no better than chance has a value of 0.50. In this

case, investigators could apply the now carefully defined screening criteria to an existing data set of pharmaceutical claims, such as from a two to five year period. Then information would be needed on outcomes of interest, such as overdoses (e.g., emergency room visits or hospitalizations with ICD-9 codes for drug intoxication), substance misuse, or mortality for the same population over the same period. Such a study would demonstrate the validity of the screening criteria as a means of identifying high-risk prescribing practices.

Other Considerations

Of course, developing a claim-based system for identifying high risk prescribing practices is only one strategy for addressing the problem. It is also important to have a system for educating providers about basic standards in opioid prescribing. Giving providers feedback about their practices, such as how they perform compared to other providers on the potential screening criteria, can be a particularly effective improvement strategy.

Using the guidelines and systematic reviews, we have examined a number of other issues related to opioid prescribing practices that people often hope will reduce the risks of adverse outcomes and improve the likelihood of attaining the favorable goals of pain control and improvements in functional status. These include recommendations related to minimizing opioid prescriptions when appropriate, and using risk stratification, urinary drug testing, and written treatment agreements to mitigate the risks associated with long-term opioid therapy for chronic pain.

California stakeholders and policymakers may find several other resources that to be useful:

- National Alliance for Model State Drug Laws. This is a non-profit corporation that has no ties to industry, is funded by Congress, and provides legislative and policy services on drug and alcohol laws to a variety of stakeholders at the state and national level. Go to www.NAMSDL.org.
- Substance Abuse and Mental Health Services Administration (SAMHSA). SAMHSA is a congressionally funded federal agency that provides leadership and devotes its resources to preventing and helping people recover from mental and substance use disorders. http://www.samhsa.gov/index.aspx
- National Association of State Alcohol and Drug Abuse Directors. The National Association of State Alcohol and Drug Abuse Directors, Inc. (NASADAD) is a private, not-for-profit educational, scientific, and informational organization. NASADAD's basic purpose is to foster and support the development of effective alcohol and other drug abuse prevention and treatment programs throughout every state. NASADAD serves as a focal point for the examination of alcohol and other drug related issues of common interest to both other national organizations and federal agencies (it has worked with just about every relevant federal agency on the issue). http://nasadad.org/

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Appendix 1: Abstraction Instructions for Risky Opioid Prescribing Practices

This document contains the abstraction instructions. The Abstraction Form is where responses should be recorded for individual documents.

First Author and Year: _____

Article or Guideline #: _____

Name of Reviewer: _____

1. **What type of document is this?**
    a. Guideline
    b. Systematic review
    c. Original research paper
    d. Standard prescribing information
    e. Information from FDA
    f. Other, specify _____
2. **What types of pain does the document address?**
    a. Chronic pain in general (pain that lasts longer than the expended time of tissue healing, generally longer than three to six months)
    b. Acute or subacute pain in general (pain that is not chronic)
    c. Neuropathic pain
    d. Pain in a particular part of the body, such as back pain
    e. Other, specify _____
3. **Which of the following domains are addressed in this document? List all that apply:**
    a. Maximum daily dose
    b. Drug type, route of administration, or formulation and association with outcomes (association can be stated or implied in document)
    c. Maximum cumulative dose
    d. Duration of opioid therapy
    e. Concomitant use of other medications that increase the risk for adverse events
    f. Use of opioids vs. NSAIDS (non-steroidal anti-inflammatory drugs)
    g. Use of opioids vs. acetaminophen
    h. Usefulness of pain contracts (providing patient with written information about plan for managing his or her pain, including expectations for patient behavior and adherence and potential consequences of non-adherence)
    i. Usefulness of urinary drug testing

j. Usefulness of screening for substance abuse by taking medical history

k. Other domain with a strong effect on outcomes, specify: _____

Use Tables 2 and 3 to abstract detailed information from the document.

- **Table 2 addresses issues relating to opioid prescriptions themselves, such as doses, formulations, etc.**
- **Table 3 addresses other care practices relevant to the prescribing of opioids, such as the use of urinary drug testing, etc.**

For Table 2, include one line in the table for each set of exposures, outcomes and patient subgroups mentioned in the document, such as one line per study cited.

5. Type of exposure studied: (List code letter/number in Table 2, e.g., a)

a. Maximum daily dose (often reported in milligrams and/or morphine equivalents, convert if possible)

b. Drug type, route of administration, or formulation and association with outcomes (association can be stated or implied in document)

c. Maximum cumulative (often dose reported in milligrams/and or morphine equivalents, convert if possible)

d. Duration of therapy reported (weeks)

e. Potential drug-drug interaction (see list under Question 7)

6. Type of outcome studied: (List code letter/number in Table 2, e.g., a-i)

a. Control of pain

   i. Self-reported pain

   ii. Other, Specify _____

b. Functional status

   i. Self-reported functional status

   ii. Ability to work

   iii. Other, Specify _____

c. Adverse events

   i. Overdose

   ii. Substance abuse or addiction

   iii. Death

   iv. Other, Specify _____

7. Patient subgroups studied (Describe in Table 2)

8. Specific opioid medications studied: (List code letter/number in Table 2, e.g., j-iiv)

k. Morphine equivalents or not specified

l. Morphine (MS Contin, Kadian, Avinza, Roxanol, Oramorph SR, MSIR, DepoDur)

m. Oxycodone (Roxicodone, OxyContin, Percolone, OxyIR, OxyFAST)

n. Fentanyl

o. HydroMORPHONE (Dilaudid, Exalgo)

p. Levorphanol (Levo-Dromoran)

q. Meperedine (Demerol, pethidine)

r. Methadone (Diskets, Dolophine, Methadose)

s. Codeine

t. Oxymorphone (Opana, Opana ER)

u. Combinations with acetaminophen

iv. Hydromorphone/acetaminophen (Anexsia

v. Codeine/acetaminophen (Tylenol or Capital with codeine)

vi. Codeine/acetaminophen/butalbital/caffeine (Fioricet with codeine)

vii. Hydrocodone/acetaminophen (Vicodin, Lorcet, Lortab, Maxidone, Norco, Xodol, Zydone)

viii. Oxycodone/acetaminophen (Percodet)

ix. Pentazocine/acetaminophen (Talcen)

x. Oxycodone/acetaminophen (Tylox)

xi. Propoxyphene/acetaminophen (Wygesic)

v. Combinations with ibuprophen

i. Oxycodone/ibuprofen (Combunox)

ii. Hydrocodone/ibuprofen (Vicoprofen, Ibudone)

w. Combinations with aspirin

ii. Codeine/ASA (Empirin with codeine)

iii. Codeine/ASA/butalbital/caffeine (Fiorinal with codeine)

iv. Hydrocodone/acetaminophen (Lorcet)

v. Oxycodone/ASA (Percodan, Roxicet)

vi. Coceine/ASA/carisoprodol (SOMA with codeine)

vii. Dihydrocodeine/ASA/caffeine (Synalgos-DC)

x. Other

i. Tramadol (Ultram)

ii. Tapentadol

9. Routes of administration and/or formulations studied: (List code letter/number in Table 2, e.g., f-iiv)

a. Not specified

b. Oral pill/capsule, short-acting formulations

c. Oral liquid/elixir

d. Topical patch

i. Fentanyl (Duragesic)

e. Lollypop or lozenges

i. Fentanyl (Actiq)

f. Buccal tab or film

i. Fentanyl (Fentora, Onsolis)

g. Oral extended release formulations

i. Morphine (MS Contin, Kadian, Avinza, Oramorph SR)

ii. Oxycodone (OxyContin)

iii. hydroMORPHONE (Exalgo)

iv. Oxymorphone (Opana, Opana ER)

h. Other, specify_____

10. Details of exposure: (Describe or list code letter/number in Table 2, e.g., a-iiv)

a. Dose per day: (Write number in Table 2)

b. Dose per ___ (unit of time): (Write number in Table 2)

c. Duration: (Write number in Table 2)

d. Potential drug-drug interactions reported: (list code letter/number, e.g., d-iiv)

i. Chlordiazepoxide (Librium)

ii. Clonazepam (Klonopin)

iii. Clorazepate (Tranxene)

iv. Diazepam (Valium, Diastat, Diastat AcuDial)

v. Flurazepam (Dalmane)

vi. Estazolam (ProSom)

vii. Lorazepam (Ativan)

viii. Temazepam (Restoril)

ix. Alprazolam (Xanax, Xanax XR, Niravam)

x. Oxazepam (Serax)

xi. Triazolam (Halcion)

xii. Buspirone (BuSpar, Vaspar)

xiii. Chloral hydrate (Aquachloral suprettes, Somnote)

xiv. Eszopiclone (Lunesta)

xv. Ramelteon (Rozerem)

xvi. Zaleplen (Sonata)

xvii. Zolpidem (Ambien, Ambien CR, Zolpimist, Edluar)

xviii. Baclofen (Lioresal, Kemstro)

xix. Carisoprodol (Soma)

xx. Chlorzoxazone (Parafon Forte DSC)

xxi. Cylobenzarine (Amrix, Flexeril, Fexmid)

xxii. Dantroline (Dantrium)

xxiii. Metaxalone (Skelaxin)

xxiv. Methocarbamol (Robaxin)

xxv. Orphenadrine (Norflex)

xxvi. Tizanidine (Zanaflex)

xxvii. Other

e. Not applicable

11. Study design:

a. Randomized controlled trial data
b. Prospective cohort data with control group
c. Case-control study
d. Case series (no control group)
e. Prospective, uncertain whether control group
f. Retrospective, uncertain whether control group
g. Consensus
h. Guideline recommendation
    i. Strength A
    ii. Strength B
    iii. Strength C

12. Effects of exposure: Describe change in outcome associated with exposure. Include any factors that can mitigate risk associated with exposure. (Describe in Table 2)

- Control of pain:
- Functional status: E.g., relative risk, hazard ratio, number needed to harm, etc.
- Adverse events: E.g., relative risk, hazard ratio, number needed to harm, incidence rate, etc.

For Table 3, include one line in the table for each set of exposures, outcomes and patient subgroups mentioned in the document, such as one line per study cited.

13. Type of intervention studied: (List code letter/number in Table 3, e.g., a)

a. Use of opioids vs. NSAIDS (non-steroidal anti-inflammatory drugs)
b. Use of opioids vs. acetaminophen
c. Usefulness of pain contracts
d. Usefulness of urinary drug testing
e. Usefulness of screening for substance abuse by taking medical history
f. Other intervention with a strong effect on outcomes, specify: _____

14. Type of outcome studied: (List code letter/number in Table 3, e.g., a-i)

a. Control of pain
   i. Self-reported pain
   ii. Other, Specify _____
b. Functional status
   i. Self-reported functional status
   ii. Ability to work
   iii. Other, Specify _____
c. Adverse events
   i. Overdose
   ii. Substance abuse or addiction
   iii. Death
   iv. Other, Specify _____

15. Patient subgroups studied (Describe in Table 3)

16. Specific opioid medications studied:

a. Morphine equivalents or not specified
b. For specific opioids, see list for Question 5 above

17. Timing of intervention: (Describe or list code letter/number in Table 3, e.g., a-iiv)

a. Before the patient receives the first opioid prescription, Specify ____
b. Simultaneous with the first opioid prescription
c. Shortly after the first opioid prescription, Specify _____
d. At regular intervals during long-term opioid therapy, Specify _____
e. At random times during long-term opioid therapy

f. Other, Specify _____

18. Other details of intervention: Describe other key details about how the intervention was implemented. (Describe in Table 3)

19. Study design:

a. Randomized controlled trial data
b. Prospective cohort data with control group
c. Case-control study
d. Case series (no control group)
e. Prospective, uncertain whether control group
f. Retrospective, uncertain whether control group
g. Consensus
h. Guideline recommendation
    i. Strength A
    ii. Strength B
    iii. Strength C

20. Effects of intervention: Describe change in outcome associated with the intervention. (Describe in Table 3)

- Control of pain:
- Functional status: E.g., relative risk, hazard ratio, number needed to harm, etc.
- Adverse events: E.g., relative risk, hazard ratio, number needed to harm, incidence rate, etc.

Appendix 2. Documents Identified by Searches of Databases and Websites, and Reasons for Exclusion

Document Information	Source Searched	Included	Reasons for Excluding Documents from Consideration								
			Dupli-cate	Not Pain Mgt	Other Treat-ment	Specific Condi-tion	Specific Popula-tion	Specific Type of Pain	Specific Setting	Not a Guide-line	Before 2007
(1) Nursing care of dyspnea: the 6th vital sign in individuals with chronic obstructive pulmonary disease (COPD). (2) Nursing care of dyspnea: the 6th vital sign in individuals with chronic obstructive pulmonary disease (COPD) 2010 supplement. 2005 Mar (addendum released Feb 2010). NGC:008382 Registered Nurses' Association of Ontario - Professional Association.	National Guide-lines Clearing-house	No		1							
(1) Nursing care of dyspnea: the 6th vital sign in individuals with chronic obstructive pulmonary disease (COPD). (2) Nursing care of dyspnea: the 6th vital sign in individuals with chronic obstructive pulmonary disease (COPD) 2010 supplement. 2005 Mar (addendum released Feb 2010). NGC:008382 Registered Nurses' Association of Ontario - Professional Association.	National Guide-lines Clearing-house	No	1								
2009 Clinical Guidelines from the American Pain Society and the American Academy of Pain Medicine on the use of chronic opioid therapy in chronic noncancer pain: what are the key messages for clinical practice? Chou R. Pol Arch Med Wewn. 2009 Jul-Aug;119(7-8):469-77. Review.	MEDLINE	No								1	

2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 1995 Nov 1 (revised 2009 Apr 14). NGC:008024 American College of Cardiology Foundation - Medical Specialty Society; American Heart Association - Professional Association; International Society for Heart and Lung Transplantation - Professional Association.	National Guide-lines Clearing-house	No		1							
Accidental drug deaths in Fulton County, Georgia, 2002: characteristics, case management and certification issues. Graham JK, Hanzlick R. Am J Forensic Med Pathol. 2008 Sep;29(3):224-30	MEDLINE	No								1	
ACOEM Guidelines for Chronic Use of Opioids	Specialty Society Website	No								1	
ACR Appropriateness Criteria® management of vertebral compression fractures. 2010. NGC:008483 American College of Radiology - Medical Specialty Society.	National Guide-lines Clearing-house	No				1					
ACR Appropriateness Criteria® management of vertebral compression fractures. 2010. NGC:008483 American College of Radiology - Medical Specialty Society.	National Guide-lines Clearing-house	No	1								
ACR–SIR practice guideline for sedation/analgesia. 2010. NGC:008417 American College of Radiology - Medical Specialty Society; Society of Interventional Radiology - Medical Specialty Society.	National Guide-lines Clearing-house	No							1		
Acute coronary syndrome and myocardial infarction. 2001 Apr 30 (revised 2011 Mar 1). NGC:008520 Finnish Medical Society Duodecim - Professional Association.	National Guide-lines Clearing-house	No	1								

Acute coronary syndrome and myocardial infarction. 2001 Apr 30 (revised 2011 Mar 1). NGC:008520 Finnish Medical Society Duodecim - Professional Association.	National Guide-lines Clearing-house	No		1							
Acute low back pain. 1997 (revised 2010 Jan). NGC:008009 University of Michigan Health System - Academic Institution.	National Guide-lines Clearing-house	No				1					
Acute pain assessment and pharmacological management practices for the older adult with a hip fracture: review of ED trends. Herr K, Titler M. J Emerg Nurs. 2009 Jul;35(4):312-20. Epub 2008 Dec 20.	MEDLINE	No								1	
Adapting your practice: general recommendations for the care of homeless patients. 2004 (revised 2010). NGC:007876 Health Care for the Homeless (HCH) Clinician's Network - Medical Specialty Society; National Health Care for the Homeless Council, Inc. - Nonprofit Organization.	National Guide-lines Clearing-house	No					1				
Adapting your practice: recommendations for the care of homeless adults with chronic non-malignant pain. 2011. NGC:008653 National Health Care for the Homeless Council, Inc. - Nonprofit Organization.	National Guide-lines Clearing-house	No					1				
Adapting your practice: treatment and recommendations for homeless patients with hypertension, hyperlipidemia & heart failure. 2004 (revised 2009 Dec). NGC:007679 Health Care for the Homeless (HCH) Clinician's Network - Medical Specialty Society; National Health Care for the Homeless Council, Inc. - Nonprofit Organization.	National Guide-lines Clearing-house	No		1							

Adherence to clinical guidelines for opioid therapy for chronic pain in patients with substance use disorder. Morasco BJ, Duckart JP, Dobscha SK. J Gen Intern Med. 2011 Sep;26(9):965-71. Epub 2011 May 12 .	MEDLINE	No								1	
Adult low back pain. 1994 Jun (revised 2010 Nov). NGC:008193. Institute for Clinical Systems Improvement - Nonprofit Organization.	National Guide-lines Clearing-house	No				1					
American College of Chest Physicians consensus statement on the management of dyspnea in patients with advanced lung or heart disease. Mahler DA, Selecky PA, Harrod CG, Benditt JO, Carrieri-Kohlman V, Curtis JR, Manning HL, Mularski RA, Varkey B, Campbell M, Carter ER, Chiong JR, Ely EW, Hansen-Flaschen J, O'Donnell DE, Waller A. Chest. 2010 Mar;137(3):674-91. Review.	MEDLINE	No		1							
American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults	Specialty Society Website	No		1							
American Society of Clinical Oncology clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. 2000 Mar (revised 2011). NGC:008441 American Society of Clinical Oncology - Medical Specialty Society.	National Guide-lines Clearing-house	No				1					
An estimate of meperidine usage in West Virginia hospitals. Lafferty HW, Terpening CM. W V Med J. 2010 Jul-Aug;106(5):20-3	MEDLINE	No								1	

An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, Calverley PM, Gift AG, Harver A, Lareau SC, Mahler DA, Meek PM, O'Donnell DE; American Thoracic Society Committee on Dyspnea. Am J Respir Crit Care Med. 2012 Feb 15;185(4):435-52.	MEDLINE	No		1							
Ankle & foot (acute & chronic). 2003 (revised 2011 Apr 7). NGC:008511 Work Loss Data Institute - For Profit Organization.	National Guide-lines Clearing-house	No				1					
Antiretroviral therapy for HIV infection in adults and adolescents. 2010. NGC:008303 World Health Organization - International Agency.	National Guide-lines Clearing-house	No		1							
Antisocial personality disorder. Treatment, management and prevention. 2009 Jan. NGC:007209 National Collaborating Centre for Mental Health - National Government Agency [Non-U.S.].	National Guide-lines Clearing-house	No		1							
ASIPP Opioid Guidelines: Opioid Guidelines in the Management of Chronic Non-Cancer Pain. American Society of Interventional Pain Physicians	Specialty Society Website	Yes									

Aspects of primary care for the HIV-infected substance user. 2004 (revised 2010 Jul). NGC:007975 New York State Department of Health - State/Local Government Agency [U.S.].	National Guide-lines Clearing-house	No					1				
Assessment and management of chronic pain. 2005 Nov (revised 2009 Nov). NGC:007602 Institute for Clinical Systems Improvement - Nonprofit Organization.	National Guide-lines Clearing-house	Yes									
Assessment and management of chronic pain. 2005 Nov (revised 2009 Nov). NGC:007602 Institute for Clinical Systems Improvement - Nonprofit Organization.	National Guide-lines Clearing-house	No	1								
Audit of extrapleural local anaesthetic infusion in neonates following repair of tracheo-oesophageal fistulae and oesophageal atresia via thoracotomy. Palmer GM, Thalayasingam P, McNally CM, Tingay DG, Smith KR, Clarnette TD, Penrose S, Dowden SJ, Chalkiadis GA. Anaesth Intensive Care. 2012 Jan;40(1):172-80	MEDLINE	No								1	
Bending the prescription opioid dosing and mortality curves: impact of the Washington State opioid dosing guideline. Franklin GM, Mai J, Turner J, Sullivan M, Wickizer T, Fulton-Kehoe D. Am J Ind Med. 2012 Apr;55(4):325-31. doi: 10.1002/ajim.21998. Epub 2011 Dec 27	MEDLINE	No								1	
BSACI guidelines for the investigation of suspected anaphylaxis during general anaesthesia. Ewan PW, Dugué P, Mirakian R, Dixon TA, Harper JN, Nasser SM; BSACI. Clin Exp Allergy. 2010 Jan;40(1):15-31.	MEDLINE	No		1							

Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 1: general population. Kahan M, Mailis-Gagnon A, Wilson L, Srivastava A; National Opioid Use Guideline Group. Can Fam Physician. 2011 Nov;57(11):1257-66, e407-18	MEDLINE	Yes									
Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 2: special populations. Kahan M, Wilson L, Mailis-Gagnon A, Srivastava A; National Opioid Use Guideline Group. Can Fam Physician. 2011 Nov;57(11):1269-76, e419-28	MEDLINE	No	1								
Cancer pain management (general). In: Guidelines on pain management. 2009 Mar (revised 2010 Apr). NGC:007978 European Association of Urology - Medical Specialty Society.	National Guide-lines Clearing-house	No				1					
Care of the movement disorder patient with deep brain stimulation. 2009. NGC:007395 American Association of Neuroscience Nurses - Professional Association.	National Guide-lines Clearing-house	No		1							
Care of the patient with aneurysmal subarachnoid hemorrhage. 2007 (revised 2009 Dec). NGC:008695 American Association of Neuroscience Nurses - Professional Association.	National Guide-lines Clearing-house	No		1							
Carpal tunnel syndrome. 2011. NGC:008689 American College of Occupational and Environmental Medicine - Medical Specialty Society.	National Guide-lines Clearing-house	No				1					

Central poststroke pain: a review of pathophysiology and treatment. Kumar B, Kalita J, Kumar G, Misra UK. Anesth Analg. 2009 May;108(5):1645-57. Review.	MEDLINE	No								1	
Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. 2010 Mar. NGC:007890 National Clinical Guideline Centre for Acute and Chronic Conditions - National Government Agency [Non-U.S.].	National Guide-lines Clearing-house	No				1					
Chronic neuropathic pain management in spinal cord injury patients. What is the efficacy of pharmacological treatments with a general mode of administration? (oral, transdermal, intravenous). Attal N, Mazaltarine G, Perrouin-Verbe B, Albert T; SOFMER French Society for Physical Medicine and Rehabilitation. Ann Phys Rehabil Med. 2009 Mar;52(2):124-41. Epub 2009 Feb 21.	MEDLINE	No								1	
Chronic obstructive pulmonary disease. Management of chronic obstructive pulmonary disease in adults in primary and secondary care. 2004 Feb (revised 2010 Jun). NGC:007907 National Clinical Guideline Centre for Acute and Chronic Conditions - National Government Agency [Non-U.S.].	National Guide-lines Clearing-house	No		1							
Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. 2004	Specialty Society Website	No									1
Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. American Academy of Pain Medicine.	Specialty Society Website	No	1								

Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, Donovan MI, Fishbain DA, Foley KM, Fudin J, Gilson AM, Kelter A, Mauskop A, O'Connor PG, Passik SD, Pasternak GW, Portenoy RK, Rich BA, Roberts RG, Todd KH, Miaskowski C; American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. J Pain. 2009 Feb;10(2):113-30.	MEDLINE	Yes									
Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. 2009 Feb. NGC:007852 American Academy of Pain Medicine - Professional Association; American Pain Society - Professional Association.	National Guide-lines Clearing-house	Yes									
Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. 2009 Feb. NGC:007852 American Academy of Pain Medicine - Professional Association; American Pain Society - Professional Association.	National Guide-lines Clearing-house	No	1								
Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain." American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Opioid Treatment Guidelines. (referenced by AAFP website)	Specialty Society Website	No	1								

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype. Crews KR, Gaedigk A, Dunnenberger HM, Klein TE, Shen DD, Callaghan JT, Kharasch ED, Skaar TC; Clinical Pharmacogenetics Implementation Consortium. Clin Pharmacol Ther. 2012 Feb;91(2):321-6. doi: 10.1038/clpt.2011.287. Epub 2011 Dec 28	MEDLINE	No		1							
Clinical practice guideline for eating disorders. 2009 Feb 1. NGC:008629 Catalan Agency for Health Information, Assessment and Quality - State/Local Government Agency [Non-U.S.]; Ministry of Health and Consumer Affairs (Spain) - National Government Agency [Non-U.S.].	National Guide-lines Clearing-house	No		1							
Clinical practice guideline: polysomnography for sleep-disordered breathing prior to tonsillectomy in children. 2011 Jul. NGC:008654 American Academy of Otolaryngology - Head and Neck Surgery Foundation - Medical Specialty Society.	National Guide-lines Clearing-house	No		1							
Clinical practice guidelines for quality palliative care. 2004 May (revised 2009 Jan). NGC:007218 National Consensus Project - Disease Specific Society.	National Guide-lines Clearing-house	No					1				

Comparison of health care use and costs in newly diagnosed and established patients with fibromyalgia. White LA, Robinson RL, Yu AP, Kaltenboeck A, Samuels S, Mallett D, Birnbaum HG. J Pain. 2009 Sep;10(9):976-83. Epub 2009 Jun 24.	MEDLINE	No								1	
Consensus guidelines for the selection and implantation of patients with noncancer pain for intrathecal drug delivery. Deer TR, Smith HS, Cousins M, Doleys DM, Levy RM, Rathmell JP, Staats PS, Wallace M, Webster LR. Pain Physician. 2010 May-Jun;13(3):E175-213.	MEDLINE	No				1					
Consistent adherence to guidelines improves opioid dependent patients' first year outcomes. Trafton JA, Humphreys K, Harris AH, Oliva E. J Behav Health Serv Res. 2007 Jul;34(3):260-71. Epub 2007 Jul 4.	MEDLINE	No								1	
Control of pain in adults with cancer. A national clinical guideline. 2000 Jun (revised 2008 Nov). NGC:006856 Scottish Intercollegiate Guidelines Network - National Government Agency [Non-U.S.]. View all guidelines by the developer(s)	National Guide-lines Clearing-house	No				1					
COPD – Chronic obstructive pulmonary disease. In: Pulmonary (acute & chronic). 2009 Jan. NGC:007586 Work Loss Data Institute - For Profit Organization.	National Guide-lines Clearing-house	No		1							
COPD management in the long-term care setting. 2003 (revised 2010). NGC:008398 American Medical Directors Association - Professional Association.	National Guide-lines Clearing-house	No		1							

Designing an automated clinical decision support system to match clinical practice guidelines for opioid therapy for chronic pain. Trafton JA, Martins SB, Michel MC, Wang D, Tu SW, Clark DJ, Elliott J, Vucic B, Balt S, Clark ME, Sintek CD, Rosenberg J, Daniels D, Goldstein MK. Implement Sci. 2010 Apr 12;5:26.	MEDLINE	No								1	
Dextromethorphan poisoning: an evidence-based consensus guideline for out-of-hospital management. Chyka PA, Erdman AR, Manoguerra AS, Christianson G, Booze LL, Nelson LS, Woolf AD, Cobaugh DJ, Caravati EM, Scharman EJ, Troutman WG; American Assiciation of Poison Control Centers. Clin Toxicol (Phila). 2007 Sep;45(6):662-77.	MEDLINE	No								1	
Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. 2010 Feb. NGC:007681 DMD Care Considerations Working Group - Independent Expert Panel.	National Guide-lines Clearing-house	No		1							
Diagnosis and management of headache in adults. A national clinical guideline. 2008 Nov. NGC:006857 Scottish Intercollegiate Guidelines Network - National Government Agency [Non-U.S.].	National Guide-lines Clearing-house	No						1			
Diagnosis and treatment of headache. 1998 Aug (revised 2011 Jan). NGC:008263 Institute for Clinical Systems Improvement - Nonprofit Organization.	National Guide-lines Clearing-house	No						1			

Diagnosis and treatment of headache. 1998 Aug (revised 2011 Jan). NGC:008263 Institute for Clinical Systems Improvement - Nonprofit Organization.	National Guide-lines Clearing-house	No	1								
Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society	Specialty Society Website	No				1					
Diagnostic testing and treatment of low back pain in United States emergency departments: a national perspective. Friedman BW, Chilstrom M, Bijur PE, Gallagher EJ. Spine (Phila Pa 1976). 2010 Nov 15;35(24):E1406-11.	MEDLINE	No								1	
Different components of opioid-substitution treatment predict outcomes of patients with and without a parent with substance-use problems. Trafton JA, Tracy SW, Oliva EM, Humphreys K. J Stud Alcohol Drugs. 2007 Mar;68(2):165-72.	MEDLINE	No								1	
Disease-specific approaches. In: II guidelines for perioperative evaluation. 2007 (revised 2011). NGC:008594 Brazilian Society of Cardiology - Medical Specialty Society.	National Guide-lines Clearing-house	No							1		
Does following research-derived practice guidelines improve opiate-dependent patients' outcomes under everyday practice conditions? Results of the Multisite Opiate Substitution Treatment study. Humphreys K, Trafton JA, Oliva EM. J Subst Abuse Treat. 2008 Mar;34(2):173-9. Epub 2007 May 14.	MEDLINE	No								1	
Drug Misuse: Opioid Detoxification. National Collaborating Centre for Mental Health (UK). Leicester (UK): British Psychological Society; 2008	MEDLINE	No					1				

Effect of nalmefene 20 and 80 mg on the corrected QT interval and T-wave morphology: a randomized, double-blind, parallel-group, placebo- and moxifloxacin-controlled, single-centre study. Matz J, Graff C, Vainio PJ, Kallio A, Højer AM, Struijk JJ, Kanters JK, Andersen MP, Toft E. Clin Drug Investig. 2011 Nov 1;31(11):799-811	MEDLINE	No								1	
Effect of Nalmefene 20 and 80 mg on the Corrected QT Interval and T-Wave Morphology: A Randomized, Double-Blind, Parallel-Group, Placebo- and Moxifloxacin-Controlled, Single-Centre Study. Matz J, Graff C, Vainio PJ, Kallio A, Højer AM, Struijk JJ, Kanters JK, Andersen MP, Toft E. Clin Drug Investig. 2011 Sep 23	MEDLINE	No								1	
EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, Nurmikko T; European Federation of Neurological Societies. Eur J Neurol. 2010 Sep;17(9):1113-e88. Epub 2010 Apr 9. Review.	MEDLINE	No				1					
EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. 2006 Nov (revised 2010 Sep). NGC:008162 European Federation of Neurological Societies - Medical Specialty Society.	National Guide-lines Clearing-house	No						1			
Elbow (acute & chronic). 2003 (revised 2011 Apr 28). NGC:008513 Work Loss Data Institute - For Profit Organization.	National Guide-lines Clearing-house	No				1					

Endometriosis: diagnosis and management. 2010 Jul. NGC:007969 Society of Obstetricians and Gynaecologists of Canada - Medical Specialty Society.	National Guide-lines Clearing-house	No				1					
Espoguia (clinical guidelines for patients with spondyloarthritis). 2010. NGC:008550 Spanish Society of Rheumatology - Medical Specialty Society.	National Guide-lines Clearing-house	No				1					
Establishing "best practices" for opioid rotation: conclusions of an expert panel. Fine PG, Portenoy RK; Ad Hoc Expert Panel on Evidence Review and Guidelines for Opioid Rotation. J Pain Symptom Manage. 2009 Sep;38(3):418-25.	MEDLINE	Yes									
EULAR evidence-based recommendations for the management of fibromyalgia syndrome. Carville SF, Arendt-Nielsen S, Bliddal H, Blotman F, Branco JC, Buskila D, Da Silva JA, Danneskiold-Samsøe B, Dincer F, Henriksson C, Henriksson KG, Kosek E, Longley K, McCarthy GM, Perrot S, Puszczewicz M, Sarzi-Puttini P, Silman A, Späth M, Choy EH; EULAR. Ann Rheum Dis. 2008 Apr;67(4):536-41. Epub 2007 Jul 20. Review.	MEDLINE									1	
Evaluation of musculoskeletal pain management practices in rural nursing homes compared with evidence-based criteria. Decker SA, Culp KR, Cacchione PZ. Pain Manag Nurs. 2009 Jun;10(2):58-64. Epub 2008 Nov 7.	MEDLINE	No								1	
Evaluation of pain management documentation. DeRemer CE, Fleming VH, Brown S, May JR. South Med J. 2011 Sep;104(9):629-33	MEDLINE	No								1	

Evaluation of the acceptability and usability of a decision support system to encourage safe and effective use of opioid therapy for chronic, noncancer pain by primary care providers. Trafton J, Martins S, Michel M, Lewis E, Wang D, Combs A, Scates N, Tu S, Goldstein MK. Pain Med. 2010 Apr;11(4):575-85. Epub 2010 Mar 1.	MEDLINE	No								1	
Evidence-based guideline: treatment of painful diabetic neuropathy. Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. 2011 May 17. NGC:008504 American Academy of Neurology - Medical Specialty Society; American Academy of Physical Medicine and Rehabilitation - Medical Specialty Society; American Association of Neuromuscular and Electrodiagnostic	National Guide-lines Clearing-house	No				1					
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Prevention of falls (acute care). Health care protocol. 2008 Mar (revised 2010 Apr). NGC:007848 Institute for Clinical Systems Improvement - Nonprofit Organization.	National Guide-lines Clearing-house	No		1							

Primary biliary cirrhosis. 2000 Apr (revised 2009 Jul). NGC:007372 American Association for the Study of Liver Diseases - Nonprofit Research Organization.	National Guide-lines Clearing-house	No		1							
Primary care approach to the HIV-infected patient. 2004 (revised 2011 Apr). NGC:008648 New York State Department of Health - State/Local Government Agency [U.S.].	National Guide-lines Clearing-house	No				1					
Primary care clinician adherence to guidelines for the management of chronic musculoskeletal pain: results from the study of the effectiveness of a collaborative approach to pain. Corson K, Doak MN, Denneson L, Crutchfield M, Soleck G, Dickinson KC, Gerrity MS, Dobscha SK. Pain Med. 2011 Oct;12(10):1490-501	MEDLINE	No								1	
Primary care monitoring of long-term opioid therapy among veterans with chronic pain. Krebs EE, Ramsey DC, Miloshoff JM, Bair MJ. Pain Med. 2011 May;12(5):740-6. doi: 10.1111/j.1526-4637.2011.01099.x. Epub 2011 Apr 11	MEDLINE	No								1	
Primary care survey of the value and effectiveness of the Washington State Opioid Dosing Guideline. Morse JS, Stockbridge H, Egan KB, Mai J, Wickizer T, Franklin GM. J Opioid Manag. 2011 Nov-ec;7(6):427-33	MEDLINE	No								1	
Psychotropic drugs for terminally ill patients with respiratory disease. Kanemoto K, Satoh H, Kagohashi K, Kurishima K, Ishikawa H, Ohtsuka M. Tuberk Toraks. 2007;55(1):5-10.	MEDLINE	No								1	

Putting evidence into practice: evidence-based interventions to prevent, manage, and treat chemotherapy- and radiotherapy-induced diarrhea. 2009 Jun 1. NGC:007732 Oncology Nursing Society - Professional Association.	National Guide-lines Clearing-house	No		1							
Putting evidence into practice: evidence-based interventions to prevent, manage, and treat chemotherapy- and radiotherapy-induced diarrhea. 2009 Jun 1. NGC:007732 Oncology Nursing Society - Professional Association.	National Guide-lines Clearing-house	No	1								
Putting evidence into practice: what are the pharmacologic interventions for nociceptive and neuropathic cancer pain in adults? 2009 Dec 1. NGC:007738 Oncology Nursing Society - Professional Association.	National Guide-lines Clearing-house	No				1					
Quality improvement guidelines for transhepatic arterial chemoembolization, embolization, and chemotherapeutic infusion for hepatic malignancy. 2009 Jul. NGC:008334 Society of Interventional Radiology - Medical Specialty Society.	National Guide-lines Clearing-house	No		1							
Racial differences in primary care opioid risk reduction strategies. Becker WC, Starrels JL, Heo M, Li X, Weiner MG, Turner BJ. Ann Fam Med. 2011 May-Jun;9(3):219-25	MEDLINE	No								1	

Randomized trial of web-based training about opioid therapy for chronic pain. Sullivan MD, Gaster B, Russo J, Bowlby L, Rocco N, Sinex N, Livovich J, Jasti H, Arnold R. Clin J Pain. 2010 Jul-Aug;26(6):512-7.	MEDLINE	No								1	
Real-world practice patterns, health-care utilization, and costs in patients with low back pain: the long road to guideline-concordant care. Ivanova JI, Birnbaum HG, Schiller M, Kantor E, Johnstone BM, Swindle RW. Spine J. 2011 Jul;11(7):622-32. Epub 2011 May 20	MEDLINE	No								1	
Recommendations for neuropathic pain treatment. Demarin V, Basić-Kes V, Zavoreo I, Bosnar-Puretić M, Rotim K, Lupret V, Perić M, Ivanec Z, Fumić L, Lusić I, Aleksić-Shihabis A, Kovac B, Ivanković M, Skobić H, Maslov B, Bornstein N, Niederkorn K, Sinanović O, Rundek T; Ad hoc Committee of the Croatian Society for Neurovascular Disorders; Croatian Medical Association. Acta Clin Croat. 2008 Sep;47(3):181-91.	MEDLINE	No				1					
Research gaps on use of opioids for chronic noncancer pain: findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. Chou R, Ballantyne JC, Fanciullo GJ, Fine PG, Miaskowski C. J Pain. 2009 Feb;10(2):147-59. Review.	MEDLINE	No								1	

Scandinavian clinical practice guidelines on general anaesthesia for emergency situations. Jensen AG, Callesen T, Hagemo JS, Hreinsson K, Lund V, Nordmark J; Clinical Practice Committee of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine. Acta Anaesthesiol Scand. 2010 Sep;54(8):922-50. Review.	MEDLINE	No							1		
Screening, diagnosis and referral for substance use disorders. 2003 Aug (revised 2011 Sep). NGC:008745 Michigan Quality Improvement Consortium - Professional Association.	National Guide-lines Clearing-house	No				1					
Sedation and anesthesia in GI endoscopy. 2003 (revised 2008 Nov). NGC:007200 American Society for Gastrointestinal Endoscopy - Medical Specialty Society.	National Guide-lines Clearing-house	No		1							
Sedation and anesthesia in GI endoscopy. 2003 (revised 2008 Nov). NGC:007200 American Society for Gastrointestinal Endoscopy - Medical Specialty Society.	National Guide-lines Clearing-house	No	1								
Sedation and anesthesia in GI endoscopy. 2003 (revised 2008 Nov). NGC:007200 American Society for Gastrointestinal Endoscopy - Medical Specialty Society.	National Guide-lines Clearing-house	No	1								
Self-prescribed and other informal care provided by physicians: scope, correlations and implications. Gendel MH, Brooks E, Early SR, Gundersen DC, Dubovsky SL, Dilts SL, Shore JH. J Med Ethics. 2012 May;38(5):294-8. Epub 2012 Feb 7	MEDLINE	No								1	

SOGC clinical practice guidelines: Substance use in pregnancy: no. 256, April 2011. Wong S, Ordean A, Kahan M; Society of Obstetricians and Gynecologists of Canada. Int J Gynaecol Obstet. 2011 Aug;114(2):190-202	MEDLINE	No							1		
Substance use and dependence among HIV-infected adolescents and young adults. 2009 Mar. NGC:007404 New York State Department of Health - State/Local Government Agency [U.S.].	National Guide-lines Clearing-house	No					1				
Substance use in pregnancy. Wong S, Ordean A, Kahan M; Maternal Fetal Medicine Committee; Family Physicians Advisory Committee; Medico-Legal Committee; Society of Obstetricians and Gynaecologists of Canada. J Obstet Gynaecol Can. 2011 Apr;33(4):367-84	MEDLINE	No							1		
Substance use in pregnancy. 2011 Apr. NGC:008510 Society of Obstetricians and Gynaecologists of Canada - Medical Specialty Society.	National Guide-lines Clearing-house	No					1				
Substance use in pregnancy. 2011 Apr. NGC:008510 Society of Obstetricians and Gynaecologists of Canada - Medical Specialty Society.	National Guide-lines Clearing-house	No	1								
Supporting clients on methadone maintenance treatment. 2009 Jul 1. NGC:007659 Registered Nurses' Association of Ontario - Professional Association.	National Guide-lines Clearing-house	No					1				
Supporting clients on methadone maintenance treatment. 2009 Jul 1. NGC:007659 Registered Nurses' Association of Ontario - Professional Association.	National Guide-lines Clearing-house	No	1								

Supporting clients on methadone maintenance treatment. 2009 Jul 1. NGC:007659 Registered Nurses' Association of Ontario - Professional Association.	National Guide-lines Clearing-house	No	1								
Symptom management for the adult patient dying with advanced chronic kidney disease: a review of the literature and development of evidence-based guidelines by a United Kingdom Expert Consensus Group. Douglas C, Murtagh FE, Chambers EJ, Howse M, Ellershaw J. Palliat Med. 2009 Mar;23(2):103-10. Review.	MEDLINE	No					1				
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The cost of concordance with opiate substitution treatment guidelines. Barnett PG, Trafton JA, Humphreys K. J Subst Abuse Treat. 2010 Sep;39(2):141-9. Epub 2010 Jul 3.	MEDLINE	No								1	
The course of opioid prescribing for a new episode of disabling low back pain: opioid features and dose escalation. Cifuentes M, Webster B, Genevay S, Pransky G. Pain. 2010 Oct;151(1):22-9. Epub 2010 Aug 11.	MEDLINE	No								1	
The Guidelines for Treatment of Chronic Pain, ACP Guidelines that link to website for AZ	Specialty Society Website	No								1	

The pharmacological mechanisms of electroacupuncture. Fukazawa Y, Maeda T, Kishioka S. Curr Opin Investig Drugs. 2009 Jan;10(1):62-9. Review.	MEDLINE	No								1	
The treatment of symptomatic osteoporotic spinal compression fractures. 2010 Sep 24. NGC:008195 American Academy of Orthopaedic Surgeons (AAOS) - Medical Specialty Society.	National Guide-lines Clearing-house	No				1					
The U.S. Mandatory Guidelines for Federal Workplace Drug Testing Programs: current status and future considerations. Bush DM. Forensic Sci Int. 2008 Jan 30;174(2-3):111-9. Epub 2007 Apr 16.	MEDLINE	No		1							
The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of substance use and related disorders. Part 2: Opioid dependence. Soyka M, Kranzler HR, van den Brink W, Krystal J, Möller HJ, Kasper S; WFSBP Task Force on Treatment, Guidelines for Substance Use Disorders. World J Biol Psychiatry. 2011 Apr;12(3):160-87. Erratum in: World J Biol Psychiatry. 2011 Aug;12(5):397. Lingford-Hughes, Anne [removed].	MEDLINE	No					1				

Treatment of patients with substance use disorders, second edition. American Psychiatric Association. Kleber HD, Weiss RD, Anton RF Jr, George TP, Greenfield SF, Kosten TR, O'Brien CP, Rounsaville BJ, Strain EC, Ziedonis DM, Hennessy G, Connery HS, McIntyre JS, Charles SC, Anzia DJ, Cook IA, Finnerty MT, Johnson BR, Nininger JE, Summergrad P, Woods SM, Yager J, Pyles R, Cross CD, Peele R, Shemo JP, Lurie L, Walker RD, Barnovitz MA, Gray SH, Saxena S, Tonnu T, Kunkle R, Albert AB, Fochtmann LJ, Hart C, Regier D; Work Group on Substance Use Disorders; American Psychiatric Association; Steering Committee on Practice Guidelines. Am J Psychiatry. 2007 Apr;164(4 Suppl):5-123. Review. No abstract available.	MEDLINE	No								1	
Type 2 diabetes. The management of type 2 diabetes. 2004 Jun 17 (revised 2009 May). NGC:007460 National Clinical Guideline Centre for Acute and Chronic Conditions - National Government Agency [Non-U.S.].	National Guide-lines Clearing-house	No		1							
Utah clinical guidelines on prescribing opioids for treatment of pain. Rolfs RT, Johnson E, Williams NJ, Sundwall DN; Utah Department of Health. J Pain Palliat Care Pharmacother. 2010 Sep;24(3):219-35.	MEDLINE	Yes									

VA/DoD clinical practice guideline for management of concussion/mild traumatic brain injury. 2009 Apr. NGC:007713 Department of Defense - Federal Government Agency [U.S.]; Department of Veterans Affairs - Federal Government Agency [U.S.]; Veterans Health Administration - Federal Government Agency [U.S.].	National Guide-lines Clearing-house	No				1					
VA/DoD clinical practice guideline for management of opioid therapy for chronic pain. 2003 Mar (revised 2010 May). NGC:007864 Department of Defense - Federal Government Agency [U.S.]; Department of Veterans Affairs - Federal Government Agency [U.S.]; Veterans Health Administration - Federal Government Agency [U.S.].	National Guide-lines Clearing-house	Yes									
VA/DoD clinical practice guideline for management of opioid therapy for chronic pain. 2003 Mar (revised 2010 May). NGC:007864 Department of Defense - Federal Government Agency [U.S.]; Department of Veterans Affairs - Federal Government Agency [U.S.]; Veterans Health Administration - Federal Government Agency [U.S.].	National Guide-lines Clearing-house	No	1								
VA/DoD clinical practice guideline for management of post-traumatic stress. 2004 Jan (revised 2010 Oct). NGC:008249 Department of Defense - Federal Government Agency [U.S.]; Department of Veterans Affairs - Federal Government Agency [U.S.]; Veterans Health Administration - Federal Government Agency [U.S.].	National Guide-lines Clearing-house	No		1							

VA/DoD clinical practice guideline for management of post-traumatic stress. 2004 Jan (revised 2010 Oct). NGC:008249 Department of Defense - Federal Government Agency [U.S.]; Department of Veterans Affairs - Federal Government Agency [U.S.]; Veterans Health Administration - Federal Government Agency [U.S.].	National Guide-lines Clearing-house	No	1								
VA/DoD clinical practice guideline for management of substance use disorders (SUD). 2001 Sep (revised 2009 Aug). NGC:007712 Department of Defense - Federal Government Agency [U.S.]; Department of Veterans Affairs - Federal Government Agency [U.S.]; Veterans Health Administration - Federal Government Agency [U.S.]. View all guidelines by the developer(s)	National Guide-lines Clearing-house	No					1				
VA/DoD clinical practice guideline for management of substance use disorders (SUD). 2001 Sep (revised 2009 Aug). NGC:007712 Department of Defense - Federal Government Agency [U.S.]; Department of Veterans Affairs - Federal Government Agency [U.S.]; Veterans Health Administration - Federal Government Agency [U.S.].	National Guide-lines Clearing-house	No				1					
VA/DoD clinical practice guideline for management of substance use disorders (SUD). 2001 Sep (revised 2009 Aug). NGC:007712 Department of Defense - Federal Government Agency [U.S.]; Department of Veterans Affairs - Federal Government Agency [U.S.]; Veterans Health Administration - Federal Government Agency [U.S.].	National Guide-lines Clearing-house	No				1					

VA/DoD clinical practice guideline for the management of stroke rehabilitation. 2003 Feb (revised 2010 Oct). NGC:008250 American Heart Association - Professional Association; American Stroke Association - Disease Specific Society; Department of Defense - Federal Government Agency [U.S.]; Department of Veterans Affairs - Federal Government Agency [U.S.]; Veterans Health Administration - Federal Government Agency [U.S.].	National Guide-lines Clearing-house	No		1							
Valproic acid poisoning: an evidence-based consensus guideline for out-of-hospital management. Manoguerra AS, Erdman AR, Woolf AD, Chyka PA, Caravati EM, Scharman EJ, Booze LL, Christianson G, Nelson LS, Cobaugh DJ, Troutman WG; American Association of Poison Control Centers. Clin Toxicol (Phila). 2008 Aug;46(7):661-76. Review.	MEDLINE	No								1	
Whole fentanyl patch ingestion: a multi-center case series. Mrvos R, Feuchter AC, Katz KD, Duback-Morris LF, Brooks DE, Krenzelok EP. J Emerg Med. 2012 May;42(5):549-52. Epub 2011 Jun 16	MEDLINE	No								1	
Work-related complex regional pain syndrome (CRPS): diagnosis and treatment. 1997 Jun (revised 2011 Oct 1). NGC:008719 Washington State Department of Labor and Industries - State/Local Government Agency [U.S.].	National Guide-lines Clearing-house	No						1			

World Gastroenterology Organisation Global Guideline: irritable bowel syndrome: a global perspective. 2009 Apr. NGC:007472 World Gastroenterology Organisation - Medical Specialty Society.	National Guide-lines Clearing-house	No		1							

Appendix 3. Quality of Guideline Literature Searches

Table: AMSTAR Ratings for Guidelines Included in Review*

	ASA	NICE Neuro	APS-AAPM	ICSI	UofM	EFNS	WLDI	ACOEM	ASIPP	AGS	Canada	Utah	Fine	CPS
1. Was an 'a priori' design provided?	Y	Y	Y	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	Y
2. Was there duplicate study selection and data extraction?	?	?	Y	?	?	Y	?	?	Y	N	Y	?	?	Y
3. Was a comprehensive literature search performed?	?	?	Y	Y	Y	Y	Y	Y	?	Y	Y	N	?	?
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	?	?	?	?	?	?	Y	N	?	?	N	N	?	?
5. Was a list of studies (included and excluded) provided?	N	N	N	N	N	Y	N	N	N	N	N	N	N	N
6. Were the characteristics of the included studies provided?	N	Y	Y	Y	N	Y	N	N	N	N	N	N	N	N
7. Was the scientific quality of the included studies assessed and documented?	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Y	Y	Y	?	?	?	?	?	Y	Y	Y	N	?	?
9. Were the methods used to combine the findings of studies appropriate?	Y	Y	?	?	?	?	?	n/a	?	?	?	?	?	?
10. Was the likelihood of publication bias assessed?	N	N/A	N	N	N	N	?	n/a	N	N	?	N	?	?
11. Was the conflict of interest stated?	N	?	N	N	N	N	N	N	N	N	N	N	N	N
Score on 1 to 11 Scale	4	5	6	4	3	6	4	2	3	4	5	1	1	2
Percentage of Highest Possible, Excluding N/A Questions	4/11 =36%	5/10 =50%	6/11 =55%	4/11 =36%	3/11 =27%	6/11 =55%	4/11 =36%	2/9 = 22%	3/11 =27%	4/11 =36%	5/11 = 45%	1/11 =09%	1/11 =09%	2/11 =18%

*Response codes: Y = Yes, N = No, ? = unable to answer, N/A = Not applicable (not included in denominator)

The VA guideline is based on the literature review performed for the APS-AAPM guideline. The California Medical Treatment Utilization Schedule guideline for opioids is based on the guideline from the Work Loss Data Institute. No lit search was described for any of the three WA state guidelines, including the Washington State Interagency Guideline and the two guidelines listed on the Washington State Labor and Industries website. Not literature searches were available for the American College of Physicians PIER guideline or the Colorado workers' compensation guideline.

Appendix 4. Quality of Literature Searches from Systematic Reviews

Table: AMSTAR Ratings

	Noble 2008	Noble 2010	Dembe	Papel-eontiou	Turk	Starrels	Fishbain	Kalso	Furlan 2006
1. Was an 'a priori' design provided?	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Was there duplicate study selection and data extraction?	Y	Y	N	Y	Y	Y	Y	?	Y
3. Was a comprehensive literature search performed?	Y	Y	Y	Y	N	Y	Y	Y	Y
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Y	Y	N	?	N	Y	?	?	?
5. Was a list of studies (included and excluded) provided?	N	Y	N	N	N	N	Y	N	?
6. Were the characteristics of the included studies provided?	Y	Y	Y	Y	Y	Y	Y	Y	N
7. Was the scientific quality of the included studies assessed and documented?	Y	Y	N	Y	N	Y	Y	Y	Y
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Y	Y	N	Y	?	Y	Y	Y	Y
9. Were the methods used to combine the findings of studies appropriate?	Y	Y	?	Y	?	N	?	Y	Y
10. Was the likelihood of publication bias assessed?	?	Y	N	Y	N	?	N	N	Y
11. Was the conflict of interest stated?	N	Y	N	Y	N	Y	N	N	Y
Score on 1 to 11 Scale	9	11	3	9	3	8	7	6	8
Percentage of Highest Possible, Excluding N/A Questions	9/11 =82%	11/11 =100%	3/11 =27%	9/11 =82%	3/11 =27%	8/11 =73%	7/11 =64%	6/11 =55%	8/11 =73%

*Response codes: Y = Yes, N = No, ? = unable to answer, N/A = Not applicable (not included in denominator)

Appendix 5. Information from FDA Warnings

All information below is taken from FDA Drug Approval Reports or FDA Drug Safety Alerts. If the latter source was used, it is indicated as such. We reviewed Drug Safety Alerts from 2009 to 2012.

For ALL opioids, the FDA warns about respiratory depression, hypotension and death; abuse and diversion; interactions with alcohol and other drugs; and dependence.

Morphine: MS Contin, Kadian, Avinza, Oramorph SR

- Can be abused, legal or illicit
- Not intended for use as prn analgesic
- 100 and 200 mg tablets are to be used only in opioid-tolerant patients
- Taking broken, chewed, crushed MS Contin tabs leads to overdose and is potentially fatal
- Kadian and Avinza capsule content can be taken sprinkled in apple juice but pellets cannot be chewed for the same reason
- Avinza should not be used with alcohol, which can induce rapid release of morphine and overdose
- Safety Alerts 2011: All drugs with long-acting formulations will soon be subject to "Risk Evaluation and Mitigation Strategy" or REMS policy. Concerns involve misuse, overdose, and safe storage and disposal.

Oxycodone: Roxicodone, OxyContin, Percodan, Oxycodone hydrochloride

- Potential for abuse similar to morphine
- Long-acting formulations – only for moderate to severe continuous pain, not prn
- 60 and 80 mg sustained release tabs are only to be used in opioid-tolerant patients
- SR tabs must be swallowed whole. Breaking, crushing or dissolving tabs results in potentially fatal overdose
- concomitant use with cytochrome P450 3A4 inhibitors such as macrolide antibiotics and protease inhibitors may result in an increase in oxycodone plasma concentrations and may cause potentially fatal respiratory depression
- Safety Alerts 2011: All drugs with long-acting formulations will soon be subject to "Risk Evaluation and Mitigation Strategy" or REMS policy. Concerns involve misuse, overdose, and safe storage and disposal.

Fentanyl: Fentora, Onsolis, Actiq, Abstral (transmucosal), Duragesic (patch)

- Abuse liability similar to other opioid analgesics.
- Use with cytochrome P450 3A4 inhibitors such as macrolide antibiotics and protease inhibitors may cause fatal respiratory depression.
- Immediate release preparations are only FDA approved for use in cancer patients due high abuse potential.
- Due to the risk of fatal respiratory depression, immediate release preparations are contraindicated in opioid non-tolerant patients
- Immediate release preparations are available only through a restricted program called the TIRF REMS Access program. Outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors are required to enroll in the program
- Duragesic should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to Duragesic 25 mcg/h.

- Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid.
- Safety Alert 2011: All drugs with long-acting formulations, including fentanyl patch, will soon be subject to "Risk Evaluation and Mitigation Strategy" or REMS.
- Safety Alert 2007: FDA has issues a Public Health Advisory in 2005 due to high number of fatal overdoses among users of fentanyl patch. Overdoses can be caused by exposure to heat, changing patch too often, using extra patches. Number of fatal overdoses remained high in the years following the Advisory.

Hydromorphone: Dilaudid, Palladone, Exalgo
- Dilaudid HP is for use in opioid tolerant patients only
- Safety Alerts 2011: All drugs with long-acting formulations will soon be subject to "Risk Evaluation and Mitigation Strategy" or REMS policy. Concerns involve misuse, overdose, and safe storage and disposal.
- Safety Alert: Palladone marketing was suspended due to the fact that alcohol disrupted the extended release system, leading to rapid release and overdose.

Meperidine: Demerol
- Use in patients with SVT can increase ventricular response
- Can aggravate preexisting seizure disorder

Methadone: Diskets, Dolophine, Methadose
- Death may occur during initiation of methadone treatment due to respiratory or cardiac effects of methadone and too-rapid titration without appreciation for the long half-life of methadone
- Respiratory depression is the chief hazard associated with methadone administration.
- QT interval prolongation and torsades de pointes - most cases involve patients being treated with large, multiple daily doses of methadone
- When used for the treatment of opioid addiction in detoxification or maintenance programs, should be dispensed in oral form only by opioid treatment certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority.
- Safety Alerts 2011: All drugs with long-acting formulations will soon be subject to "Risk Evaluation and Mitigation Strategy" or REMS policy. Concerns involve misuse, overdose, and safe storage and disposal.
- Safety Alert 2006: Public Health Advisory issued in 2006 specifically for methadone use for pain treatment due to high number of fatal overdoses.

Oxymorphone: Opana
- Opana ER has black box warning similar to other sustained release opioids – not prn, not to be broken, crushed, etc, not to be used with alcohol
- Safety Alerts 2011: All drugs with long-acting formulations will soon be subject to "Risk Evaluation and Mitigation Strategy" or REMS policy. Concerns involve misuse, overdose, and safe storage and disposal.

Codeine
- Ultra-rapid metabolizers (genetic, up to 10% of general population, higher in some small ethnic groups) may have very rapid elevations of morphine levels after intake, resulting in overdose symptoms at usual dose
- Careful monitoring is necessary when prescribed with P-450 enzyme inducers or inhibitors

Pentazocine

- Risk of hallucinations, seizures, porphyria attacks, elevated blood pressure
- Tylenol related warnings due to use in combination pills

Propoxyphene

- Overdose frequent - many of the propoxyphene related deaths have occurred in patients with previous histories of mental illness and/ or on other CNS-depressant drugs. Do not prescribe propoxyphene for patients who are suicidal or have a history of suicidal ideation.
- The levels of propoxyphene can be increased by strong CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazadone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil). Patients receiving propoxyphene and any CYP3A4 inhibitors should be carefully monitored for an extended period of time and dosage adjustments should be made
- Safety Alert 2010: FDA plans to withdraw propoxyphene from the market due to safety concerns.

Tramadol

- Seizure risk within the recommended dosage range. Concomitant use of tramadol increases the seizure risk in patients with epilepsy, CNS disease or taking selective serotonin re-uptake inhibitors, tricyclic antidepressants and other tricyclic compounds (e.g., cyclobenzaprine, promethazine), other opioids, MAO inhibitors, neuroleptics, or any other drugs that reduce seizure threshold
- Suicide risk: do not prescribe ULTRAM ER for patients who are suicidal or addiction-prone
- Serotonin Syndrome Risk - may occur with the use of tramadol products, particularly with concomitant use of serotonergic drugs

Source: Drugs@FDA, FDA Approved Drug Products. available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?CFID=2065805&CFTOKEN=a5470174d8edc8a2-57D97DA0-5056-9B01-A3441510BB681CCD#apphist, last accessed May 13, 2012.

Safety Alerts:

http://www.fda.gov/NewsEvents/Speeches/ucm254856.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=morphine&utm_content=14

http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm252649.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=oxycodone&utm_content=12

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm234337.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=oxycodone&utm_content=20

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm114961.htm

http://www.fda.gov/ICECI/CriminalInvestigations/ucm260715.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=fentanyl&utm_content=12

http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm078366.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=fentanyl&utm_content=44

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm051743.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=hydromorphone&utm_content=4

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm124346.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=methadone&utm_content=7