AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

Opioids

Effective Date: April 20, 2017

CONTRIBUTORS

Editor-in-Chief:
Kurt T. Hegmann, MD, MPH, FACOEM, FACP

Evidence-based Practice Opioids Panel Chair:
Michael S. Weiss, MD, MPH, FACOEM, FAAPMR, FAANEM

Evidence-based Practice Opioids Panel Members:
Kirk Bowden, PhD, NAADAC
Fernando Branco, MD
Kimberly DuBrueler, PharmD, RPh
Charl Els, MBChB, FCPsych, MMed Psych, ABAM, MROCC
Steven Mandel, MD, FACOEM, FAAN, FAADEP
David W. McKinney, MD, MPH
Rafael Miguel, MD
Kathryn L. Mueller, MD, MPH, FACOEM
Robert J. Nadig, MD, MPH, FACOEM
Michael I. Schaffer, PhD, MS, DABFT, NRCC-TC
Larry Studt, MD
Russell L. Travis, MD
Thomas Winters, MD, FACOEM, FACPM

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

Methodology Committee Consultant:
Jeffrey S. Harris, MD, MPH, FACOEM

Research Conducted By:
Kurt T. Hegmann, MD, MPH, FACOEM, FACP
Matthew S. Thiese, PhD, MSPH
Ulrike Ott, PhD, MSPH
Atim C. Effiong, MPH
Deborah G. Passey, MS
William G. Caughey, MS
Holly Uphold, PhD
Alzina Koric, MPP
Zac Carter, BS
Zachary C. Arnold, BS
Katherine Schwei, BS
Kylee Tokita, BS

Leslie M. Cepeda-Echeverria
Ninoska De Jesus
Jeremiah L. Dortch, BS
Pranjal Abhinav Muthe
Harkomal Kaur
Emilee Eden, BS
Michael Northrup
Jenna K. Lindsey

Specialty Society and Society Representative Listing:

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

American Academy of Family Physicians
Robert L. Rich, Jr., MD, FAAFP

American Academy of Physical Medicine and Rehabilitation
Clinical Practice Guidelines Review Committee
Elissa J. Charbonneau, DO, MS
Joseph Feinberg, MD
Alan Novick, MD
Armando Miciano, MD, FAAPMR
K. Rao Poduri, MD, FAAPMR

American Association of Occupational Health Nurses
Kathleen Golden McAndrew, DNP, ANP-C, COHN-S, CCM, FAAOHN, FAANP

American Board of Independent Medical Examiners
Mohammed I. Ranavaya, MD, JD, MS, FRCPI, CIME

American College of Physicians
Michael Fingerhood, MD, FACP, AAHIVS

American Society of Addiction Medicine
Edward C. Covington, MD
Michael Weaver, MD, DFASAM

American Society of Anesthesiologists

American Association of Neurological Surgeons and Congress of Neurological Surgeons – Joint Section on Pain
Andre Machado, MD
Jennifer Sweet, MD

The American Occupational Therapy Association, Inc.
Joyce M. Engel, PhD, OT/L

Other Reviewers:
Stephen V. Cantrill, MD, FACEP
Benjamin Hatten, MD, MPH
Paul Papanek, MD, MPH, FACOEM
Michael Turturro, MD

Table of Contents

Overview

This Opioids Treatment Guideline is designed to provide health care providers who are the primary target users of this guideline with evidence-based guidance on the use of opioids for treatment of working age adults who have acute, subacute, chronic, or post-operative pain. While the primary patient population target is working adults, it is recognized that this guidance may apply more broadly. This guideline does not address pain associated with malignancy, although the U.S. Food and Drug Administration (FDA) has recognized that there does not appear to be evidence that cancer-related, non-terminal pain should be treated differently.[1] Pain has been defined as an "unpleasant sensory and emotional experience,"[2] and has been traditionally thought of as associated with tissue damage, although it may also occur due to central nervous system (CNS) and psychological causes.

Topics of this guideline include evaluations of: baseline patient evaluation, comparative effectiveness of opioids, indications for use, informed consent, opioid treatment agreements, benefits, harms and adverse effects, dose escalation, dose limits, mortality, risk factors, screening tools, drug screening and monitoring, intrathecal pumps, tapering and safety in working populations. This guideline does not

address comprehensive pain management including pharmacological and nonpharmacological methods for patients. Instead, those are addressed by disorder in other chapters of the ACOEM Practice Guidelines. It is recognized that there are differences in workers' compensation systems.[3] There also are regional differences in treatment approaches.[4-6] [961, 962] The Evidence-based Practice Opioids Panel and the Research Team have complete editorial independence from the American College of Occupational and Environmental Medicine (ACOEM) and Reed Group, neither of which have influenced the guideline. The literature is routinely monitored and formally searched at least annually for evidence that would overturn this guidance. The guideline is planned to be updated at least every three years or more frequently should evidence require it.

The health questions for acute, subacute, chronic and post-operative pain addressed by this guideline are:

- What evidence supports the need for a history and physical before prescribing opioids?
- Are opioids superior to other medications or other treatments for pain relief and functional improvement?
- What evidence supports use of these medications in safety sensitive jobs?
- Is screening for risk factors effective for reducing adverse effects of treatment from opioids?
- What is the dose-response relationship between morphine-equivalent dose and fatalities, overdoses and other adverse effects?
- What evidence addresses the balance of risk and benefits of opioid use for acute, subacute, chronic and post-operative pain?
- What evidence supports the use of opioids for treatment of acute, subacute, chronic and post-operative non-malignant pain?
- Are opioid treatment agreements (opioid contract, doctor/patient agreement, or informed consent) effective?
- What is the prevalence of aberrant urine drug testing results among patients using opioids for treatment of chronic pain?
- What evidence supports the use of intrathecal drug delivery systems for treatment of chronic, non-malignant pain?
- What tapering regimens are effective for weaning off opioids?

A detailed methodology document used for guideline development including evidence selection, scoring, incorporation of cost considerations,[7] and formulation of recommendations is available on the web as a full-length document [8] and also summarized.[9, 10] [963] The only noteworthy additions regarding this guideline are inclusion of large epidemiological studies for evidence of harms used for guidance and a change in the databases searched. All evidence in the prior opioids guidelines [11-19] [964] [965] from 7 databases searched was included in this Guideline (Medline, EBM Online, Cochrane, TRIP, CINAHL, EMBASE, PEDro). Additionally, new comprehensive searches for evidence were performed with both Pubmed and Google Scholar up through October 2013 to help assure complete capture. There was no limit on year of publication. Search terms are listed with each table of evidence. A more detailed search strategy is available in ACOEM's Methodology (https://www.acoem.org/guidelines_methodology.aspx).

Guidance is developed with sufficient detail to facilitate assessment of compliance [Institute of Medicine (IOM] and auditing/monitoring [Appraisal of Guidelines for Research and Evaluation (AGREE)]. [7, 20] Alternative options to manage conditions are provided succinctly below when comparative trials are available, however, alternative management strategies are provided in greater detail in other guidelines. [11-19] [964]

This guideline has undergone extensive external peer review. All AGREE, [22] IOM, [26] AMSTAR, and GRADE criteria were adhered to. In accordance with the IOM's Trustworthy Guidelines, detailed records are kept, including responses to external peer reviewers.[20]

Summary of Recommendations and Evidence

The Evidence-based Practice Opioids Panel has 100% agreement on these recommendations. Recommendations are based on critically appraised higher quality research evidence and on expert consensus observing First Principles(9) [963] when higher quality evidence was unavailable or inconsistent. **The reader is cautioned to utilize the more detailed indications, specific appropriate diagnoses, temporal sequencing, prior testing or treatment, and contraindications that are elaborated in more detail in the body of this Guideline in using these recommendations in clinical practice or medical management.** These recommendations are not simple "yes/no" criteria, and the evidence supporting them is in nearly all circumstances developed from typical patients, not unusual situations or exceptions.

Recommendations are made under the following categories: [8, 9][963]

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

Basic Principles and Definitions

Aberrant Drug Behaviors: Departure from strict adherence to the prescribed therapeutic plan of care. These behaviors range from self-escalation of dose, using medication for purposes other than prescribed, and hoarding to overt diversion. [21, 22]

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

Acute pain: For purposes of these guidelines, this is defined as pain within the first month.

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

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

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

2. Evidence of one or more of a group of associated behaviors, including:
   a. Manipulation of the treating physician or medical system for the purpose of obtaining additional drug (e.g., altering prescriptions),
   b. Dose escalation,

c. Acquisition of drugs from other medical sources or from a non-medical source,
d. Drug hoarding or sales, and/or
e. Unapproved use of other drugs (particular alcohol or other sedatives/hypnotics) during opioid therapy.

Advocagenesis: Influences that are conscious or unwitting influences of lawyers and/or litigation processes on patients, including injured workers, that make the clinical presentation foment, worse, prolonged, or in some other manner, worse than would otherwise be.[25] Examples of these influences include overt manufacture of symptoms, instructions from legal counsel to misstate facts, and instructions to not comply with treatment. Advocagenesis is parallel to iatrogenesis.

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

Dependency: Drug dependence means that a person needs a drug to function normally. Abruptly stopping the drug leads to withdrawal symptoms.[26]

Iatrogenesis: Inadvertent and preventable induction of disease or complications by the medical treatment or procedures of a physician, surgeon or other healthcare provider.(27) Iatrogenesis usually refers to acts by which physicians and other health professionals cause or prolong undesirable events in patients. This includes failure to recognize chronic pain as an expression of emotional distress. The term "social iatrogenesis" was suggested in 1976 as a descriptor for illness caused or prolonged by wider sociopolitical inputs, which could also include marketing-induced demand.[27, 28]

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

Medicalization: A normal condition of life that is transformed in the mind of the patient into a disease or disorder. Also, known as pathologization, this includes expressions of emotional distress as chronic pain. For example, medicalization of low back pain may lead the sufferer to believe that an abnormality is present of sufficient gravity to require ongoing medical treatment such as the use of opioids."[29, 30]

Opioids: Opioids are derived from the opium poppy and have long been used to treat pain. They are potent analgesics widely viewed as helpful in managing moderate to severe acute pain and cancer pain.[13] They reduce the intensity of pain signals reaching the brain and affect those brain areas controlling emotions. Effects include diminishing reactions to painful stimuli, elevating mood, sedation and reduction in anxiety.[31]

Opioid withdrawal: Opioid withdrawal is a constellation of symptoms and signs that may occur with cessation of ongoing opioid use, whether in the setting of medical management of pain, during opioid agonist therapy for opioid use disorder, in the context of private recreational use, or following attempts to self-treat symptoms of mental disorders with opioids. [133] Signs and symptoms may include: 1) Dysphoric mood, 2) nausea and/or vomiting,3) muscle aches, 4) lacrimation or rhinorrhea, 5) pupillary dilation, piloerection and/or sweating, 6) diarrhea, 7) yawning, 8) fever and 9) insomnia. Opioid withdrawal is distinct from opioid use disorder and does not necessarily occur in the presence of the drug-seeking behavior associated with opioid use disorder.

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

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

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

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

Opioid Use Disorder: A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. A persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of an opioid.
    Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic opioid withdrawal syndrome
    b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms." [133]
    Note: The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) definition no longer makes a distinction between substance abuse and substance dependence. Both of these conditions are now included within Substance Use Disorder, which can be measured on a continuum from mild to severe. [133, 134].

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

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

History of Opioids

Opium is derived from the opium poppy and its use for the treatment of pain was described in the Ebers Papyrus more than 4,000 years ago. Opiate refers to natural opium alkaloids, while opioid refers to either natural or synthetic derivatives. Opioid use was largely unregulated until increased recognition of

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

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

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

Beginning in the 1990s, there were a series of legal actions alleging that providers were undertreating pain. In 1999, the Oregon Board of Medical Examiners disciplined a physician for not prescribing enough pain medication; similarly, other lawsuits for undertreatment of pain have been filed.[37-39] In 2001, a California jury convicted a doctor of elder abuse for undertreating a patient's pain.[40] In 2000, the Veterans Administration launched the National Pain Management Strategy, adopting the increasingly common recognition of pain as the "5th Vital Sign" and calling providers "barriers to pain treatment" due to fear of patient addiction and adverse effects.[41, 42] Also, in 2000, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) issued a pain management standard requiring recognition of the rights of patients to appropriate pain management.[43]

Later, the JCAHO provided standards for the evaluation of pain and provisions for withholding accreditation, which would result in threatened/punitive financial consequences for health care institutions that do not meet them. These regulations require health care organizations to implement and give priority to pain management strategies across all departments. These strategies must include ongoing education of providers and patients, pain assessment throughout the hospitalization, discharge planning that includes pain management, and quality management programs that measure progress.[44]

Over the past 15 years, there are increasing numbers of guidelines and policies that have been developed to address this epidemic.[13, 45-71] The Federation of State Medical Boards has recently detailed its model policy for opioids used for chronic pain.[72] All states have now creaed "prescription monitoring programs" with controlled substances databases, although the impact of these actions remains somewhat unclear.

Impact

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

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

than directed by their doctor, while 72% had leftover medication and 71% retained the leftover medication.[981] [961]

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

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

Opioid use and deaths associated with opioids have risen closely together.[962, 993-999] [1000, 1001] Deaths related to opioid overdoses more than tripled from 1999 through 2006 in the U.S., increasing from 4,000 to 13,800 and further increasing to 33,091 deaths in 2015. [1002], Population-based studies have reported opioids have surpassed motor vehicle crashes as the cause of death in several states. [981, 1001, 1003-1006] There were a total of 52,404 prescription drug related overdoses in 2015, and 33,091 (63.1%) of these were opioid related.[961] More men die from drug overdoses than women, although the percentage increase in deaths has been greater among women since 1999 and more women have died from drug overdoses than from motor vehicle injuries each year since 2007.[1007] Deaths are not confined to urbanized areas, as drug overdose deaths in rural Virginia increased 300% from 1997 to 2003, most of which (74.0%) were prescription opioids. [1008] Also, most opioid-related deaths in Connecticut occurred in suburban towns and rural areas.[1009]

Recommendations

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

Conducting Comprehensive History and Physical Evaluation

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

Indications – All patients being considered for opioid therapy.

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

Harms – Negligible.

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

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – High

Rationale for Recommendation

Appropriate pain management is a responsibility of those treating pain. It requires adequate knowledge about, and assessments of, a patient's pain and function. Pain management often requires multiple pharmacological and nonpharmacological methods to safely and appropriately control pain that should be evaluated.[1, 72, 114, 115] A comprehensive evaluation and documentation includes: a history, prior treatment, vocation, avocational activities, current functional level, past medical history, family history, social history including substance(s) use (tobacco, alcohol, and illicit substances), review of systems, laboratory testing, and imaging studies as appropriate.[71, 72, 114-117] This systematic approach should result in a clear diagnosis to treat as evidence allows. [72, 114, 116] In many cases of chronic pain, the most accurate diagnosis may be a symptom, e.g., chronic low back pain. An evidence-based treatment plan should focus on addressing that diagnosis. Obstacles for treatment and rehabilitation should be identified and addressed.

When considering prescribing an opioid, the treating physician should have a clear, quantified treatment plan and functional goals.[49, 72, 115, 118, 119] SMART goals have been recommended – **S**pecific, **M**easurable, **A**chievable, **R**ealistic, and **T**ime-based. It is also recommended that the documentation include a discussion and plan for the 5As: **A**nalgesia (reduction in pain), **A**ctivity increase (improved in level of functional and meaningful activities, especially in work-related injuries returning to work, even part-time or gradually),[120] **A**dverse effects (any side effects, especially constipation, dizziness, confusion and inability to function due to the opioids),[86] **A**berrant behaviors (self-dose escalation, poor compliance, continued 'pain behaviors' despite use of opioids) and **A**ffect (mood changes such as worsening of depression).[72, 115]

Documentation should also include informed consent,[71, 72, 121] including an agreed-on opioid treatment contract (for subacute or chronic pain patients), and monitoring results (see detailed sections below).[71, 72] Provider and organizational barriers to implement this recommendation are few.

Evidence for Conducting Comprehensive History and Physical Evaluation
There are no quality studies for this analysis.

Workers in Safety-Critical Jobs

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

Use of Opioids by Workers in Safety-critical Jobs

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

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

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

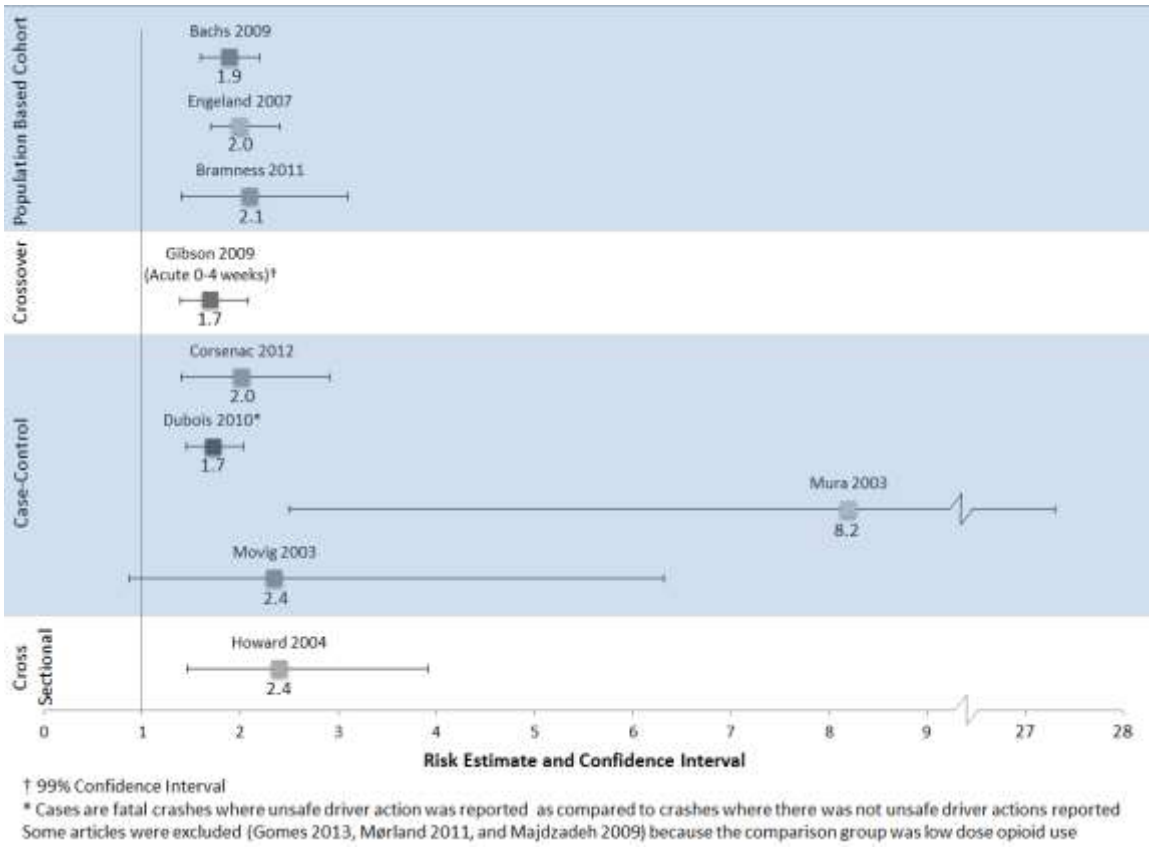
Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – Moderate

Rationale for Recommendation

Opioids are centrally acting drugs that produce sedation and otherwise hinder or impair higher cognitive function. [85-87, 122, 126, 160-165] Both strong and weak opioids have been consistently associated with increased risk of motor vehicle collisions (MVCs) in all large epidemiological studies of working age adults sufficiently powered to detect MVC risk with the risk estimates ranging from 29 to more than 800% increased risk (see Figure 1). [82-84] One study, although likely underpowered with only 28 motorists being prescribed opiates (8 cases vs. 20 controls), still had a risk estimate of 2.3-fold (OR = 2.3, 95% C.I.0.87-6.32).[166] Another study additionally found an association with unsafe driving actions (especially failure to stay in the lane) that preceded fatal crashes.[85] There also is some evidence suggestive of a dose-response relationship. [82, 164] Some evidence suggests higher risk with acute opioid use, but risk remained elevated throughout treatment with an opioid and reversed on cessation.[83] Preclusion of safety-critical job functions while under treatment with opioids is recommended. Among those treated with opioids, sufficient time after the last dose is recommended to eliminate approximately 90% of the drug and active metabolites from their system. Considerable caution is also warranted for those consuming other depressant medications such as benzodiazepines and sedating antihistamines. Provider and organizational barriers to implement this recommendation are relatively few. However, there may be some patients taking opioids while employed in safety-critical jobs, and there are no validated tools to assess whether they can perform their job safely.

Figure 1. Risk Estimates and Confidence Intervals of Included Studies Assessing Relationships Between Opioid Use and Crashes



Evidence for Use of Opioids in Safety-Critical Jobs

There are 12 studies incorporated into this analysis.

Search Strategy: A total of 21,478 article abstracts (176 PubMed, 1552 EBSCO, 19,750 Google Scholar) of epidemiological studies were found. All were evaluated. A total of 12 articles were included in these analyses.

Acute Pain (up to 4 Weeks)

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

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

Harms – May inadequately treat acute, severe pain.

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

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

Level of Confidence – High

Opioids for Treatment of Acute, Severe Pain

Opioids are recommended for treatment of acute, severe pain (e.g., crush injuries, large burns, severe fractures, injury with significant tissue damage) uncontrolled by other agents and/or with functional deficits caused by pain. They also may be indicated at the initial visit for a brief course for anticipated pain accompanying severe injuries (i.e., failure of other treatment is not mandatory). Tramadol[ii] may be indicated if there is true allergy to nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, other contraindication to an alternative medication, or insufficient pain relief with an alternative. A Schedule II opioid may be indicated for more severe pain. Recommend to taper off opioid use in 1 to 2 weeks.

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

Indications **–** Patients should meet all of the following:
1) Severe injury with a clear rationale for use (objective functional limitations due to pain resulting from the medical problem, e.g., extensive trauma such as forearm crush injury, large burns, severe radiculopathy).[iii]
2) Other more efficacious treatments should have been instituted,[iv] and either:
2a) documented to have failed and/or
2b) have reasonable expectations of the immediate need for an opioid to obtain sleep the evening after the injury.
3) Prescription databases (usually referred to as Prescription Drug Monitoring Program (PDMP)) should be checked and not show evidence of concomitant prescriptions, conflicting opioid prescriptions from other providers or evidence of misreporting. Any of these are strong contraindications for a prescription, especially in the absence of severe objective injury. [v] When the PDMP indicates other opioids medications have been recently used, yet there is need for a second prescription of opioids, a

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

few days of prescription at a low dose (e.g., 20mg morphine equivalent dose (MED)) may be reasonable with close monitoring.

4) Non-opioid prescriptions (e.g., NSAIDs, acetaminophen) absent contraindication(s) should nearly always be the primary treatment and accompany an opioid prescription. Due to greater than 10-fold elevated risks of adverse effects and death, considerable caution is warranted among those using other sedating medications and substances including:

i) benzodiazepines,
ii) anti-histamines (H_1-blockers), and/or
iii) illicit substances. [976, 1009, 1018, 1019] Patients should not receive opioids if they use illicit substances unless there is objective evidence of significant trauma or at least moderate to severe injuries.

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

Due to elevated risk of death and adverse effects, caution is also warranted when considering prescribing an opioid for patients with any of the following characteristics: use of other psychotropic medications, current tobacco use, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), impulse control problems, thought disorders, chronic obstructive pulmonary disease (COPD), or recurrent pneumonia. [976, 981, 1004, 1008, 1020-1038]

Additional risks and/or adverse effects are thought to be present from other comorbidities such as chronic hepatitis and/or cirrhosis, [1039] coronary artery disease, dysrhythmias, cerebrovascular disease, orthostatic hypotension, asthma, thermoregulatory problems, advanced age (especially with mentation issues, balance problems, fall risk, debility), osteopenia, osteoporosis, water retention, severe obesity, testosterone deficiency, erectile dysfunction, abdominal pain, gastroparesis, constipation, prostatic hypertrophy, oligomenorrhea, human immunodeficiency virus (HIV), ineffective birth control, herpes, allodynia, dementia, cognitive dysfunction and impairment, gait problems, tremor, concentration problems, insomnia, coordination problems, and slow reaction time. There are considerable drug-drug interactions that have been reported (see Appendices 2-3).

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

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

Dispensing quantities should be only what is needed to treat the pain. Generally, the first prescription should not exceed 3 days treatment, and rarely more that 7 days (Surgeon General August 2016; CDC 16; MMWR 2017). Emergency departments and urgent care clinics without continuity should generally not dispense refills. At 3 to 7 days, continuity should either be established or in the process of establishment with reassessment recommended to ascertain curative treatment(s), function, progress, other adjunctive treatments to consider.

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

Indications for Discontinuation – Resolution of pain, sufficient improvement in pain, intolerance or adverse effects, non-compliance, surreptitious medication use, consumption of medications or substances advised to not take concomitantly (e.g., sedating medications, alcohol, benzodiazepines), or use beyond 2 weeks.

Harms – Adverse effects are many (see section below on "Opioids Benefits and Harms").

Benefits – Improved short-term pain control.

Strength of Evidence **– Recommended, Evidence (C)**

Level of Confidence – High

Initial Screening of Patients Prior to Initiation of Opioids

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

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

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

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – High

Maximum Daily Oral Opioid Doses for Patients in Acute Pain

The maximum daily oral dose recommended for opioid-naïve, acute pain patients based on risk of overdose/death is 50mg MED [193].† **Only the dose, frequency and numbers of pills required should be dispensed.** In rare cases with documented functional improvement, higher doses may be

considered; however, risks are substantially higher and greater monitoring is also recommended (see Subacute/Chronic Opioid recommendations). Lower doses should be used for patients at higher risk of dependency, addiction, or other adverse effects. Monitoring is also recommended and consultation may be considered for those patients on higher doses.

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

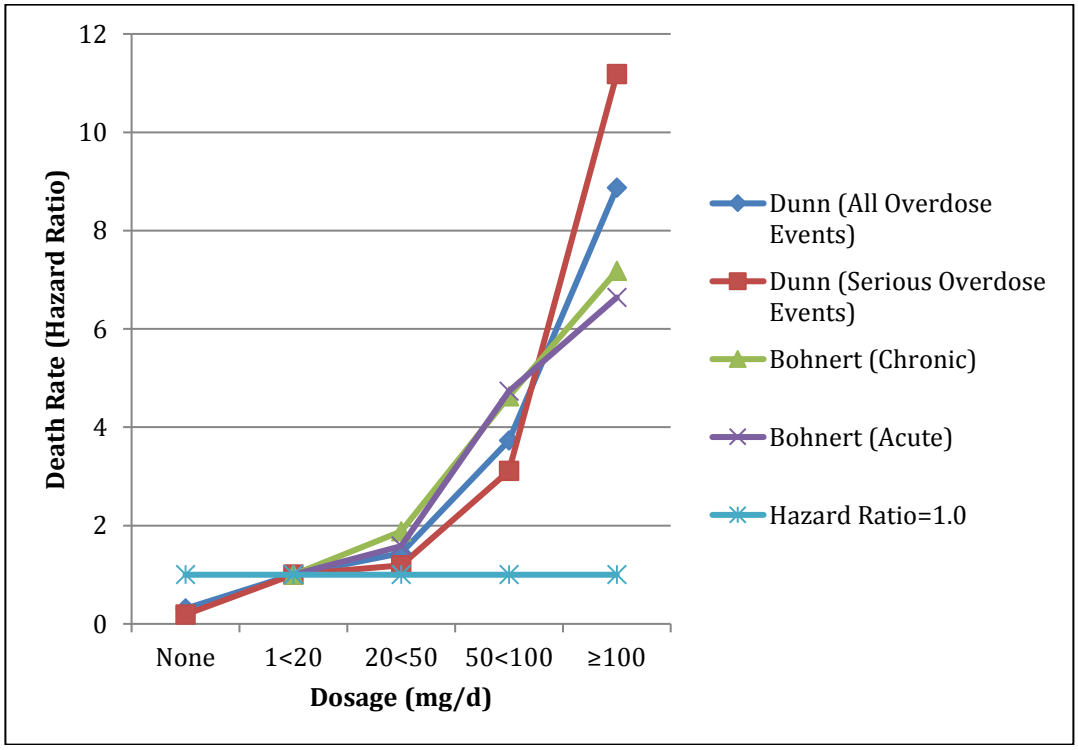
Benefits – Reduced risk for adverse physical and cognitive effects, dependency, addiction and opioid-related overdoses and deaths.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – Moderate

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

Figure 2. Death Rate (Hazard Ratio) vs. Morphine Equivalent Dosage (mg/d)*



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

Table 1. Examples of Decision Logic*

INJURY CLASSIFICATION	OPIOIDS RECOMMENDATION	RECOMMENDATION DETAILS
MILD INJURY (e.g. strains, tendonitis, non-specific pain, mild	Opioids NOT indicated	• Primary treatments generally not medication(s). Primary treatments usually are related to physical activity; reduction in exposure especially if high force; passive and active range of motion; heat/cold therapies. Consider physical therapy and/or manipulation for spine pain especially if mild pain problem persists.

to moderate low back pain)		(see Low Back Disorders Guideline; See Low Back Disorders Algorithm. See Cervical and Thoracic Spine Disorders Guideline. See Cervical and Thoracic Spine Disorders Algorithm. See Shoulder Disorders Guideline. See Shoulder Disorders Guideline Algorithm.) • NSAIDs or acetaminophen should be first medication(s) utilized first unless contraindicated. Consider gastric protection in those with high risks. • Generally, muscle relaxants also not indicated for mild spine pain; may be indicated for persistent or pain unresponsive to above treatments.
MODERATE (e.g. severe sprains of moderate or large joints, moderate trauma, moderate to severe low back pain)	Opioids MAY BE indicated	• Other treatments are indicated as primary treatments (see above; see links). • Muscle relaxant is preferable to opioid, and indicated especially for nocturnal use for treatment of moderately severe spine pain. • A short-acting opioid may be indicated. Few days of treatment may be indicated.
SEVERE (e.g. fractures, major trauma, large burns)	Opioids ARE indicated	• Other treatments are indicated as primary treatments (see above). Definitive treatment (e.g., fracture treatment) are indicated. • Muscle relaxant is preferable to opioid, and indicated especially for nocturnal use for treatment of spine pain. • Prescribe weaker opioids and the lowest effective dose. • Stronger opioids may be considered only if weaker ones are ineffective or not tolerated.

*Adapted from California, Opioids Guideline.

POST-OPERATIVE PAIN (UP TO 4 WEEKS) (After 4 weeks, see Subacute Pain)

Oral opioids are commonly prescribed after sinus surgery,[194] major non-cardiac surgical procedures,[195] mastectomy and immediate breast reconstruction (IBR),[196, 197] coronary artery bypass graft surgery,[198] major abdominal surgery (abdominal laparoscopic, abdominal hysterectomy, bowel resection or radical hysterectomy),[199-202] orthopedic surgery,[203] and molar extraction.[204]

Limited Use of Opioids for Post-operative Pain

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

Indications – For post-operative pain management, a brief prescription of short-acting opioids as an adjunct to more efficacious treatments (especially Cox-2 NSAIDs such as celecoxib, non-selective NSAIDs after risk of bleeding is no longer a concern). [More efficacious treatments also include therapeutic exercises, e.g., progressive ambulation especially for moderate to extensive procedures (e.g., arthroplasty, fusion).]

A brief course of opioids is often needed for minor surgical procedures. However, minor wound laceration repairs often require no opioids. Evidence suggests peri-operative pregabalin for 14 days and/or continuous femoral nerve catheter analgesia instead of solely using oral opioids results in superior knee arthroplasty functional outcomes with less venous thromboses.[205] Additional considerations include:

1) Non-opioid prescriptions (e.g., NSAIDs, acetaminophen) should nearly always be the primary treatment and accompany an opioid prescription. Computerized programs may also assist in optimal management.[206]
2) Planning for opioids use to treat post-operative pain should begin during the pre-operative assessment.
3) Prescription databases (usually referred to as PDMP) should be checked for other opioid prescriptions.
4) Due to greater than 10-fold elevated risks of adverse effects and death, considerable caution is warranted among those using other sedating medications and substances including:
    i) benzodiazepines,
    ii) anti-histamines (H_1-blockers), and/or
    iii) illicit substances.[105, 109, 167, 168] Patients should not receive opioids if they use illicit substances unless there is objective evidence of significant trauma or at least moderate to severe injuries.

    Considerable caution is also warranted among those who are (have):
    i) older (>65 yrs.),
    ii) pregnant,
    iii) sleep apnea,
    iv) psychiatric/mental health disorders (anxiety, depression, personality disorder, suicidal),
    v) drug-seeking behavior,
    vi) current or past substance abuse,
    vii) consuming alcohol in combination with opioids,
    viii) renal insufficiency,
    ix) hepatic insufficiency, and who are
    x) unemployed (10-fold risk of death).[109, 167]

    Due to elevated risk of death and adverse effects, caution is also warranted when considering prescribing an opioid for patients with any of the following characteristics: other psychotropic medications, current tobacco use, attention deficit hyperactivity disorder (ADHD), PTSD, impulse control problems, thought disorders, COPD, or recurrent pneumonia.[78, 102, 104, 108, 109, 169-186]

    Additional risks and/or adverse effects are thought to be present from other comorbidities such as chronic hepatitis and/or cirrhosis,[187] coronary artery disease, dysrhythmias, cerebrovascular disease, orthostatic hypotension, asthma, thermoregulatory problems, advanced age (especially with mentation issues, balance problems, fall risk, debility), osteopenia, osteoporosis, water retention, severe obesity, testosterone deficiency, erectile dysfunction, abdominal pain, gastroparesis, constipation, prostatic hypertrophy, oligomenorrhea, human immunodeficiency virus (HIV), ineffective birth control, herpes, allodynia, dementia, cognitive dysfunction and impairment, gait problems, tremor, concentration problems, insomnia, coordination problems, and slow reaction time. There are considerable drug-drug interactions that have been reported (see Appendices 2-3).

    Inpatient management may moderate these recommendations provided there is careful monitoring, although these same management issues then apply post-discharge.
5) For patients taking opioids chronically prior to surgery, consultations with anesthesiology and/or pain management are generally needed as post-operative dosing may be very high and management is often quite challenging.

6) Ongoing prescriptions of opioids after the immediate post-operative period should generally be for patients who have undergone a major surgery or have other condition(s) necessitating opioids. Most patients should be making progress towards functional restoration, pain reduction and weaning off the opioids. Patients who have not progressed should be carefully evaluated for physical complications or psychiatric comorbidity, adherence to active treatments, and pending development of addiction or dependency.
7) Patients should be educated on the proper storage and disposal of opioids at the time of the initial prescription and at every visit, as secondary fatalities from misuse and accidental poisonings of children are common.

Frequency/Duration – For moderate and major surgeries, opioids are generally needed on a scheduled basis in the immediate post-operative period. Other post-operative situations may be sufficiently managed with an as needed opioid prescription schedule. Provision of opioids sufficient to participate in therapeutic exercise (e.g., progressive ambulation) and allow sleep may be needed.

The lowest effective dose of a short-acting opioid should be used,[188] as well as weaker opioids if possible.[112, 189] Short-acting opioids are recommended for treatment of acute pain. Long-acting opioids are not recommended. High dose use at night is not recommended due to respiratory depression and disruption of sleep architecture. Low-dose opioids may be needed in the elderly who have greater susceptibility to the adverse risks of opioids. Those of lower body weight may also require lower opioid doses. Dispensing should be only what is needed to treat the pain. (Generally, this should be sufficient to cover two weeks of treatment. Prescriptions of 90-day supplies in the post-operative setting are not recommended.) Weaning should begin as soon as function is recovering and pain is subsiding. Subsequent weaning to as needed opioid use is recommended. Tapering is generally required if the use has been continuous and over 2 weeks duration.

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

Harms – Adverse effects are many (see section on “Opioids Benefits and Harms”).

Benefits – Improved short-term, post-operative pain control. Some studies suggest this may modestly improve functional outcomes in the post-operative population.

Strength of Evidence **– Recommended, Evidence (C)**

Level of Confidence - High

Screening Patients Prior to Continuation of Opioids

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

consultation examination(s) for complicating conditions and/or appropriateness of opioids, and iv) if ongoing opioids are prescribed, ensure more frequent (e.g., quarterly) assessments for treatment compliance, achievement of functional gains,[120, 167, 192] and symptoms and signs of aberrancy.

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

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

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – High

Maximum Daily Oral Opioid Dose for Post-operative Pain Patients

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

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

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

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

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

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

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

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

Harms – May inadequately treat severe subacute or chronic pain.

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

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

Level of Confidence – High

Opioids for Treatment of Subacute or Chronic Severe Pain

The use of an opioid trial is recommended if other evidence-based approaches for functional restorative pain therapy have been used, and documented to have provided inadequate improvement in function.[72, 115] An opioids trial is then recommended for treatment of both function and pain impaired by subacute or chronic severe pain (e.g., inability to work due to any of the following: chronic severe radiculopathy, chronic severe peripheral neuropathies, complex regional pain syndrome (CRPS), and severe arthroses). Ongoing opioids treatment beyond the trial period would be dependent on the results of the opioids trial [120].

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

1) A complete history and physical should be done, if not previously accomplished.
2) Reduced function is attributable to the pain. Pain or pain scales alone are insufficient reasons. [1, 118, 120, 167, 208-217]
3) Both function and pain treatment goals should be established (CDC 16) before an opioid trial of 1 to 3 weeks is attempted. Before initiating opioids, there should be plans for discontinuation in the event the goals are not met (CDC 16). Opioids should only be continued beyond the opioids trial period if both goals are met and these outweigh risks to patient safety (CDC 16). Assessment of function and pain at least monthly in the first 3 months of treatment and then quarterly should be documented. There should be at least 30% improvement in both pain and function to continue opioids treatment.
4) A severe disorder warranting potential opioid treatment is present [e.g., CRPS, severe radiculopathy, advanced degenerative joint disease (DJD)].[1]
5) Other more efficacious treatments have been documented to have failed.(1) Other approaches that should have been first utilized include physical restorative approaches, behavioral interventions, self-applied modalities, non-opioid medications (including NSAIDs, acetaminophen, topical agents, norepinephrine adrenergic reuptake blocking antidepressants or dual reuptake inhibitors; also antiepileptic medications particularly for neuropathic pain) and functional restoration. For LBP patients, this also includes[vi] fear avoidant belief training and ongoing progressive aerobic exercise, and strengthening exercises. For CRPS patients, this includes progressive strengthening exercise. For DJD, this includes NSAIDs, weight loss, aerobic and strengthening exercises.
6) Be engaged in an ongoing active exercise program and comply with that prescription.
7) Be prescribed a non-opioid prescription(s) (e.g., NSAIDs, acetaminophen) absent a contraindication. Such non-opioids should nearly always be the primary pain medication and accompany an opioid prescription (CDC 16). Other medications to consider include topical agents, norepinephrine adrenergic reuptake blocking antidepressants or dual reuptake inhibitors; also antiepileptic medications particularly for neuropathic pain).
8) The lowest effective dose should be used.[188] Weaker opioids should be used whenever possible.[112, 189] Meperidine is not recommended for chronic pain due to bioaccumulation and adverse effects.
9) Low-dose opioids may be needed in the elderly who have greater susceptibility to the adverse risks of opioids. Those of lower body weight may also require lower opioid doses.
10) Dispensing should be only what is needed to treat the pain.[vii]
11) Patients should be periodically reminded to not take benzodiazepines, alcohol, diphenhydramine (included in many OTC medications), other sleep medication, or use other sedating medications.
12) Patients should be educated on the proper storage and disposal of opioids at the time of the initial prescription and at every visit, as secondary fatalities from misuse and accidental poisonings of children are common.
13) If an opioids trial is successful and there is a decision to transition to long-term opioids, extended-

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

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

release/long-acting opioids may be selectively used. Long-acting opioids should be used on a scheduled basis, rather than as needed.[1] As needed opioids should generally be avoided for treatment of chronic pain, although limited use for an acute painful event (e.g., fracture, sprain) is reasonable. Sublingual fentanyl is not recommended for treatment of subacute or chronic pain. Caution is warranted with fentanyl patches due to unpredictable absorption.

14) Prescription databases (usually referred to as PDMP) should be checked for conflicting opioid prescriptions from other providers or evidence of misreporting.
15) Due to greater than 10-fold elevated risks of adverse effects and death, considerable caution is warranted among those using other sedating medications and substances including:
    i) benzodiazepines,
    ii) anti-histamines (H_1-blockers), and/or
    iii) illicit substances.[105, 109, 167, 168]

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

    Considerable caution is also warranted among those who are:
    - older (>65 yrs.),
    - pregnant,
    - sleep apnea,
    - psychiatric/mental health disorders (anxiety, depression, personality disorder, suicidal),
    - drug-seeking behavior,
    - current or past substance abuse,
    - consuming alcohol in combination with opioids,
    - renal insufficiency,
    - hepatic insufficiency, and who are
    - unemployed (10-fold risk of death).[109, 167]

    Due to elevated risk of death and adverse effects, caution is also warranted when considering prescribing an opioid for patients with any of the following characteristics: other psychotropic medications, current tobacco use, attention deficit hyperactivity disorder (ADHD), PTSD, impulse control problems, thought disorders, COPD, or recurrent pneumonia.[78, 102, 104, 108, 109, 169-186]

    Additional risks and/or adverse effects are thought to be present from other comorbidities such as chronic hepatitis and/or cirrhosis,[187] coronary artery disease, dysrhythmias, cerebrovascular disease, orthostatic hypotension, asthma, thermoregulatory problems, advanced age (especially with mentation issues, balance problems, fall risk, debility), osteopenia, osteoporosis, water retention, severe obesity, testosterone deficiency, erectile dysfunction, abdominal pain, gastroparesis, constipation, prostatic hypertrophy, oligomenorrhea, human immunodeficiency virus (HIV), ineffective birth control, herpes, allodynia, dementia, cognitive dysfunction and impairment, gait problems, tremor, concentration problems, insomnia, coordination problems, and slow reaction time. There are considerable drug-drug interactions that have been reported (see Appendices 2-3).
16) Attempt to wean twice a year to lower than 90mg MED if patients were previously prescribed those doses.

Frequency/Duration – Opioids use is generally initiated as a "trial" to ascertain whether the selected opioid produces functional improvement. Opioid use is generally prescribed on a regular basis,[218] [1043] at night or when not at work.[82] Only one opioid is recommended to be prescribed in a trial. More than one opioid should rarely be used. Lower opioid doses are preferable as they tend to have the better safety profiles, less risk of dose escalation,[188] less work loss,(112) and faster return to work.[189] [1042] Patients should have ongoing visits to monitor efficacy, improvement in functional

status (e.g., return to work), adverse effects, compliance and surreptitious medication use. Opioid prescriptions should be shorter rather than longer duration.[219]

Indications for Discontinuation – Opioids should be discontinued based on lack of functional benefit [115], resolution of pain, improvement to the point of not requiring opioids, intolerance or adverse effects, non-compliance, surreptitious medication use, medication misuse (including self-escalation and sharing medication), aberrant drug screening results, diversion, consumption of medications or substances advised to not take concomitantly (e.g., sedating medications, alcohol, benzodiazepines). (FDA 16; Dasgupta 15)

Harms – Adverse effects are many (see section on "Opioids Benefits and Harms"). May lead to opioid dependency.

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

Strength of Evidence **– Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Screening Patients Prior to Initiation of Opioids

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

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

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

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – High

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

The maximum daily oral dose recommended for subacute or chronic pain patients based on risk of overdose/death is 50mg MED.[171, 193, 1022, 1046] (See Opioid Dose Calculator at http://www.agencymeddirectors.wa.gov/Calculator/DoseCalculator.htm.) In rare cases with documented functional improvements occurring with use above 50 mg MED, subsequent doses up to 90 mg may be considered (CDC 16), however, risks of death are much greater and more intensive monitoring is then

also recommended. Lower doses should be considered in high risk patients. Caution appears warranted in all patients as there is evidence the risk of dose escalation is present even among patients enrolled in a "hold the line (stable dose) prescribing strategy" treatment arm who experienced an approximately 17% increase in dose over 12 months compared with 79% in the liberal escalating dose arm.[222] [1047] Extrapolated linearly, the hold-the-line prescribing strategy would result in average doses over 50mg within approximately 3.5 years while the liberal policy exceeded 50mg in approximately 11 months.

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

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

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

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – High

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

The use of an opioid treatment agreement (opioid contract, doctor/patient agreement, or informed consent) is recommended to document patient education, understanding, acknowledgement of potential benefits, adverse effects, and agreement with the expectations of opioid use (see Appendix 1). [71, 72, 223-233] **If consent is obtained, it is recommended that appropriate family members be involved in this agreement.**

Harms – Negligible.

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

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Urine Drug Testing

Baseline and random urine drug testing, qualitative and quantitative, is recommended for patients prescribed opioids for the treatment of subacute or chronic pain to evaluate presence or absence of the drug, its metabolites, and other substance(s) use. In certain situations, other screenings (e.g., hair particularly for information regarding remote use [234-239] [1048-1052] [1053] [1054] **or blood (for acute toxicity) may be appropriate.**

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

Frequency – Screening is recommended at baseline, randomly at least twice and up to 4 times a year and at termination. Should be 4 times/yr if MED > 50mg. More intensive screening is recommended for those consuming more than 50mg MED (see above). Federal guidelines recommend at least 8 tests a year among those utilizing opioid treatment programs.[77] [1055] Screening should also be performed "for cause" (e.g., provider suspicion of substance misuse including over-sedating, drug intoxication, motor vehicle crash, other accidents and injuries, driving while intoxicated, premature prescription renewals, self-directed dose changes, lost or stolen prescriptions, using more than one provider for prescriptions, non-pain use of medication, using alcohol for pain treatment or excessive alcohol use, missed appointments, hoarding of medications, and selling medications). Standard urine drug/toxicology screening processes should be followed (consult a qualified medical review officer).[240-242] If there is an aberrant drug screen result (either positive for unexpected drugs or unexpected metabolites or unexpectedly negative results), there should be a careful evaluation of whether there is a plausible explanation (e.g., drug not tested, drug metabolite not tested, laboratory cutpoint and dosing interval would not capture the drug/metabolite, laboratory error). In the absence of a plausible explanation, those with an aberrant drug test showing an unexpected drug should have the opioid discontinued or weaned due to opioid contract violation and high risk of overdose. Those with a drug test that shows absence of the prescribed opioid (or metabolites) should have the opioid discontinued due to either not taking the opioid, having already detoxified from the opioid, and/or diverting the opioid. [115][1056]

Harms – No adverse clinical effects if properly interpreted.

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

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

Opioids Rotation

Rotation of Opioids is selectively recommended.

Indications – Patients on opioids for subacute or chronic pain who appear to lose evidence of efficacy or experience intolerable adverse effect(s) [1057, 1058] [1059, 1060]. May be reasonable to also rotate from one opioid to a second opioid on a one-time basis when there was no opioids trial, there is lack of evidence of efficacy, and there is concern there could be benefit demonstrated with a different opioid. Caution is warranted in converting to methadone, as there is no safe and dependable conversion table.

Frequency/Dose – Generally, opioid rotation should be an infrequent requirement. If becomes more frequent need, there is consideration for adherence to the functional exercise requirements, as well as increasing drug screening surveillance to assure proper use and not misuse. Morphine equivalent dose is recommended to be reduced by 50% when rotating from one opioid to another [1057]; [1060]. Rotation schedules are typically accomplished over 3 to 10 days Choquette 08; [1060]. Functional gains should be carefully tracked. If there are no functional gains, further taper and complete cessation of the opioid is generally indicated.

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

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

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

Rationale for Recommendations: General Considerations and Study Design Issues

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

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

Rationale for Recommendations: Trial Sponsorship

The vast majority of the trials of opioids are industry-sponsored. Sponsored studies have been frequently reported to have better results and lower complication rates than studies conducted by independent investigators.[253-256] [1020] A prior review of 546 pharmaceutical trials found 63% were primarily funded by industry, 14% by government and 23% by nonprofit or nonfederal organizations.[253] Industry sponsorship for this systematic review and guideline on opioids was greater still especially for chronic pain. For acute pain, 42.1% of 19 trials for acute pain patients,[ix] 60.0% of 20 perioperative and postoperative trials,[x] and 87.1% of 93 chronic pain patient trials[xi] with sponsorship identified had partial or full industry sponsorship. When analyzing only the studies that had a minimum level of follow-up time (1, 7, and 30 days for acute, postoperative and chronic pain respectively), 80.0%, 80.0% and 93.9% had partial or full industry sponsorship, respectively.

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

Rationale for Recommendations: Health Outcomes

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

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

[x] For treatment of peri- and post-operative patients, there were 27 high- or moderate-quality trials; of those mentioning COI and funding (n = 20), 12 (60.0%) were at least partially industry sponsored, 1 (5.0%) non-governmental organization, and 7 (35.0%) had no industry sponsorship or remote industry-related COI. However, when limiting the data to those with at least 7 days of followup, there were only 5 studies, 4 (80.0%) of which had at least partial industry sponsorship and one did not mention COIs.

[xi] For treatment of chronic pain, there were 101 high- or moderate-quality trials; of those mentioning conflicts of interest and funding (n = 93), 81 (87.1%) were at least partially industry sponsored, 5 (5.4%) government funded, 1 (1.1%) non-governmental organization funded, 5 (5.4%) hospital funded and 2 (2.2%) identified no conflict of interest. However, when limiting the data to those with at least 30 days of followup, there were only 66 studies remaining that identified COI: 62 (93.9%) were at least partially industry sponsored, 1 (1.5%) non-governmental organization, and 1 (1.5%) with no COI.

[xii] Of those comparative trials mentioning sponsorship and COI, 4 of 6 (66.7%) of acute pain, 4 of 5 (80.0%) of peri/postoperative and 9 of 12 (75.0%) chronic pain had partial or full industry sponsorship.

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

Rationale for Recommendations: Adverse Effects Recommendations (see also separate section)

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

Rationale for Recommendations: Adverse Effects (see also separate section)

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

Rationale for Recommendations: Acute Pain Treatment Recommendations

For acute pain, there is quality evidence that other medications and treatments are at least equivalent if not superior and no quality published evidence an opioid is superior for treatment of acute pain (e.g., NSAIDs; [190, 191, 269-274] [1010-1017])carisoprodol;[275][1082] transcutaneous electrical nerve stimulation [TENS]).[xiii] [276] There are many emergency department trials of very short duration treatments, with follow-ups of up to a few hours, with minimal if any differences, and thus of unclear utility for guidance.[277-288][1083] Additionally see post-operative studies below, as some studies may have analogies to other acute pain situations and findings are somewhat similar. Quality evidence indicates safety profiles are considerably worse for opioids. Studies also demonstrate worse functional outcomes for patients treated early with opioids.[289-291][1084] Among trials for treatment of acute pain, ibuprofen was reportedly superior to codeine or acetaminophen for acute injuries including fractures.[270][1011] Diflunisal was equivalent to codeine for sprains, strains and mild to moderate LBP.[273] Valdecoxib[xiv] was better tolerated and trended towards greater pain relief than tramadol for ankle sprains.[269] Valdecoxib was equivalent to oxycodone as assessed by pain ratings, but trended toward less rescue medication use and had fewer adverse effects among spine and extremity pain patients.[271] Global ratings for LBP showed carisoprodol is superior to propoxyphene and has fewer adverse effects,[1082]) although there are concerns about abuse of carisoprodol. Ketorolac was equivalent for pain relief, but superior to meperidine in terms of adverse effects for treating severe LBP. [1013] Ketorolac was also superior to codeine/acetaminophen for acute LBP treated in emergency departments.[1014] Ketorolac appeared superior as a primary pain treatment supplemented with opioids compared with opioids alone for spine and joint procedures.[1085] Diflunisal was superior to codeine/APAP for LBP. [1015] There are no quality

[xiii]Flutirpine also has evidence of efficacy, although not currently approved in the U.S.
[xiv]Valdecoxib is currently withdrawn from the market.

trials to suggest superiority of opioids to other active treatments. Prolonged use of opioids after an acute event has been associated with worse functional outcomes.[289-291]

Thus, routine use of opioids for treatment of acute pain is strongly not recommended. The lowest effective dose of a short-acting opioid is recommended for those with acute, severe pain uncontrolled by other agents such as NSAIDs.[1040] Lower potency opioids are recommended when sufficient for pain relief and dispensing only quantities sufficient for the pain are recommended. A morphine equivalent dose limit of 50mg is recommended [1046] (see Figure 2). Exceeding that should be based on documented need and increased surveillance for adverse effects. PDMPs are recommended to be checked. NSAIDs or acetaminophen should generally accompany an opioid prescription. Considerable caution is recommended among those with other CNS depressing medications such as benzodiazepines, or other risk factors for adverse effects, overdose and death.[79, 102, 104, 105, 108, 109, 167-186] Due to risk of impairments and lost time from work,[1041, 1042] opioids should be prescribed at night or while not working when possible.[985] It is recommended to taper off the opioid in 1-2 weeks.

Rationale for Recommendations: Post-operative Pain Treatment Recommendations

Similar to the literature for acute pain, findings are comparable that treated post-operative pain (see evidence table). However, studies also include at least one showing modestly improved long-term knee range of motion and less opioid use with pregabalin for 14 days plus epidural and opioid management after total knee arthroplasty.[1070] Another trial found superior range of motion and fewer venous thromboses after continuous femoral nerve catheters analgesia instead of solely using oral narcotics.[1071] Thus, quality evidence suggests opioids may have deleterious post-operative effects other than when used as adjuncts. Additional differences from the acute pain recommendations include that NSAIDs have been administered at the time of surgery without undue complications, [274, 293-297] although these studies would likely be underpowered for rare complications. It is also recommended to dispense only what is needed, and not 90-day or other lengthy treatment supplies to avoid either over-medication and/or diversion. Also, closely monitored inpatient settings may somewhat moderate the cautions about the recommended dose limits and overdoses; however, the evidence that early ambulation is critical to functional recovery while it also limits complications is overwhelming and so oversedation remains a concern. For patients on chronic opioids pre-operatively, especially moderate to high doses, consultation with a physician experienced in managing these complex cases may be necessary.

Rationale for Recommendations: Subacute and Chronic Pain Treatment Recommendations

There are no long-term trials documenting efficacy of opioids. There is quality evidence that other medications and treatments are at least equivalent if not superior for subacute or chronic pain [e.g., NSAIDs,[258, 298-300] nortriptyline,[1086] clonidine,[1087] and flupirtine. [1088] Safety profiles are considerably worse for subacute and chronic use of opioids. There are no quality trials to suggest superiority of opioids to other common active treatments. One trial suggests morphine is superior to benztropine for pain, but not function.[1089] Among trials for treatment of subacute or chronic pain, one trial failed to find superiority of morphine to nortriptyline for treatment of chronic lumbar radiculopathy. [1086] Another found neither morphine nor mexiletine superior to placebo. [1090] Another found celecoxib superior to tramadol for chronic LBP.[298] Diclofenac was superior to dextropropoxyphene/ APAP for treatment of hip or knee osteoarthritis.[1091] Diclofenac was approximately equivalent to tramadol in another trial.[1072] Naproxen was equivalent to oxycodone for treatment of chronic LBP. [1092] Few trials primarily targeted subacute pain patients, and these patients are included in the chronic pain patient section due to the speed with which dependency can arise. The main exception is one trial finding flupirtine was equivalent to tramadol for subacute LBP. [1088] There are no trials documenting improved objective functional outcomes, with more than 100 studies documenting many adverse effects (see evidence table below). [989] There is quality evidence that opioids are associated with *reduced* pain thresholds. [1093] Thus, there is strong evidence that other medications and treatments should be used

prior to consideration of an opioid prescription for chronic/subacute pain patients [119] (see evidence table).

Rationale for Recommendations: Tramadol Issues

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

Rationale for Recommendations: Tolerance, Addiction and Drug Screening Considerations

Tolerance is a common occurrence, although generally not significantly problematic. Addiction and drug-seeking behaviors are less common.[245, 304, 307-310] Yet, approximately 80% of patients experience some adverse effects from opioids and approximately 33 to 80% do not finish a clinical trial with opioids due primarily to these adverse effects (the large range in estimates is in part due to trial design such as whether a wash-out phase was included, length of treatment, and severity of pain).[1061, 1095, 1096] Drug screening may also determine that the person is not actually taking the prescribed opioid(s).

Rationale for Recommendations: Opioid Agreement Recommendations

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

Rationale for Recommendations: Opioid Rotation

There are no quality studies showing efficacy of opioids rotations [1059] [1057] [1099] [1060] [1100] [1057, 1101]. Opioids rotations are thought to be successful in a some patients. This involves reduction in MED and then rotation to another opioid. Functional gains should be carefully tracked.

Rationale for Recommendations: Overall Literature Assessment and Conclusions

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

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

Opioids are moderate to high cost depending on duration of treatment. Provider and organizational barriers to implement recommendations to prescribe non-opioid medications and therapies are low,

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

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

There are 4 high- or moderate-quality placebo-controlled clinical trials addressing opioid use for acute pain patients. There are 67 high- or moderate-quality placebo-controlled clinical trials addressing opioid use for chronic pain patients. Of these, 52% lasted up to 1 month, 12% were 1 to 2 months, and 34% were 3 months in duration. There was one trial of longer than 3 months which lasted 16 weeks. [1106]

Altogether, there are 25 high-[257, 269-271, 274, 275, 277, 284, 287, 301, 319-333] and 132 moderate-quality RCTs incorporated into this analysis.[190, 191, 205, 222, 245-250, 258, 260, 261, 272, 273, 276, 278-283, 285, 286, 288, 293-300, 302-305, 318, 334-426]

There are 21 low-quality RCTs [335, 339, 427-445] and 2 other studies [1069, 1107] in Appendix 4. There are additional trials beyond the scope of these guidelines. [447-455]

Discontinuation and Tapering of Opioids

Discontinuation and Tapering of Opioids

Discontinuation of opioids is recommended for acute pain and post-operative patients who have reached meaningful functional recovery. Patients treated for acute pain who are opioid-naïve should generally require no tapering. Patients with acute pain treated with continuous opioids over 50mg MED for longer than 2-3 weeks duration may benefit from brief tapering over three to seven days.

Discontinuation is also recommended for subacute and chronic pain patients who: i) used opioids on a chronic basis, and ii) [any one of] no demonstrated functional gain, non-compliance, aberrant drug screening results and/or diversion, adverse effects (e.g., cognitive impairment, falls, poor judgment, untreated sleep apnea, psychological disorders, and concurrent use of depressant medications such as benzodiazepines and diphenhydramine)].[64, 115]

Immediate discontinuation without tapering is recommended for those who have a urine drug screen (UDS) showing unexpected absence of the prescribed drug. Among those with urine drug testing results showing non-prescribed licit or illicit substance(s) use, discontinuation is recommended, although tapering may be advisable if the opioid is thought to be taken as prescribed (e.g., rather than partially diverted) and the dose is over 50 mg MED.

Tapering is recommended if the opioid was used at a moderate or high level (e.g., above 50-90mg[15] MED) on a chronic basis. Consultation with an addiction specialist or psychiatrist is recommended for complex patients (e.g., high-dose patients, prior withdrawal problems, complex psychosocial confounders, complicating medical conditions).

Transitioning to only an NSAID or acetaminophen or complete cessation of analgesics is/are generally indicated.

Frequency/Duration **–** Duration of a taper is empirical, dependent on dose, prior opioid use duration, and informed patient decision-making. Rates of the taper vary. The following are options:

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

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

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

A pilot study found a 22-week taper support intervention was effective (psychiatric consultation, psychiatric medication med. if indicated, opioid dose tapering, and 18 weekly meetings with a physician

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

assistant to educate, explore motivation for tapering and CBT-based learning pain self-management skills) (Sullivan 2016).

Other agents are used when weaning is challenging, and/or dependence and addiction issues are more complex and commonly include naltrexone, methadone, buprenorphine and clonidine (see below).

While death during acute withdrawal is rare in those dependent on opioids alone, death during (withdrawal) tapering is a possibility in those dependent on multiple medications (e.g., opioids and benzodiazepines, carisoprodol, and anticonvulsants. Those patients with unstable cardiovascular disease and polypharmacy dependence should be considered for in-patient detoxification under the supervision of an addiction specialist. For those using chronically high doses with difficulty tapering and/or undue anxiety, referral to a psychologist may also be helpful to address anxiety and behavioral issues.

A process is recommended:

1. Develop a taper plan. Elements of the plan include: 1) agreement to taper, 2) education on expected symptoms during the taper, 3) return visits for intolerable symptoms with consideration of a pause in the taper, and 4) other treatments to be changed or substituted.
2. The provider should be supportive and engaged in the patient's care, management and concerns. Do not 'abandon' the patient. Consider engaging the patient in other active therapies during taper (e.g., progressive active exercises, cognitive behavioral therapy, education, psychiatric consultation, psychiatric medication). Consider judicious use of passive therapies (e.g., acupuncture, TENS, manipulation) as adjuncts in assisting tapering.
3. Rate of tapering is not critical, rather the direction of the dose is. A typical rate is 10%/week to 10%/month in chronic pain patients in outpatient settings. Tapers may be faster in inpatient and more controlled settings, or when use has been for a shorter period of time. Brief negotiated pauses in the rate of a taper is acceptable.
4. Educate the patient that tapering will produce symptoms. These include anxiety, emotional distress, hyperalgesia, experiencing pain in new areas. These are expected and not contraindications to a taper, although if intolerable, may be a rationale for a brief pause in a taper.
5. The taper should be stopped if there is objective worsening of function, excessive withdrawal, and/or intolerance. After stabilization, resumption of the taper should be attempted. However, if there is a plateau level where function is achieved, that dose should be noted in the records and maintained for an ongoing basis. There is consideration for reattempting tapering in subsequent years.

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

Benefits – Reduce risk of adverse events and opioid-related deaths.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – High

Opioid Conversion/Transition

Conversion of opioids to a MED is helpful to transfer from one opioid to another. (See Opioid Dose Calculator at http://www.agencymeddirectors.wa.gov/Calculator/DoseCalculator.htm.) This is most

commonly performed to attempt to achieve a better functional outcome and/or to reduce adverse effects. Quality evidence to support this practice has not been published. Several resources are available [458, 459] that include a spreadsheet-based calculator [460] and online converting tool. [461] To avoid drug overdoses, when transferring from one opioid to another, the MED prescribed should be approximately 50% of the prior dose.[462-465]

Rationale for Recommendation

There is one moderate quality pilot trial of a supportive group compared with usual care for tapering suggesting some efficacy (Sullivan 16). There are many studies that have described various methods of tapering opioids. However, there are no high or moderate quality studies among the desired target population to define the best methods. The clinical approach is therefore largely empirical. US Federal Guidelines for those with opioid dependency recommended a taper at 2.5-10mg/week as an outpatient.[77] The rate of long term success of tapers and discontinuation is also unclear, with a database study suggesting high dose opioid use predicts long term opioid use.[1108]

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

There are many trials and other studies among heroin, licit, illicit and other undefined opioid users which use widely varying rates of detoxification mostly ranging from approximately 2 to 10 days up to indefinite but lower dose maintenance. There also are additional studies on prevention and treatment of opioid dependence. These studies are beyond the scope of these guidelines.[467, 479-570] There are a few studies on detoxifying opioid using, non-abusing inpatients that are also beyond the scope of this guideline.[571-573] There are few barriers to implementing this recommendation. Those complex patients may need referral to a program for treatment of addiction, which may be geographically limited.

Opioids Medications for Tapering: Treatment of Dependency and Addiction

Most tapering is most often safely accomplished with no adjunctive or alternative medications (see above). However, medications may be selectively used for more difficult opioid tapers, as well as for treatment of opioids dependency and addiction. Often, the same medications are used for both of these purposes, and include buprenorphine, clonidine, methadone, and naltrexone.

Buprenorphine for Opioid Tapering

Buprenorphine is selectively recommended for adjunctive treatment in opioid tapering.

Indications – Most patients are weaned without use of a controlled substance medication. Buprenorphine is sometimes used for detoxification from high-dose opioids and is recommended for select cases with opioid use at over 50-90 mg MED for at least 3 months duration (CDC 16; Addiction guidelines), as well as for the treatment of addiction. As treatment of these conditions is behaviorally and medically challenging, most are treated by addiction specialists (e.g., high-dose patients, prior withdrawal problems, complex psychosocial confounders, complicating medical conditions). Special licensing may be required for treatment with buprenorphine. When there are complex medical issues (e.g., significant cardiovascular disease), inpatient treatment may be indicated. Buprenorphine is not indicated for those with safety critical jobs (JOEM 2014).

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

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

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

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

Benefits – May help reduce opioids withdrawal symptoms. Reduced risk for abuse and diversion when using combined buprenorphine/naloxone.

Harms – Buprenorphine/naloxone may precipitate opioids withdrawal. Sedation, daytime fatigue, overdose, fatalities, however the risk of fatalities is considerably lower than with methadone. Potential for abuse (Cassidy 14). Risk for safety including motor vehicle crash and other injuries. (JOEM 2014; Rudisill 16)

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Methadone for Opioid Tapering

Methadone is selectively recommended for adjunctive treatment in opioids tapering.

Indications – Most patients are weaned without use of a controlled substance medication. Methadone is sometimes used for tapering from high dose opioids, and is recommended for select cases with opioid use at over 50-90 mg MED for at least 3 months duration (CDC 16; Addiction guidelines), as well as for the treatment of addiction. As treatment of these conditions is behaviorally and medically challenging, bioaccumulation is problematic, and special licensure is required for methadone, most are treated by trained and qualified addiction specialists. When there are complex medical issues (e.g., significant cardiovascular disease, high-dose patients, prior withdrawal problems, complex psychosocial confounders, complicating medical conditions), inpatient treatment may be indicated. Methadone is not indicated for those with safety sensitive jobs (JOEM 2014).

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

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

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

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

Benefits – May help reduce opioid withdrawal symptoms.

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

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Rationale

Methadone and buprenorphine increase adherence to treatment and reduce risk of illicit opioid use among patients with opioid use disorder. [151–155]. Methadone and buprenorphine may be used for opioid addiction, although they should be prescribed by experienced and licensed providers. These medications should be taken exactly as directed, not started/stopped or used with other medications or dietary supplements without advice of the provider. Providers should be aware of the adverse effects including overdose, fatalities, respiratory depression, prolonged QT interval (only methadone), and dysrhythmias (FDA; Washington State Guidelines). Both of these medications are also not indicated in workers with safety sensitive jobs [985-988, 990, 1126-1129] [1130]. *Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder. (CDC 2016)*

Methadone reportedly accounts for more overdose deaths when compared to hydrocodone or oxycodone. [1008, 1131, 1132] Because methadone is also used to treat substance abuse, overdose decedents tend to have used other prescription and/or illicit medications as well. [1006, 1133] Still, some methadone deaths appear to be related to the medication's tight therapeutic window. [1133-1135] Prescribers of methadone should be experienced; physicians and patients may both be unfamiliar with methadone and its potential for inappropriate dosing and long and unpredictable half life. Conversion ratios vary with dose. The 40mg diskette form of methadone may contribute to drug overdose because of the large amount of drug in each diskette. The liquid form of methadone can be subject to errors during preparation. Some medications induce the metabolism of methadone, such as anticonvulsants and rifampin, while other medications lead to increases in methadone blood levels contributing to toxicity.[1131] Methadone should not be used to treat breakthrough pain (BTP) or as an as needed medication.[1136] Switching to methadone requires careful conversion. Supervised administration of methadone is reportedly associated with lower fatality rates than unsupervised administration,[746-749] yet numerous studies have shown elevated mortality rates associated with methadone.[997, 1023, 1137]

Buprenorphine appears to be considerably safer than methadone due to its partial agonist effects. Yet, while appearing safer, it may cause respiratory depression with high doses [616, 627, 751] and has been associated with some risk of fatalities in most [669, 752-758] but not all studies especially with sedative abuse.[759] It requires training of the prescriber and is expensive.[1135] Naltrexone has been used in both oral and implantable forms, as a means of treating problematic opioid use, but only after tapering has been completed. However, while it has been associated with reduced risk, it also does not eliminate risk.[1138]

Breakthrough Pain

Breakthrough pain (BTP) is "a transient increase in pain to greater than moderate intensity, which occurred on baseline pain of moderate intensity or less."[574, 575] It is also defined as "the transient exacerbation of pain occurring in a patient with otherwise stable, persistent pain."[576] BTP is typical among cancer/terminal illness patients,[576-592] but is also reported in patients with chronic noncancer pain. It occurs in 33-65% of patients with chronic cancer pain and in ~70% of patients with chronic noncancer pain.[1139] Patients admitted to hospice have a prevalence of BTP between 40 and 86%.[1140] BTP is a transitory pain (reaching maximum severity in ~15 minutes and lasting ~60 minutes in patients with cancer) that occurs despite the management of chronic pain with long-term around-the-clock analgesia. BTP can be unpredictable and can be severe. The range of BTP occurs between 1 and 240 minutes. BTP often has a peaking intensity around 3 minutes. [1141] BTP also has a self-limiting average duration around 30 minutes.[1142] Non-cancer related BTP has been treated with opioids.[251, 574, 575, 592, 594]

Opioids for Breakthrough Nonmalignant Pain

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

Harms – May inadequately treat severe chronic pain.

Benefits – Reduced dose escalation, accident risks, risks of dependency, addiction and death.

Strength of Evidence − **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Rationale for Recommendation

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

Evidence for Breakthrough Pain

There is 1 moderate-quality RCT and 3 other studies incorporated into this analysis.

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

Intrathecal Drugs ("Pain Pumps")

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

Intrathecal Drug Delivery Systems for Chronic Non-malignant Pain Conditions

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

Harms – Device complications, fatalities, potential for dose escalation. [1143]

Benefits – Reduced pain ratings, reduced oral opioid use.

Strength of Evidence − **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – High

Rationale for Recommendation

Intrathecal drug delivery systems have not been evaluated in quality studies to determine whether treatment with these systems is superior to standard treatment options (e.g., quality functional restoration program), oral medication(s) or other treatment options for chronic nonmalignant pain patients. The medications used are potent and some are not intended for chronic use. [1144, 1145] Deaths have been associated with intrathecal opioid use, including a one-year mortality rate estimated at 3.9%.[1143] Granulomas appear to frequently develop; the expected "permanency" of neurologic abnormalities associated with their formation has not been established.[1146]

Ziconotide has been used in intrathecal delivery systems.[1147] It is not known whether there is a reduced incidence of intrathecal granuloma formation with this drug since its use has not been widely applied over the long term. Ziconotide has a narrow therapeutic margin and has been associated with severe neuropsychiatric adverse effects. Since it does not share pharmacologic actions with narcotics, there is no known method to determine prospectively whether a patient will respond favorably to this drug.

Intrathecal opioid delivery systems are invasive and costly, have significant adverse effects including potential long-term sequelae from both implantation/ retention of the devices, granulomas, and those associated with the concurrent use of intrathecal opioids. [1148] As there is also a lack of documented efficacy, these devices are not recommended. For new patients, there are few barriers for implementing this guideline. For existing patients, this guideline should not be interpreted as requiring device removal.

Evidence for the Use of Intrathecal Drug Delivery Systems

There are 2 high-quality RCTs incorporated into this analysis.

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

Naloxone (Narcan) for Prevention of Overdose Fatalities

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

Naloxone (Narcan) for Opioid Overdose

Recommended.

Naloxone has long been used as an antidote for opioid overdose. It has more recently been prescribed for treatment of opioid overdose among those on chronic opioids at home, particularly at higher doses. Legislation has been passed in many jurisdictions to allow emergency personnel, police, firefighters and others to provide naloxone to resuscitate unresponsive individuals. Naloxone is also used for treatment of pain in combination with an opioid.

Strength of Evidence − **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Indications:	Naloxone (e.g., naloxone kits) is particularly indicated to be available for family and others for those patients who are prescribed more than 50mg MED. It is indicated for those who have had serious overdoses but have not (yet) been tapered. Recommendations to have encountered and/or considered prior to a naloxone prescription is(are) adherence to evidence-based opioid guidelines which would prevent vast majority of overdoses and deaths. Earlier treatment options include: 1) prescribing active exercises for most chronic pain conditions, 2) prescribing non-opioids for pain relief first, 3) avoiding opioids in those with risk factors, 4) only prescribing chronic opioids if a trial is successful to improve objective measures of function and pain, 5) not exceeding 50mg MED, and 6) performing monitoring and discontinuation of opioids with aberrant drug screen results. Yet, for those who are already taking more than 50mg MED, a prescription for naloxone is recommended, including while instituting other treatment based guidance to reduce risks of overdose and death
Benefits:	Rescue some individuals who overdose
Harms:	Theoretical potential for the patient to learn that there is a rescue medication, which then may promote more risky behavior and overdoses in susceptible individuals.
Frequency/Dose/Duration:	Administer the medication when there is lack of responsiveness or substantially reduced sensorium. For those known to have overdosed, yet not yet experienced the adverse effects, administration of naloxone at the earliest sign of impairment while on the way to the emergency room for definitive treatment is indicated. Generally requires approximately one hour observation after resuscitation, although the length is dependent on the specific drug, dose and route (Willman 16).
Indications for Discontinuation:	Normalization of consciousness
Rationale:	There are no randomized controlled trials. There are studies of lay-dispensed naloxone that all suggest efficacy (Strang 08; Lankenau 13; McAuley 10; Galea 06; Strang 16); however, most event and recovery

data are self-reported. Lay-dispensed naloxone recoveries were approximately 8-fold more likely with naloxone administration compared with those where naloxone was not administered. Also, there are extensive case series experiences with naloxone reversing reduced consciousness or comatose states. Naloxone has negligible adverse effects other than increasing experience of pain, is low cost, has extensive empirical evidence of efficacy and is recommended to have available for treatment of overdoses and near-fatalities.

Opioids Benefits and Harms

Benefits

Pain Relief

Over 120 randomized trials have reported consistent evidence of modestly reduced short-term acute, subacute and chronic pain ratings associated with opioid use compared with placebo. Other comparative efficacy trials have largely failed to find superiority of opioids compared with other active treatments including NSAIDs (see evidence tables below).[13] Magnitudes of those pain reductions are modest compared with placebo (i.e., generally 1/10 VAS pain scale reduction) and few of those trials lasted more than one month while none were over 6 months in duration. [13] These trials and details of the results are reviewed below.

Harms

Adverse Events

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

Opioid use is associated with elevated risks of emergency and other care. One quarter to one third of enrollees in both commercially insured and Arkansas Medicaid populations had an emergency department visit in the 12 months following chronic opioid therapy. [1158] Osteoarthritis patients receiving opioids compared to those receiving NSAIDs had increased risk of cardiovascular events, hospitalization, and overall mortality.[664]

A 3-year registry study found that of 233 patients enrolled, 39/227 (17.2%) completed the study, inferring high adverse effects. Forty-four percent had dose escalation within 3 months, inferring hyperalgesia or tolerance.[1159, 1160]

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

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

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

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

Table 2. Adverse Opioid Effects by Organ System (171, 653, 659, 682, 684, 688, 691-725)

System	Effect	Clinical Effect
Cardiovascular	Myocardial infarction	Heart attack or sudden death
	Orthostatic hypotension (dizziness on standing up)	Fainting on standing up
	Abnormal heart rhythm (QT prolongation, tachyrhythmias, cardiac arrest)	Sudden death, palpitations, syncope
Gastrointestinal	Gastroparesis (slow gut movement)	Nausea, abdominal pain, early satiety
	Reduced colon motility; spasm	Constipation, bowel obstruction
	Biliary spasm	Abdominal pain
Genitourinary	Exacerbation of urinary problems	Urinary retention
Endocrine	Suppression of testosterone	Impotence or reduced sex drive and erectile dysfunction, osteoporosis, feminization, reduction of muscle mass, reduced strength
	Suppression of LH, FSH	Reduced or abnormal menstrual periods
	Adrenal suppression	Fatigue, low blood pressure, electrolyte changes
Immune	Allergic reactions to medication	Rash, shortness of breath, itchy skin, edema
Neurological/ Psychiatric	Impairment of thinking or executive function	Outbursts, inappropriate behavior, limit testing, violence, reduced impulse control, impaired mental function
	Frontal lobe atrophy	Alterations in executive function, emotional response
	Brain damage from overdose or apnea induced hypoxia	Slight to severe impairments if an overdose occurs
	Cognitive impairment	Problems thinking clearly
	Vision	Color vision impairment
	Increased CNS pressure	Headache
	Hyperalgesia	Increased pain sensitivity, increasing doses of opioids/dose escalation
	Altered sense of taste	Reduced pleasure in eating, weight loss
	Reduced seizure threshold	Seizures
	Confusion, Impaired concentration	Increased accident risks and unclear thoughts
	Drowsiness, somnolence	Crash risk and reduced functioning
	Increased reaction time	Unsafe operation of machinery, motor vehicles, motor vehicle crashes
	Impaired coordination	Unsafe operation of machinery, falls
	Non-medical use	Overdose, death
	Mood elevation, euphoria	Mistaken judgment, changed interactions with other people
	Reduction in anxiety; tranquility	Mistaken judgment, changed interactions with other people
	Depression	Altered mood, depressed feelings, suicidal
Reproductive	Birth defects	Birth defects, miscarriage
	Neonatal withdrawal	Newborn babies of mothers on opioids go through opioid withdrawal
Respiratory	Respiratory depression	Death
	Central sleep apnea	Reduced ability to breath during sleep; daytime sleepiness; death
	Obstructive sleep apnea	New or increased problems with obstructive sleep apnea; daytime sleepiness; death
	Pneumonia	Pneumonia
	Hypoventilation	Worsening asthma and chronic obstructive pulmonary disease (COPD)
Vestibular	Reduced balance	Falls, fractures

Evidence for Adverse Events

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

Myocardial Infarction

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

Immunosuppression

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

Birth Defects

An association between early pregnancy maternal opioid analgesic treatment and certain birth defects has been shown [1154] These birth defects include conoventricular septal defects, atrioventricular septal defects, hypoplastic left heart syndrome, spina bifida and gastroschisis. The literature does document the potential harms associated with prescription opioid use during pregnancy, including poor fetal growth, preterm birth, birth defects, and neonatal abstinence syndrome (Yazdy M 2015)

Addiction (Abuse/Misuse)

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

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

Evidence for Addiction

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

Depression/Anxiety

Opioids are beneficial when prescribed in lower amounts and under specific conditions (see evidence tables below), helping to decrease the perception of pain. On the other hand, when opioids are used in medium and high doses, they may acutely or chronically contribute to clinical depression, and increase perceived pain intensity.

A prospective cohort study found 7% of 768 consecutive chronic pain program patients produced a normal MMPI, 15% conversion V, 9% neurotic and 69% had a disability profile. [1045] Aberrant psychological findings were also opioid dose-dependent, although that may be confounded by the apparent colinearity between psychological findings and opioid treatment. One large case series of 500 consecutive pain patients reported depression, anxiety and somatization disorder in 59%, 64% and 30% of the cases. [1178] Another longitudinal study found that those who reported some opioid use at time of admission into the study, "uniformly demonstrated higher pre-rehabilitation ratings of pain, disability, and depression." [1155] Other studies suggest associations between opioid use and depression [173, 182, 185, 738-740] and anxiety.[185, 739, 740]

Evidence for Depression/Anxiety
There are 11 studies incorporated into this analysis.[173, 221, 226, 660, 737-739, 741-743] See evidence table for adverse events below. There is 1 low-quality study in Appendix 4.[1179]

Post-Traumatic Stress Disorder

Patients with PTSD are reportedly more likely to be prescribed opioids and show less improvement than those without PTSD. [1037, 1038]

Evidence for Post Traumatic Stress Disorder
There are 2 studies incorporated into this analysis. [1037, 1038] See adverse events evidence table below.

Suicide

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

Respiratory Depression

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

In overdose situations, some manifestation of anoxic brain injury is found on imaging studies with leukoencephalopathy most commonly reported.[762-769]

Evidence for Respiratory Depression
There are 13 studies incorporated into this analysis.[618-623, 627-632, 751] See adverse events evidence table below.

Post-operative Sleep Disturbances

Opioids are associated with post-operative sleep disturbances that include suppression of rapid eye movement sleep, [1185] as well as appear apparent associated association with sleep apnea.[1186] There was no association between sleep disturbance and level of pain.[1187]

Evidence for Post-operative Sleep Disturbances

There are 2 studies incorporated into this analysis. [1186, 1187] See adverse events evidence table below. There is 1 low-quality RCT in Appendix 4.[1185]

Prescription Opioid-associated Deaths

Deaths have been reported among both those prescribed opioids and those obtaining opioids through diversion.[89, 105, 109, 169, 171, 193, 772-778] The most common medications associated with opioid-related

deaths are methadone, hydrocodone, oxycodone and fentanyl, although there are regional variations based on practice patterns and diversion.[6, 89-91, 93, 95, 97, 102, 779] Long-acting oxycodone has been linked to increased mortality.[1000] Tramadol has been represented as a safer alternative, yet overdose deaths have been associated with tramadol.[752, 780-788] In a cohort study by Dunn, et al., the hazard ratios for all overdose events were 0.31 in those with no opioid usage, 1.0 in patients with a 1 to <20mg/d MED, 1.44 in those with 20 to <50mg/d MED, 3.73 in patients with 50 to <100mg/d MED, and 8.87 in those whose dosage was ≥ 100mg/day MED (see Figure 2). In those who had a serious overdose event, the hazard ratios were 0.19 for no opioid usage, 1.00 for 1 to <20mg/d, 1.19 for 20 to <50 mg/d, 3.11 for 50 to<100mg/d, and 11.18 for those whose dosage was ≥100mg/day. [1022]

In a similar case cohort study by Bohnert, et al., the hazard ratios for those with chronic pain were 1.0 in patients with a 1 to <20mg/day dosage, 1.88 in those with a 20 to <50mg/day dosage, 4.63 in patients with 50 to <100mg/ day dosage, and 7.18 in those whose dosage was ≥100mg/day. In those who had acute pain, the hazard ratios were 1.00 for 1 to <20mg/day, 1.58 for 20 to <50mg/d, 4.73 for 50 to <100mg/day, and 6.64 for those whose dosage was ≥100mg/day. [1046]

Implementation of a 120mg/day MED maximum dose in 2007 in Washington State has been at least partially credited with decreases in the percentage of workers on Schedule II opioids, patient numbers over the limit and numbers of opioid-related deaths. [1188] However, the magnitude of that state's reduction has not been large.

In a matched case control comparison, Paulozzi, et al., found 300 deaths occurred among 730,381 patients. This is 27.4 per 100,000 patients per year. It was also found that there was an association between risk and number of prescriptions, prescribers and opioid daily dose. Six controlled substance prescriptions during 6 months quadrupled the risk of overdose deaths. The odds ratios for single peak prescriptions increased after 20 morphine milligram equivalents (MME)/day and increased until about 200 MME/day. Of those who were prescribed opioids, 34.2% had an average daily dosage above 60 MME/day, 23.6% had a daily dose above 120 MME/day and 17.3% above 200 MME/day. Among the 300 deceased patients, 66.3% of them had obtained opioids from two or more prescribers, 43.0% had prescriptions from three or more, and 13.7% had prescriptions from six or more. [1024]

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

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

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

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

Evidence for Prescription Opioid Deaths/Causes of Death in Those Taking Opioids

There are 28 studies incorporated into this analysis.[104, 112, 171, 182, 185, 188, 189, 221, 289, 535, 660, 661, 663, 669, 726, 738, 757, 772, 792-801] See adverse events evidence table below.

Search Strategy:

For adverse events, we searched PubMed, EBSCO and Google Scholar without limits on publication dates. We used the following terms: incidence, prevalence, cohort, population, population-based, observational studies, population death estimates, high risk opioids, low risk opioids and hazards to find 29,107 articles. Of the 29,107 articles found, we reviewed 16 and used six. For addiction, we searched PubMed and Google Scholar without limits on publication dates. We used the following terms: incidence, prevalence, cohort, population, population-based, observational studies, population death estimates to find 7,004 articles. Of the 7,004 articles found, we reviewed 3 and used one. For Depression/Anxiety, we searched PubMed and Google Scholar without limits on publication dates. We used the following terms: opioids, risk factors, abuse to find 36,088 articles. Of the 36,088 articles, we reviewed 14 and used 11. For post-traumatic stress disorder, we searched PubMed and Google Scholar without limits on publication dates. We used the following terms: opioids, post-traumatic stress disorder to find 6,844 articles. Of the 6.844 articles, we reviewed two, and both were used. For Respiratory Depression, we used the following search terms: respiratory depression, respiratory insufficiency, respiratory failure and ventilator depression. The search terms were used in Google Scholar, PubMed and EBSCO databases. Most of the articles were found using the PubMed database; with a total of 52 articles. However, only 13 were used in the draft. There was no limit on dates for these searches. For Post-operative sleep disturbances, we used the following search terms: sleep disturbance, sleep disorder, and dyssomnia. The search terms were used in Google Scholar, PubMed, and EBSCO databases. Most of the articles were found using the PubMed database with eight. However, only three were used in the draft. There was no limit on dates for these searches. For Prescription opioids deaths, we used the following search terms: Chronic Pain, Complex Regional Pain Syndrome (CRPS), Neuropathic Pain, Radicular Pain, Peripheral Neuropathic Pain, and Chronic Persistent Pain (CPP). The search terms were used in Google Scholar, PubMed, and EBSCO databases. Most of the articles were found in PubMed with 94 articles and in EBSCO with 4 articles. However, only eight were used in the draft. Other searches were done to look at the harms and benefits of opioid use. For causes of death in those taking opioids, we used the following search terms: death, opioids, incidence, prevalence, cohort, population, population-based, observational studies, and population death estimates. The search terms were used is Google Scholar, PubMed, and EBSCO databases. Google Scholar found eight and PubMed only found one article. However, only for of the articles were used in the draft. There was no limit on dates for these searches.

Financial Costs Associated with Opioid Usage

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

Evidence for Financial Costs of Opioid Usage

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

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

Comorbidities

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

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

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

Evidence for Comorbidities

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

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

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

FDA has suggested risk evaluation and mitigation strategies (REMS) with three components: a medication guide, elements to assure safe use, and timetable for submission of assessments for extended release and long acting opioids. The medication guide would provide patients with more information about the safety and risks associated with their medication. Elements to assure safe use would focus on provider training specific to safe opioid prescribing, product information, and patient counseling. Evaluations should be implemented to determine the effectiveness of the REMS.[820]

Opioids have long played an important role in the control of cancer-related and non-cancer pain. At the same time, they have contributed significantly to morbidity and mortality. According to the Centers for Disease Control and Prevention (CDC), “opioid analgesics, such as oxycodone, hydrocodone, and methadone, were involved in about 3 of every 4 pharmaceutical overdose deaths (16,651),” illustrating the importance of appropriate prescribing and patient monitoring. (CDC 13) In an effort to address the magnitude of this public health crisis, the federal government developed the Risk Evaluation and Mitigation Strategies (REMS) program. The effectiveness of this program has recently come in to question in a document published in 2013 by the Department of Health and Human Services Office of Inspector General entitled *FDA Lacks Comprehensive Data to Determine Whether Risk Evaluation and Mitigation Strategies Improve Drug Safety*.

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

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

Within this context, FDA has identified three mechanisms that manufacturers may be required to include in the risk evaluation and mitigation process involving opioids: 1) use of a medication guide and/or a package insert; 2) elements to assure safe use (ETASU), and 3) communication plans. Risk management and evaluation strategies further require manufacturers to establish a timetable for submission of risk assessments for brand name drugs including extended release and long-acting opioids. Under the ETASU section, FDA requires the manufacturer to assure that the prescribers of opioids have received proper training on the drug and have been supplied with appropriate patient education materials. Additionally, the manufacturer is required to notify the prescriber that REMS exists for a particular opioid and of the need for training.

The effectiveness of the original 1999 REMS was evaluated by FDA’s Office of Inspector General in 2013. Concerns were identified related to the effectiveness of REMS mandated between the years 2008-2011. Findings of the study concluded that almost 50% of 49 REMS reviewed lacked data required by the assessment plan implemented by FDA with 14% meeting all required goals. The report stated that “FDA has not identified reliable methods to assess the effectiveness of REMS.” (Office Insp General 13) The Inspector General’s Office made the following seven recommendations to address these findings, and FDA accepted the first six:

1) Develop and implement a plan to identify, develop, validate, and assess REMS components.
2) Identify REMS that are not meeting their goals and take appropriate actions to protect the public health.

3) Evaluate the ETASUs of one REMS each year as required by Federal law.
4) Clarify expectations for sponsors' (drug manufacturer's) assessments in FDA assessment plans.
5) Ensure that assessment reviews are timely.
6) Identify incomplete sponsor assessments and work with sponsors to obtain missing information.
7) Seek legislative authority to enforce FDA assessment plans.

Providers play an integral role in the chain of pain control. As a result, they remain key stakeholders in all processes related to opioid prescribing and patient monitoring. Concerns by prescribers over REMS have arisen since its release as some prescribers opined of the burdensome need to take mandatory training classes, suggesting actions to stopping prescribing opioids, and thus preventing patients from receiving pain medication. (Slevin 11) Additionally, REMS may require prescribers to receive certification or participate in certain programs prior to prescribing certain opioids creating added burdens. In response to these concerns, FDA has held public meetings inviting stakeholders to participate in commentary on the standardization of REMS. (Dal Pan 12) REMS remains a work in progress and may be but one relatively weak tool to address the multi-factorial issue of opioid abuse/misuse and inappropriate prescribing.

Diagnostics and Monitoring

Opioid treatment agreements are used to monitor patients on opioids. Commonly, these include provision for urine drug testing for assessing compliance for use of that particular opioid, as well as ascertaining other illicit substance use. Finding either type of urine drug testing discrepancy is normally considered grounds for opioid cessation.

Drug testing most commonly measures drugs, or their metabolites, in urine or hair. There is expanding use of this diagnostic tool in pain management and addiction medicine. Urine is most commonly assayed. Hair testing may also be used, primarily for its advantage of assessing drug(s) use over a longer timeframe, although it cannot be used for acute toxicity and its interpretation is frequently, considerably more difficult[16]. With the common 1" to 1.5" (2-3cm) scalp hair specimen evaluates a 'window of detection' of drug use over roughly the past 3 months. For those with no scalp hair, if body hair is submitted for testing the 'window of detection' may be as long as 1 year. Thus hair testing is used only to evaluate for the use of drugs not prescribed by or reported to the treating physician. The "window of detection" is too long to determine if the person is actually currently (still) taking the prescribed opioids(s).

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

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

The NIDA 5 measures the cocaine metabolite benzoylecgonine, marijuana metabolites (principally delta 9 tetrahydrocannabinol, some opiates (e.g., codeine, morphine, 6-monoacetyl morphine [a heroine metabolite], amphetamines (methamphetamine, amphetamine, MDMA (3,4 methylenedioxy-methamphetamine) MDA (3,4 methlyenedioxypamphetamine), MDEA (3,4 methylenedioxy-N-ethylamphetamine), and phencyclidine (PCP). (DOT 10) Many commercial labs do this testing, and offer "expanded panel" tests that will detect commonly used opioids including oxycodone, hydrocodone, oxymorphone, hydromorphone, tramadol, Fentanyl, carisoprodol, barbiturates, benzodiazepines, etc. Thus, it is important to decide which panel will provide the best assessment for a specific situation. In general, the NIDA 5 is insufficient for monitoring opioid use, even if the patient is to be taking only a natural opiate due to insufficient coverage of other opioids. The NIDA 5 was developed to detect heroin use in US Military troops in Vietnam in the 1960s, and not for detecting use of most current prescription opioids. To be useful, one must choose a test that the laboratory states will detect the presence of the opioid being prescribed, assuming the patient is actually taking and not diverting the medication. It is also important that the test chosen is able to detect the drugs that might be used/abused surreptitiously, and that increase the risk of accidental overdose mortality (e.g., benzodiazepines, barbiturates, etc.).

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

The NIDA-5 drug testing "panel" is commonly the extent of required testing for many federally regulated safety sensitive employees;[17] these employees generally should not be taking opioids if in a "full duty" safety sensitive work status. This drug testing panel also is the most common test done by private employers as a "pre-employment" drug test. The opiates in this test are effectively a heroin detection system pioneered by the US Army for testing American soldiers serving in the Vietnam War. The new synthetic and semi-synthetic pharmaceutical opiates are not detected by this panel.

Multiple laboratories conduct urine drug testing. Each lab offers testing for the basic 5 categories, but each lab typically also offers "expanded panel" testing capable of detecting many more classes of drugs. Testing for more classes of drugs costs more per test. The choice of which test to order depends on what medications are being prescribed, and on what substances are potentially available for the patient to abuse. The prescribing physician must consult with the laboratory to determine which drugs are detectable by which tests, and then choose a test that would detect each prescribed controlled substance, and a test that would detect what other abusable drugs the person might be surreptitiously taking.

Urine drug testing should be done in federally certified labs. The certified labs use a 2-step process. The initial screening test is generally an enzyme-mediated immunoassay. Negative immunoassays conclude testing for a specific drug, or drug class. However, the screening test method frequently cross-reacts with other drugs. Thus, the immunoassay screening test has the possibility that positive tests are true positives, but also the possibility that positive tests are false positives due to cross-reacting substances.

If the screening test is positive, the certified labs do step 2, which is gas chromatography-mass spectroscopy (GC-MS). This test is more expensive, but detects the unique chemical "finger print" of every specific chemical. With GC-MS, there are no false positive tests.

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

Proper interpretation of test results requires an understanding of the metabolism of medications.[832] Hydrocodone is metabolized to hydromorphone (Dilaudid) before excretion, and the USD of individuals taking hydrocodone thus, usually detects both hydrocodone and a lower concentration of hydromorphone. If the last dose of hydrocodone was taken near the limit of the approximately 3-day window of detection, patients prescribed and taking just hydrocodone may test negative for hydrocodone (all metabolized), but still positive in low concentration for hydromorphone.

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

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

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

Evidence for Diagnostics and Monitoring

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

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

Screening Tools

While the clinical interview remains an important method to identify risk for aberrant drug-related behaviors, it is neither systematic nor efficient. Thus, there are many screening methods that have been developed. The three tools with the largest volume of research are the Screener and Opioid Assessment for Patients with Pain (SOAPP) and its revised version (SOAPP-R), the Pain Medication Questionnaire (PMQ), and the Current Opioid Misuse Measure (COMM). All three of these tools have undergone partial validations, although none of these has been fully validated to document prevention of opioid misuse/abuse. The Pain Disability Index is also widely used, it is also wholly subjective and has somewhat fewer supportive data.

The SOAPP was designed to reflect the consensus of experts and determine the circumstances, and characteristics, related to aberrant drug use by a self-administered screening tool for chronic pain patients. The patient-self report items for the SOAPP were generated based on the concept mapping results, literature, and clinical experience of the patients. (Butler 04) However, a SOAPP-R was created later to place limitations, and improve the original assessment. (Butler 08) The SOAPP-R has been reportedly reliable and valid as a screening tool for those chronic pain patients with risk of aberrant drug-

behavior, having undergone partial validations, yet the likelihood ratios are unhelpfully near 1 (CDC 16). (see Appendix 1).

The second assessment tool is the COMM. The COMM, also a self report instrument, was developed to complement other screening assessments tools for opioid misuse. It also helped physicians to evaluate patients risk for aberrant use of opioids. The COMM appears to be a reliable screening tool to identify chronic pain patients with aberrant drug related behaviors (see Appendix 1).

The third tool is the Pain Medication Questionnaire (PMQ). It has also undergone partial validation.

Other tools including the Prescription Drug Use Questionnaire, DIRE score, Opioid Risk Tool (ORT) (see Appendix 1), Pain Assessment and Documentation Tool, Brief Risk Interview, and Addiction Behaviors Checklist are reportedly helpful to identify future aberrant drug-related behaviors, although there is considerably less robust literature supporting them.

Genetic Factors

Opioid deaths have been associated with CYP2D6 and OPRMI gene variations, with the CYP cytochromes (CYP 3A4/3A5, CYP 2D6, CYP 2C9, CYP2D9) responsible for metabolism through the cytochrome P450 system, and genetic variations impairing opioid metabolism (see Appendix 3). As one example of potential clinical impacts, there is a strong tendency for those of Chinese ancestry, as well as some Caucasians to not metabolize codeine to morphine. Currently, screening for genetic risks prior to opioid treatment is not in widespread use. Cytochrome blocking drugs and cytochrome inducing pharmaceuticals also influence efficacy and toxicity.

Evidence for Screening Tools

There is 1 moderate-quality RCT and 28 other studies incorporated into this analysis. (Jamison 10; Butler 04; Moore 09; Akbik 06; Butler 08; Butler 09; Edwards 11; Martel 13; Jones 12; Adams 04; Holmes 06; Dowling 07; Buelow 09; Hojsted 11; Morasco 13; Jones 13; Webster 05; Witkin 13; Meltzer 11; Parhami 12; Butler 10; Wasan 07; Butler 07; Moore 09; Belgrade 06; Atluri 04; Michna 04; Compton 98; Manchikanti 04)

Search Strategy: For Screening Tools, we searched PubMed, EBSCO, and Google Scholar without limits on publication dates. We used the following search terms: preferred, questionnaires, aberrant drug behavior, and validated to find 17,639 articles. Of the 17, 639 articles, we reviewed 19 articles and included nine articles. For SOAPP-R, we searched PubMed, EBSCO, and Google Scholar. The following terms were used: Screening Tools, Screener and Opioid Assessment for Patients with Pain-Revised, and SOAPP-R. A total of 550 articles were found. We reviewed eight articles and included six. The timeframe was not limited. For PMQ, we searched PubMed, EBSCO, and Google Scholar. The following terms were used: Pain Medication Questionnaire, PMQ, Opioids, Medication, and Misuse. A total of 388 articles were found. We reviewed thirteen articles and included seven. The timeframe was not limited. For ORT, we searched PubMed, EBSCO, and Google Scholar. The following terms were used: Screening Tool, Opioid Risk Tool, and ORT. A total of 23,959 articles were found. We reviewed twelve articles and included five. The timeframe was not limited. For DIRE, we searched PubMed, EBSCO, and Google Scholar without limits on publication dates. We used the following search terms: DIRE, Diagnostic Intractability Risk Efficacy tool, and screening tool to find 16,902 articles. Of the 16,902 articles found, we reviewed two articles and included both articles. For Current Opioid Misuse Measure, we searched PubMed, EBSCO, and Google Scholar. The following terms were used: Current Opioid Misuse Measure, COMM, Validity, Reliability, Outcome Measure, and Screening. A total of 25,831 articles were found. We reviewed ten articles and included six. The timeframe was not limited.

Auditing/Monitoring Criteria

The provider is recommended to assure:

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

Evidence Tables

Search Strategy

PubMed, EBSCO, and Google Scholar were searched without limits on publication dates. The following search terms were used: clinical trial, randomized controlled trial, random, randomized, chronic pain, complex regional pain syndrome (CRPS), neuropathic pain, radicular pain, peripheral neuropathic pain, chronic persistent pain (CPP), acute pain, subacute pain, dextropropoxyphene, codeine, tramadol, tapentadol, anileridine, alphaprodine, pethidine, hydrocodone, morphine, oxycodone, methadone, diamorphine, hydromorphone, oxymorphone, levorphanol, 7-hydroxymitragynine, buprenorphine, fentanyl, sufentanil, bromadol, etorphine, dihydroetorphine, carfentanil, meperidine, propoxyphene, and naltrexone. A total of 3743 articles were found. Abstracts of the 3743 articles were reviewed. We analyzed 65 articles in detail and included 157 articles.

Evidence for Use of Opioids in Safety Sensitive Jobs

Name/Year Location Potential Conflict of Interest (COI)	Score *	Study Design	Exposure	Population Age Range Dropout Rate Case Definition	Results	Conclusion	Comments
Bachs 2009 Norway Work was funded by the Norwegian Institute of Health. Authors declared no conflict of interest.	II	Prospective cohort design	Prescription of codeine or tramadol in a national prescription database	N = 3.1 million, followed up from age 18 or from January 7, 2004 until accident date, or until age of 70 or death. Ages 18-70 years. Examined whether driver with filled prescription for codeine or tramadol is at increased risk or standardized incidence ratio (SIR) for road accident resulting in injury to persons.	181 accidents with injury with drivers on codeine (defined as within 7 days after dispensing date). 20 drivers on tramadol. SIR gender and all age groups combined: 1.9; 95% CI: 1.6−2.2. High codeine SIR 2.9 (2.3-3.6). SIR for tramadol (1.5; 95% CI: 0.9–2.3) was not significant but suggests a trend.	"[W]e found an increased SIR of motor vehicle accidents that resulted in injury and involved drivers exposed to Codeine."	Population-based study with databases for drugs. Under-powered for tramadol (non-significant 50% increased risk). Data suggest higher risk if higher codeine consumed.
Bramness 2012 Norway	II	Population-based cohort study	Individuals on methadone maintenance treatment during April 1, 2004 or	N = 4,626 person-years observed in patients exposed to methadone. Age 18-69.	26 methadone-exposed patients involved in accidents involving personal injury.	"Men exposed to methadone appear to have an increased risk of being involved in motor vehicle	Population-based study from Norway with prescription database used. Data suggest increased

Research was funded by internal funds at the Norwegian Institute of Public Health. Authors declared no conflict of interest.			from 18th birthday until date of first road traffic accident (as driver).	Investigated whether exposure to methadone affects risk of motor vehicle accident with personal injury.	For male drivers, there was an increased traffic accident risk of 2.4, 95% CI: 1.5–3.6, when exposed to methadone, and females who received methadone had no increased risk of being involved in motor vehicle accidents, SIR 1.1, 95% CI: 0.2-3.1.	accidents involving personal injuries."	risk of crash among males using methadone. Results negative for females, but under-powered. Combined male and female risk was 2.1 (95% CI 1.4, 3.1) for the relationship between methadone and traffic accident.
Engeland 2007 Norway No mention of industry sponsorship or conflict of interest.	II	Population-based cohort study	Those born between April 1934 – September 1987, living in Norway in 2004-2005. Information on prescriptions and road traffic accidents.	N = 3,115,322 persons, followed for 1.5 years. Age 19-69 Drop-out rate not reported. Examined risk of car driver involvement in road traffic accident while using prescription drugs.	Risk of being in an accident increased in users of (any) prescribed drugs; OR = 1.4, 95% CI, 1.3-1.5. Risk increased in users of natural opium alkaloids (OR = 2.0; 1.7-2.4), tranquilizing benzodiazepines (2.9; 2.5-3.5), and hypnotic benzodiazepines (3.3; 2.1-4.7).	"The increased risk of being involved in a road accident as driver while receiving prescribed opiates and benzodiazepines supported the results from other studies."	Large sample size. Study evaluated risk after initial prescription over 7 and 14 days, finding significantly increased risks.
Gibson 2009 United Kingdom No mention of industry sponsorship or conflict of interest.	II	Case-crossover and case-series analyses	1986-2004 – Data collected from medical records through The Health Improvement Network (THIN). Prescription for any of: benzodiazepines, nonbenzo-diazepine hypnotics, beta-blockers, selective serotonin	N = 49,821 ages 18-74 years in MVC using benzodiazepines, nonbenzodiazepine hypnotics, beta-blockers, selective serotonin reuptake inhibitors, tricyclic antidepressants, opioids, and antihistamines.	Opioid treatment associated with increased risk of MVC (IRR acute period up to 4 weeks = 10.9, 99% CI: 9.96-11.93; IRR 4 weeks after opioid began = 1.70, 99% CI: 1.39, 2.08), persisted throughout treatment (IRR = 1.29, 99% CI: 1.08, 1.54). This	"[T]he risk of motor vehicle crash is increased by the use of benzodiazepines, opioids, and compound analgesic preparations containing acetaminophen and an opioid for the duration of their usage, the risk decreasing once the medication is discontinued."	Data suggest increased crash risk associated with opioids. Highest risk acutely. Increased risk reversed on opioid cessation.

			reuptake inhibitors, tricyclic antidepressants, opioids, and antihistamines.		was not observed when opioids were withdrawn.		
Gomes 2013 Ontario, Canada Supported by grant from Ontario Ministry of Health and Long-term Care Drug Innovation Fund and Institute for Clinical Evaluative Sciences. COI: Dr. Mamdani reported honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer.	II	Population-based study with nested case-control	April 1, 2003 through March 31, 2011. Computerized medical records tool.	N = 549,878 given at least 1 prescription of opioid were involved in an MVC; 5,300 were matched with a control; of these, 2428 (45.81%) were drivers, 840 (15.85%) were passengers, 579 (10.92%) were pedestrians, and 1453(27.42%) were in unknown or miscellaneous position. Age range 18 to 64 years.	Drivers prescribed very low doses vs. low and moderate doses of opioid had a 21% vs. 29% increased odds of road trauma (1.21 [95% CI: 1.02-1.42] vs. 1.29 [1.06-1.57]). Drivers prescribed high and very high doses vs. low and moderate had a 42% vs. 23% increased odds of road trauma (1.42 [95% CI: 1.15-1.76] and 1.23 [1.02-1.49]).	"Among drivers prescribed opioids, a significant relationship exists between drug dose and risk of road trauma. This association is distinct and does not appear with passengers, pedestrians, and others injured in road trauma."	Data suggest opioids associated with increased risk of road trauma. Relationship appears dose-response. Data may substantially underestimate risk as comparison is low dose rather than "0" dose.
Majdzadeh 2009 Iran Study funded by Institute of Public Health Research in Tehran University of Medical Sciences. No COIs disclosed.	II	Case-crossover	Study conducted in emergency department of Shaheed Bahonar Hospital in Kerman province, the only trauma center for 400,000.	N = 75 involved in MVC and regular opium users. Participants ≥18 years old. Exposure was driving under influence of opium before accident and overlap between driving hours and hours after opium consumption until traffic accident was considered as person-hours exposed for hazard period.	Relative risk for opioid consumption 6 hours before accident was 3.2 (p = 0.05) and 3 hours before accident was 4.29, p = 0.05.	"These results suggest a heightened risk of traffic injuries after opium consumption in regular users."	Data suggest opioids associated with increased risk of crash. Data only regarding opioid users, which may underestimate risks compared with non-use.
Mørland 2011	II	Case-crossover and case-	January 2001-December 2002.	(N = 501) Denmark, (N = 463) Finland, (N = 23) Iceland,	60% of drivers in single vehicle crashes had	"[I]n Northern European countries, alcohol and impairing	Data not stratified for opioids into illicit and licit. Risk

Denmark, Finland, Iceland, Norway, and Sweden No mention of industry sponsorship. No COIs were disclosed.		series analyses	Participating laboratories collected biological samples from medico-legal autopsies and in some cases from drivers still alive shortly after accident.	(N = 344) Norway, and (N = 590) Sweden. Age range, not specified. Study aim to find which drugs/drug combinations most common in drivers who died, in particular (single vehicle crashes where crash responsibility would be referred to driver killed).	alcohol and/or drug in their blood samples vs. 30% of drivers killed in collisions with other vehicles. 40% had non-alcohol drugs in blood. Illicit-drugs found in 24% of drivers who had non-alcohol drug in their sample. Drugs range from 36 to 41% in single vehicle crashes, 68 to 71% in multiple vehicle crashes.	non-alcohol drugs are frequently detected in killed vehicle drivers, and very frequently in younger drivers killed in single vehicle accidents."	comparisons are low rather than non-use of opioids.
Corsenac 2012 France Supported by French Health Products Agency; French National Research Agency; French National Medical Research Institute; French Medical Research Foundation; and French Direction Générale de la Santé. All authors declare no competing interests.	III	Population-based case-control of police reports, healthcare insurance databases	Use of buprenorphine and methadone.	N = 72,685 drivers involved in injurious crash in France July 2005 – May 2008. Age range <29 to 49. Study objective to investigate association between risk of being responsible for road traffic crash and use of buprenorphine and methadone.	196 drivers exposed to buprenorphine or methadone on day of crash were young, largely male drivers (29-38) and using level 2 and 3 medicines or highest level risk. 387 drivers taking at least one dispensation of buprenorphine / methadone in 6 months preceding crash, showed increased responsibility risk for these drivers, OR = 1.70, 95% CI: 1.36 2.14). When excluding 159 drivers who	"Users of methadone and buprenorphine were at increased risk of being responsible for injurious road traffic crashes."	Three databases used. Increased risk of crash if buprenorphine or methadone on day of crash. Considerable use of other medications may have (partially) confounded.

					had a dispensation in prior 8 days before crash from analyses, OR = 1.52, 95% CI: 1.14-2.03. Adjusted OR for crash = 2.02, 95% CI: 1.40-2.91.		
Dubois 2010 U.S.A. District of Columbia, Puerto Rico No mention of industry sponsorship or conflict of interest.	III	Case-control design based on data from Fatality Analysis Reporting System.	1993-2006, those involved in fatal crashes.	N = 75,026 drivers tested for both alcohol and drugs had a blood alcohol level of 0. Mean age 46. Examinee impact of opioid analgesics on drivers involved in fatal accidents.	2,109/75,026 tested positive for opioid, and 380/75,026 tested positive for 2 opioids. Females who tested positive for opioids had increased odds of performing unsafe driving actions (UDA) from age 25 (OR: 1.35) to 55 (OR: 1.30), and for males from age 25 to 65 (OR: 1.66 and 1.39, respectively). Overall, testing positive for opioid increased odds of performing an UDA associated with crash by 57%.	"[T]he results of our study suggest that opioids negatively affect safe driving."	U.S. population-based NHTSA FARS, Fatal crash study, eliminated confounding by alcohol. Data suggest opioids associated with unsafe driving prior to fatal crash. Findings not found in elderly.
Movig 2004 Tilburg, region of The Netherlands No mention of industry sponsorship. No COIs were disclosed.	III	Prospective observational case-control study.	Use of alcohol and/or licit and illicit drugs	N = 110 cases injured car or van drivers admitted to ER, N = 816 randomly selected from moving traffic during 20 roadside survey sessions. Age range 18 to ≥50. To assess relationship between drug use and trauma injuries requiring hospitalization caused by motor vehicle accidents.	74% males; 40% of all cases positive for 1 or more drugs and/or alcohol, vs. 14% controls. Benzodiazepines, adjusted OR = 5.1 (95% CI: 1.8-14.0) and alcohol significantly associated with road accidents.	"[Drug] use, especially alcohol, benzodiazepines and multiple drug use and drug–alcohol combinations, among vehicle drivers increases the risk for a road trauma accident requiring hospitalization."	Likely underpowered for opioids with OR = 2.3, n = 28.

					Those concomitantly exposed to alcohol/1 or more drugs, showed highest risk for road accidents, adjusted OR = 112.2 (95% CI: 14.1–892.9. Crash risk with injuries were not statistically significantly related to opiates, adjusted OR = 2.35 (95% CI: 0.87, 6.32).		
Mura 2003 France Financial support from the French Ministry of Health, in framework of a "Programme Hospitalier de Recherche Clinique National" No COIs were disclosed.	III	Case-control study	Prevalence of: alcohol, cannabinoids, opiates, cocaine metabolites, amphetamines and therapeutic psychoactive drugs.	N = 900-1,800 drivers involved in non-fatal accident, 900 patients controls in same emergency units for non-traumatic reason. Age range 18to >50. Using blood as biological matrix to screen for prevalence of alcohol, cannabinoids, opiates, cocaine metabolites, amphetamines and therapeutic psychoactive drugs in blood samples from drivers injured in road accidents vs. controls.	Morphine prevalence between drivers was, 2.7% and patients, 0.03%, with highly significant, p < 0:001, with OR = 8.2. Psychoactive therapeutic drugs found in 142 drivers or15.8% and of 107 controls or 11.9%, p < 0.05. Benzodiazepines were found alone in 9.4% of drivers and 5.8% of patients, which led to OR = 1.7, p < 0.01.	"[A] higher prevalence of opiates, alcohol, cannabinoids and the combination of these last two compounds in blood samples from drivers involved in road accidents than in those from controls, which suggests a causal role for these compounds in road crashes."	Large sample size. Opioids associated with higher risk of crash (OR = 8.2). Licit vs. illicit use unclear.
Howard 2004 Australia	III	Cross-sectional study	To measure the prevalence of excessive sleepiness and sleep-disordered	N = 2,342 commercial vehicle drivers who completed a questionnaire and anthropomorphic measurements. N = 161 drivers	59.6% of drivers had sleep-disordered breathing and 15.8% had	"Chronic excessive sleepiness and sleep-disordered breathing are common in Australian	Data suggest an association between opioid use and risk of commercial motor vehicle accidents.

Supported by grants from Vicroads and Roads and Traffic Authority of New South Wales All authors declare no competing interests.			breathing and assess accident risk factors.	who attend in laboratory polysomno-graphy. Mean age (questionnaire) = 42.4 years; polysomno-graphy = 47.8 years. Simple random sample of 98 workplaces selected from 395 workplaces on database of Transport Workers Union in Australia.	obstructive sleep apnea syndrome. Odds ratio for reported crash in past 3 years associated with narcotics use OR = 2.40 (95% CI 1.46-3.92, p <0.01).	commercial vehicle drivers. Accident risk was related to increasing chronic sleepiness and antihistamine and narcotic analgesic use."	

*Score "I" for high- or moderate-quality randomized controlled clinical trial (score of 0-11, with 8-11 high quality, 4-7.5 moderate quality and 0-3.5 low quality). For observational studies of harms, a score of "II" is for prospective cohort studies, prospective comparative studies, case-crossover and large, population-based studies. A score of "III" is for retrospective, case control or cross-sectional studies.

Evidence for Acute Pain

Author/Year Study Type Potential Conflict of Interest	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Acute Musculoskeletal Pain						
Ekman 2006 RCT Sponsored by Pfizer Global Pharmaceuticals, one is employed by same and all have declared COIs as speakers/research funds.	I(9.5)	N = 829 acute 1st- or 2nd-degree ankle sprain	Valdecoxib 20mg QD (N = 233) vs. valdecoxib 20mg BID (N = 235) vs. Tramadol 50mg QID (N = 238) vs. placebo (N = 123) for acute mild and moderate ankle sprain. All patients received 7 days of treatment.	Valdecoxib 20mg BID vs. valdecoxib 20mg QD vs. Tramadol 50 mg QID vs. placebo. Patient global assessment good/very good: Day 4 no differences, Day 7 (76.4 vs. 67.3 vs. 59.6 vs. 55.5) p <0.001 for BID vs. placebo. APS questionnaire: 33.9 vs. 26.6 vs. 20.6 vs. 24.4 (p = 0.009, Day 4). Patient assessment of return to walking with/without pain Day 4 (47.5/44.6/38.4/35.0) p = 0.002; Day 7 (79.4/72.5/67.3/ 63.9) p = 0.001.	"Valdecoxib 20 mg bid was at least as effective as Tramadol 50 mg 4 times daily and significantly better than placebo."	Data suggest valdecoxib 20mg BID superior to placebo and trended towards better than tramadol for acute pain relief at Days 4 and 7. No difference in tramadol and placebo at Day 4, with higher withdrawal rates in tramadol.
Clark 2007 RCT Partially supported by Children's Hospital of E. Ontario Research Institute grant and salary support from same. No COIs disclosed.	I(9.5)	N = 336 children with pain from acute musculoskeletal injuries including fractures	Acetaminophen (n = 112) vs. ibuprofen (n = 112) vs. codeine as a single dose (n = 112). Single dose study. Parents received a 2-day follow-up phone call.	After 60 minutes, patients in ibuprofen group showed significantly greater improvement compared to codeine and acetaminophen groups for pain score, (p <0.001). No difference between codeine and acetaminophen for changes in pain scores. No difference in patients requiring more analgesic, (p = 0.32).	"[A]mong children with pain from acute musculoskeletal injuries presenting to a pediatric ED, a single dose of ibuprofen provides greater pain relief than codeine or acetaminophen."	Single dose treatment evaluated 60 minutes after treatment. No stratification by injury type. Data suggest ibuprofen superior than codeine.
Chang 2006 RCT No outside funding or support received. No mention of COIs.	I(8.5)	N = 198 in emergency department with acute severe pain	Hydromorphone at 0.015mg/kg IV (N = 99) vs. morphine at 0.1mg/kg IV (N = 99). Research assistants enrolled patients consecutively 24 hours per day and collected ED data from October 2004 to January 2005.	Adverse events by group was not significant (hydromorphone 35%, morphine 32%; p = 0.86). Pain ratings lower in hydromorphone vs. morphine (-5.4 vs. -4.5; -0.9 difference (95% CI -1.8 to 0.0).	"ED patients who received intravenous hydromorphone had a greater decrease in mean pain score than those who received intravenous morphine. The CI around this difference of -1.3 ranges from -2.2 to -0.5, with the upper end of the CI only half a numeric rating scale unit below 0."	Acute pain study with 2 hour follow-up suggesting hydromorphone at 0.015mg/kg may be an alternative to morphine 0.1mg/kg IV. No longer-term data reported.

Bounes 2010 RCT Double-blind Sponsored by Toulouse University Hospital. No mention of COIs.	I(8.5)	N = 108 with acute severe pain caused by trauma.	Sufentanil: 0.15µg/kg, followed by 0.075µg/kg (n = 54) vs. morphine: 0.15mg/kg, followed by 0.075 mg/kg (n = 54). Doses given IV Q3 minutes until pain relief. Follow-up at baseline, 3, 6, 9, 12, 15, and 30 minutes after 1st injection.	At 15 minutes, 74% of sufentanil group had numeric rating scale (NRS) score ≤3 vs. 70% morphine group (Δ4%; 95% CI: 13% to 21%). At 90 minutes, 65% sufentanil vs. 46% morphine group had NRS ≤3 (Δ 18%; 95% CI: 0.1% to 35%). Median dose for those with relief was 0.225 mg/kg (IQR 0.225 to 0.375 mg/kg) in morphine vs. 0.225 µg/kg (IQR 0.225 to 0.3µg/kg) in sufentanil group.	"[D]espite a slight advantage in very early analgesia, sufentanil is not superior to morphine for traumatic pain relief in an out-of-hospital setting."	Data suggest no significant differences in pain reductions and analgesia duration favored morphine.
Turturro 1998 RCT Prospective Double-blind Support by the Emergency Medicine Association of Pittsburgh. No mention of COIs.	I(8.5)	N = 68 adult emergency department (ED) patients with acute musculo-skeletal pain caused by minor trauma. Most fractures distal extremities. Age 18 to 70.	Tramadol: 100 mg PO (n = 33) vs. Hydrocodone-acetaminophen: 5/500 mg PO (n = 35). Follow-up at 30, 60, 90, 120, and 180 minutes.	Mean pain scores lower in hydrocodone-acetaminophen group vs. tramadol group at 30/60/90/120/ 180 minutes: 50.7±18.5 vs. 62.7±19.1/39.8±23.4 vs. 53.7±24.4/ 35.0±23.5 vs. 52.6±26.2/30.7±22.5 vs. 52.2±27.1/23.4±21.5 vs. 51.2±29.1 (p = 0.03/ 0.02/ <0.01/ <0.01/ <0.01).	"Tramadol provides inferior analgesia to hydrocodone-acetaminophen in ED patients with acute musculoskeletal pain."	Patients not well described. Short-term trial in ED. Data suggests hydrocodone/ APAP 5/325 provided better pain relief.
Lovell 2004 RCT No mention of industry sponsorship or COIs.	I(8.0)	N = 51 acute musculo-skeletal pain (<24 hours, ≥5/10). Approximately 50% spine, 50% extremity.	Oral valdecoxib 40mg PO (n = 26) vs. oxycodone 10 mg plus acetaminophen 650 mg PO (n = 25). Single dose study, 24 hours follow-up.	Mean pain (95% CI) at baseline/60 minutes comparing valdecoxib vs. oxycodone/APAP: 81(75, 86)/47(37, 57) vs. 75(69, 82)/51(42/60). Adverse events (%) sedation/dizziness: 15 vs. 11, (p = 0.03). Nausea/dyspepsia: 3 vs. 3, (p = 0.96).	"Valdecoxib is as effective as an oxycodone-acetaminophen combination in treating ED patients with acute musculoskeletal pain at 30 minutes and less likely to cause sedation or the need for rescue analgesia over the next day."	Valdecoxib at least as effective for pain, trended towards less rescue med. use (11/24 vs. 17/23) and fewer adverse effects. No mention of industry sponsorship.

Chang 2009b RCT Funding through a restricted Research Training Grant from the Society for Academic Emergency Medicine. No mention of COIs.	I(7.5)	N = 194 ED patients with acute severe pain. Age 75±8 years.	Hydromorphone: single dose of 0.0075mg/kg IV (n = 97) vs. morphine 0.05mg/kg IV (n = 97). Follow-up at 10 minutes, 30 minutes, and 2 hours.	Both groups had decreased pain (p ≤ 0.001), but no significant difference in pain reduction between groups. Hydromorphone group had mean decrease in pain of 3.8 NRS unit vs. 3.3 NRS unit in MS (95% CI: -0.2 to 1.3) from baseline to 30 minutes (NS). 57.0% hydromorphone vs. 58.9% morphine group did not reach ≥50% pain reduction within 30 minutes.	"For the treatment of acute, severe pain in these older adults in the ED, a single dose of 0.007S-mg/kg IV hydromorphone had efficacy and safety profiles at 30 minutes postbaseline not significantly different from O.OS-mg/kg IV morphine."	Data suggest comparable efficacy.
Marco 2005 RCT Supported in part by grant from The Douglass Foundation, Toledo, Ohio. No mention of COIs.	I(7.5)	N = 73 ED adults with acute fracture and severe pain. Patients ≥12 years old.	Oxycodone 5mg PO with acetaminophen (n = 35) vs. hydrocodone 5 mg PO with acetaminophen (n = 32). Follow-up at baseline, and 30 and 60 minutes after 1st dose.	Pain relief at 30 minutes (oxycodone: 3.7, 95% CI: 2.9 to 4.6; hydrocodone: 2.5, 95% CI: 1.7 to 3.3) and 60 minutes (oxycodone: 4.4, 95% CI: 3.2 to 5.6; hydrocodone: 3.0, 95% CI: 2.1 to 3.9). No difference between groups at 30 (-0.6, 95% CI: -1.8 to 0.5) and 60 minutes (-0.5, 95% CI: -2.0 to 1.0). No differences in adverse effects.	"[R]esults suggest that oxycodone and hydrocodone have similarly potent analgesic effects in the first hour of treatment for ED patients with acute fractures."	Data suggest comparable efficacy over 60 minutes.
Chang 2011 RCT Double-blind Controlled No mention of industry sponsorship. No COIs.	I(7.0)	N = 350 ED patients with acute severe pain.	1+1 hydromorphone group had initial dose hydromorphone mg IV (n = 167) vs. usual care group initial dose of opioid IV (n = 171). Follow-up at 5, 15, 30, 45, and 60 minutes after first administration.	1+1 hydromorphone was statistically significant more successful treatment vs. usual care [95% CI: 10.2 (2.0 to 18.3)] in the intention-to-treat analysis. In the per-protocol analysis, 1+1 group declined additional pain medicine at 15 [95% CI: 11.5 (1.8 to 20.9)] and 60 minutes [95% CI: 13.2 (3.3 to 22.7)] vs. usual care.	"When analyzed per protocol or with the more conservative intention-to-treat analysis, the 1+1 hydromorphone protocol is statistically and clinically more efficacious than usual care. Safety profiles were similar in both groups."	Usual care not well described. Data suggest no differences in pain rating, but moderately better success with hydromorphone.
Jalili 2012 RCT Study was part of a thesis supported by Tehran University of Medical Sciences. No COIs.	I(7.0)	N = 110 ED adults with acute bone fracture.	Buprenorphine 0.4 mg SL plus NS 5mL IV (n = 44) vs. MS 5mg IV plus placebo SL (n = 45). Follow-up at 30 and 60 minutes after first dose. 4 lost to follow-up in MS vs. 5 in buprenorphine group.	No differences between groups in pain scores. Mean difference pain numeric rating scale scores at 30 minutes: 0.0 (95% CI -0.6 to 0.8), (p = 1.0) and 60 minutes was 0.0 (-0.3 to 0.3), (p = 0.9). No differences in adverse effects.	"For adults with acute fractures, buprenorphine 0.4 mg sublingually is as effective and safe as morphine 5 mg intravenously."	Data suggest comparable pain reductions. More acute hypotension with MS.

Chang 2013a RCT Supported by a K23 award (1K23AG033100-01A2) from the National Institute on Aging (NIA). No mention of COIs.	I(6.0)	N = 350 ED patients with severe pain.	Hydromorphone 2mg IV (n = 175) vs. 1+1 hydromorphone titration protocol: 1mg IV and another 1mg at 15 minutes if wanted additional pain medication (n = 175). Follow-up at 0, 5 (pain measurements recorded every minute), 15, 30, 45, 60, 90, and 120 minutes after first dose.	Main efficacy outcomes by groups included: declined additional analgesia after 60 minutes [difference 95% CI: 0.2 (-9.7 to 10.2)], mean change in numeric rating scale score from baseline to 60 min [0.4 (-0.3 to 1.1)], and reported none or mild pain at 60 minutes [0.8 (-9.2 to 10.8)].	"A hydromorphone 1+1 titration protocol provides similar pain relief to an initial 2 mg bolus dose, with no apparent clinical advantage to the latter. The 1+1 titration protocol had an opioid-sparing effect because 50% less opioid was needed to achieve satisfactory analgesia for 42.3% of patients allocated to this protocol."	Sparse results. Data suggest hydromorphone 1mg + 1mg PRN equivalent to 2mg.
Chang 2013b RCT No mention of industry sponsorship. No COIs.	I(6.0)	N = 350 ED patients with acute severe pain. Age 21 to 64.	Hydromorphone 2mg IV (n = 164) vs. usual care: any opioid, dose, and frequency by ED attending (n = 161). Follow-up at 15, 30, 45, 60, 90, and 120 minutes after first dose.	At 30 minutes, 74 % in hydromorphone 2mg IV group significantly declined additional pain medication vs. 65.8% usual care group (95%; 11.6% CI: 1.8 to 21.1%). At 120 minutes, total median opioid dose in usual care group was 7 morphine equivalent units (MEU) (IQR = 4 to 14 MEU) vs. 14 MEU (IQR 14 to 14 MEU) in hydromorphone 2mg group. 32% (n = 52) usual care group received additional opioids between 30 and 120 minutes vs.13% (n = 22) in hydromorphone group [18.5% (95% CI: 9.6% to 27.1%)]. Pruritus more common in hydromorphone group vs. usual care [95% CI: 9.6 (2.6 to 16.6)].	"Using a simple dichotomous patient-centered endpoint in which a difference of 10% in proportion obtaining adequate analgesia was considered clinically significant, 2 mg of hydromorphone in a single IV dose is clinically and statistically more efficacious when compared to usual care for acute pain management in the ED."	Usual care comparison group not well described. Higher opioid dosing in the 2mg group.
Chang 2013c RCT Chang is supported by a grant from the NIA. No other authors have any financial or personal conflicts of interest.	I(6.0)	N = 350 aged ≥65 years in ED with acute pain of sufficient severity to need IV opioids (ED attending physician's judgment).	Hydromorphone titration (initial dose of 0.5mg IV) group (n = 175) vs. usual care: initial dose of IV opioid, type/dose determined by treating ED attending physician (n = 175). After 15 minutes, both groups asked if additional pain	Initial mean dose in MEU: hydromorphone (3.5 MEU) vs. usual care (4.7 MEU), p <0.001. Total mean dose over 1 hour period: hydromorphone (5.3 MEU) vs. usual care (6.0 MEU), p = 0.03. Second dose request at 15 minutes: hydromorphone (95.3% requested and received dose) vs. usual care (67.3% requested and received dose), p <0.001. No significant	"A low-dose, two-step, hydromorphone titration protocol was very similar to usual care with respect to both efficacy and safety for treatment of acute pain in older adults presenting to the ED."	Usual care not well described. Data suggest comparable outcomes.

			medication needed. Hydromorphone group then received additional 0.5mg IV. Usual care group received additional medication at physician's discretion. Questioned again 60 minutes after initial dose. Study lasted 1 hour.	differences between groups for primary, secondary, or safety outcomes.		
Turturro 1991 RCT Double-blind, prospective Funding provided by The Center for Emergency Medicine of Western Pennsylvania and Central Pharmaceuticals.	I(6.0)	N = 62 adult ED patients with acute musculo-skeletal pain. Age range 18 to 70 years.	Hydrocodone/APAP 5/500mg group. (n= 25) vs. codeine/APAP 30/500mg group. Medicines Q4 hours after discharge PRN (n = 25). Follow-up at 0, 1, 2, 4, 8, 24, and 48 hours.	Mean pain scores lower in hydrocodone group but not significantly different. Adverse effects in hydrocodone (n = 8) vs. codeine (n = 18), p = 0.005). Six hydrocodone / acetaminophen patients experienced "drowsiness" or "dizziness" vs. 16 codeine/ acetaminophen patients (p <0.005).	"Although pain scores were not significantly different, hydrocodone may be a more effective analgesic than codeine in acute musculoskeletal pain, as demonstrated by significantly fewer treatment failures. Central nervous system side effects are less common with hydrocodone than with codeine."	Not well described – but higher adverse effects with codeine. Pain relief effects statistically comparable.
Chang 2009a RCT Supported by Society for Academic Emergency Medicine Research Training Grant. No mention of COIs.	I(5.5)	N = 224 ED patients with acute severe pain. Age range 21 to 64 years.	1+1 hydromorphone patient-driven protocol group: 1mg IV with 2nd 1mg dose 15 minutes later if wanted more medication (n = 112) vs. physician-driven group: received opioid IV in dose chosen by ED attending physician (n = 112). Follow-up at 5 (pain measurements recorded every minute), 15, 30, and 60 minutes after first dose.	At 60 minutes, 94% patients of the patient-driven group achieved adequate analgesia. The pain in the patient-driven group significantly decreased vs. the physician-driven (p = 0.01). The difference was 1.1 numeric rating scale units, which is significant; however, it did not reach the minimum clinically significant difference in pain of 1.3 numeric rating scale units.	"The 1+1 hydromorphone patient-driven protocol is statistically superior and at least as clinically efficacious and safe as traditional physician-driven treatment of ED patients with acute severe pain. More than 9 of 10 patients randomized to the study protocol achieved satisfactory pain control, as defined by the patient, within an hour or less."	Data suggest moderately better pain reduction with patient driven protocol.
Ordog 1987 RCT - double-blind Funding through a restricted Research	I(4.5)	N = 100 acute trauma outpatients. Age ≥21.	Functioning TENS-PAC (n = 25) vs. Nonfunctioning or placebo TENS-PAC unit (n = 25) vs. Functioning TENS-PAC plus	No differences in pain levels between groups. Significant reduction in pain severity with functioning TENS versus placebo unit at day 2, but not at day 30. No p-values provided.	"Transcutaneous electrical nerve stimulators have been shown to be effective in the management of acute traumatic pain	Patients not well described. TENS vs. sham. Codeine / APAP not blinded. Data suggest TENS and/or

Training Grant from Society for Academic Emergency Medicine. No COIs declared.			codeine/APAP (Tylenol #3) (n = 25) vs. Nonfunctioning TENS-PAC unit plus codeine/APAP, #3 (n = 25). 30 day trial. Sixteen excluded, due to exclusion criteria.	Correlation between decreasing pain and increasing time significant (p < 0.00001).	and may be indicated for patients who cannot be given medications."	Codeine/APAP comparable and superior to sham.
Veenema 2000 RCT No mention of industry sponsorship or COIs.	I(7.5)	N = 153 ER patients with pain of musculo-skeletal origin.	Ketorolac IM (60mg, n = 80) vs. Meperidine IM (1mg/kg, n = 75). Outcomes measured 60 minutes pre- and post-administration.	At 60 minutes, mean pain intensity decrease 7mm less in ketorolac group (95% CI -15mm to 2.6mm). Pain reduction ≥30% in 63% ketorolac vs. 67% meperidine (OR = 1.06, 95% CI = 0.43 to 1.61). Rescue analgesia in 36% of ketorolac vs. 37% of meperidine at 60 minutes (OR = 1.06, 95% CI 0.47 to 1.74). One meperidine subject required naloxone for severe respiratory depression.	"[A] single dose of ketorolac appears to be a useful alternative to a single moderate dose of opioids for the management of patients presenting to the ED with severe musculoskeletal LBP."	Ketorolac generally equivalent to meperidine. Ketorolac group with less sedative effects (24% vs. 71%). Data suggest ketorolac may be superior for initial management of LBP in acute care settings.
Ankle Sprain						
Hewitt 2007 RCT Supported by grant from PriCara, Unit of Ortho McNeil, Inc. No mention of COIs. 4 of 5 authors apparently employees.	I(9.5)	N = 603 adults with acute ankle sprain ≤48 hours ago and diagnosis of partial ligament tear.	Tramadol plus acetaminophen (37.5/375) QID (n = 192) vs. hydrocodone plus acetaminophen (7.5/650) QD PRN (n = 204) vs. placebo (n = 207) for acute mild and moderate ankle sprain short-term analgesia (5-day follow-up with as needed dosing). Pain scores were at rest, not with movement (scores on 4 point scale).	Tramadol/APAP vs. hydrocodone/ APAP vs. placebo (pain relief score 0-4 scale). Immediate Mean Pain Relief: tramadol better than placebo at 2, 3, 4 hours. Hydrocodone better than placebo at 1, 2, 3, 4 hours. Differences continued through Day 3. No differences between tramadol and hydrocodone.	"One or 2 capsules of 37.5 mg tramadol/325 mg acetaminophen and 1 capsule of 7.5 mg hydrocodone/650 mg acetaminophen were well tolerated, had comparable clinical utility, and were more effective than placebo in the management of acute musculoskeletal pain caused by ankle sprain."	Study of short-term analgesia. Pain scores were at rest and not with activity. Data suggest tramadol/APAP and hydrocodone/APAP equivalent.
Ekman 2006 RCT Sponsored by Pfizer Global Pharmaceuticals, one is employed by same and all have declared COIs	I(9.5)	N = 829 acute 1st- or 2nd-degree ankle sprain	Valdecoxib 20mg QD (n = 233) vs. valdecoxib 20mg BID (n = 235) vs. tramadol 50 mg QID (n= 238) vs. placebo (n = 123) for acute mild and moderate ankle sprain. All patients received 7 days of treatment.	Valdecoxib 20mg BID vs. valdecoxib 20mg QD vs. tramadol 50 mg QID vs. placebo. Patient global assessment good/very good: Day 4 no differences, Day 7 (76.4 vs. 67.3 vs. 59.6 vs. 55.5) p <0.001 for BID vs. placebo. APS questionnaire: 33.9 vs. 26.6 vs. 20.6 vs. 24.4 (p = 0.009 Day 4).	"Valdecoxib 20 mg bid was at least as effective as Tramadol 50 mg 4 times daily and significantly better than placebo."	Data suggest valdecoxib 20mg BID superior to placebo and trended towards better than tramadol for acute pain relief at Days 4 and 7; no difference in tramadol and

as speakers/research funds.				Patient assessment of return to walking with/without pain Day 4 (47.5/44.6/38.4/35.0) p = 0.002; Day 7 (79.4/72.5/67.3/ 63.9) p = 0.001.		placebo at Day 4, with higher withdrawal rates in tramadol.
Muncie 1986 RCT Study supported in part by grants from Merck, Sharp and Dohme, and the National Institutes of Health No COIs declared.	I(4.0)	N = 43 at primary care setting with mild to moderate acute pain from sprain or strain or with mild to moderate low back pain.	Diflunisal 1000 mg PO then 500mg Q12hour PRN (n = 18) vs. Codeine/APAP 60/650mg, 1-2 tabs then 1-2 Q4-6 hour PRN (n = 17). Followed for maximum of 7 days or until medication discontinued.	Final pain rating less in diflunisal group, not statistically different from acetaminophen with codeine, 1.6±1.5 codeine/APAP 1.3±1.1 vs. diflunisal. Pre- and post-treatment pain assessment showed both groups had pain relief: 3.3±0.6 to 1.6±1.5 codeine/APAP, p < 0.05, and 3.3± 0.6 to 1.3±1.1 diflunisal, p < 0.007. For those receiving full 7 days, pain rating codeine/APAP went from 3.5 ±0.5 to 2.3±1.6 vs. diflunisal group went from 3.0±0.5 to 1.5±1.0.	"[D]iflunisal was found to be an effective analgesic in the treatment of mild to moderate pain of acute soft tissue injuries."	Patients not well described. Data trended to less pain and greater function with Diflunisal.
Low Back Pain						
Baratta 1976 RCT No mention of industry sponsorship or COIs.	I(8.0)	N = 94 with low back syndrome (majority ambulatory and presented with pain, spasm, and stiffness with various disorders including, lumbosacral sprain, cervical sprain, sacroiliac sprain, and sprains of thoraco-lumbar, cervical and thoraco-spinalis areas of back).	Carisoprodol 350 mg QID (n = 33) vs. propoxyphene 65mg QID (n = 32) vs. placebo 65mg QID (N = 29) for 14 days.	Differences carisoprodol vs. propoxyphene on basis for improvement measured at flexion, back extension, passive sit-up, knee flex on abdomen, squat off heels, discomfort: p <0.01, p <0.01, p <0.01, p <0.01, p = 0.01. Carisoprodol vs. placebo measured at flexion, back extension, passive sit-up, knee flex on abdomen, side bend to knee joint, squat off heels, discomfort, stiffness, difficulty falling asleep, number of times awakened during night: p<0.01, p <0.01, p <0.01, p <0.01, p <0.01, p <0.01, p = 0.01, p <0.01, p = 0.01, p = 0.02.	"[T]he significant statistical results observed between the efficacy of carisoprodol and that of the other two groups represent a definite superiority for the treatment with carisoprodol."	Global ratings favored carisoprodol. Data suggest carisoprodol superior to propoxyphene.

Perrot 2006 RCT Sponsored by Grunenthal GmbH, Aachen, Germany. No mention of COIs	I(7.5)	N = 119 with at least moderate pain from acute or subacute LBP for 10 to 42 days.	Tramadol/Paracetamol (37.5/325mg), n = 59) vs. tramadol alone (50 mg, n = 60) for 10 days. Dose titrated up from QID over first 2 days, up to limit of 8 doses/day for a 10 day study duration.	Pain scores decreased from 67.5 to 27.9 vs. 65.3 to 24.8 (tramadol alone). Tramadol group had more adverse effects (73.3% vs. 50.8%) with CNS and GI side effects substantially higher.	"Conventional T capsules and the new P/T combination were both highly effective in the treatment of nonspecific subacute LBP."	Dose titrated up from QID over first 2 days, up to limit of 8 doses a day. No placebo. Data suggest comparable efficacy, but fewer adverse effects with paracetamol. But result may be confounded by higher tramadol dosing in tramadol-only group (e.g., 257 vs. 188mg maximum/day).
Palangio 2000 RCT Supported by Knoll Pharmaceutical Company, Mount Olive, New Jersey. No mention of COIs. All authors apparently employees.	I(7.5)	N = 147 with moderate or severe acute LBP over a period of up to 8 days.	Hydrocodone/ibuprofen (HC/IB) (7.5/200mg, n = 75) vs. oxycodone/ acetaminophen (OX/AC) (5/325mg, n = 72) Q 4-6 hours PRN up to 5 a day. Assessment done over 8 hours after randomization. Four-week study design used.	No significant differences between HC/IB and OX/AC by mean (±SD) daily pain relief scores (2.40±1.06 vs. 2.50±1.01, respectively), global evaluations, or mean scores on the modified SF-36.	"HC/IB and OX/AC are similarly effective and tolerable in relieving moderate or severe acute low back pain."	8 day trial. Baseline differences in body weight potentially favoring higher hydrocodone/ibuprofen dosing. No baseline VAS data. Higher hydrocodone dosing had higher withdrawal rates (25%). Modest differences in pain reduction likely of little clinical significance.
Innes 1998 RCT Funded by Hoffmann-LaRoche of Canada.	I(6.5)	N = 123 with acute LBP treated in ER.	Ketorolac (10mg, Q 4 to 6 hours PRN up to 4 a day, n = 62) vs. codeine/APAP (60/600mg, Q 4 to 6 hours PRN, up to 6 a day, n = 60). Subjects completed diaries for 1 week and return to hospital for follow-up. Study over 15 month period.	After 1 day, 60% of ketorolac patients had complete or major pain relief vs. 47% for codeine patients. Significantly more acetaminophen-codeine patients (64%) reported at least 1 adverse drug event during treatment, compared to 34% of ketorolac patients (p = 0.0005). Pain relief was equivalent in both groups after 6 hours.	"Both ketorolac and acetaminophen-codeine are effective for the short term management of acute low back pain. The two agents differed in cost and adverse effect profile."	Adverse drug effects twice as common with codeine/APAP. Data suggest ketorolac superior to codeine/ APAP for acute LBP.
Brown 1986 RCT	I(5.0)	N = 47 with initial or recurrent acute LBP.	Diflunisal (1,000mg then 500mg Q 12 hours, n = 19) vs. codeine plus acetaminophen (30mg/300mg 2 tablets	More adverse effects in codeine group (dizziness, fatigue, inability to concentrate, impaired vision, drowsiness, and nausea).	"[D]iflunisal and acetaminophen with codeine effectively relieved the mild to moderate pain	No placebo. Bed-rest prescribed; no mention of compliance. Data suggest diflunisal

Supported by a grant from Merck Sharp & Dohme.			then 1 Q 4 hours, n = 21) for 15 days or until pain completely relieved.	Diflunisal rated excellent more frequently.	associated with initial or recurrent acute low back strain."	superior to codeine/ APAP.
Other						
Enggaard 2001 RCT Crossover Study supported by The Danish Medical Research Council. No COIs declared.	I(8.0)	N = 18 healthy volunteers age 22 to 30.	3 study days with single oral doses of codeine 5 tablets x25mg each vs. imipramine 4 tablets x25mg each) vs. placebo. Study days were separated by washout period of ≥2 weeks. Assessments before medication and 90, 180, 270, 360, and 450 minutes after medication.	Cold pressor test peak pain (cm) median: imipramine -0.38 vs. codeine 0.98 vs. placebo -0.22, p = 0.03 codeine vs. placebo. Cold pressor test pain average (cm x s) median: imipramine -0.51 vs. codeine -0.78 vs. placebo -0.41, p = 0.04 codeine vs. placebo. Cold pressor test discomfort (mm) median: imipramine -5.0 vs. codeine -13.6 vs. placebo -4.4, p = 0.003 codeine vs. placebo. Electrical sural nerve stimulation single stimulation pain detection threshold (mA) median: imipramine 1.0 vs. codeine 1.5 vs. placebo 0.75, p = 0.04 codeine vs. placebo. Electrical sural nerve stimulation pain tolerance threshold (mA) median: imipramine 1.5 vs. codeine 1.5 vs. placebo 0.25, p = 0.05 imipramine vs. placebo; p = 0.01 codeine vs. placebo. Electrical sural nerve stimulation repetitive stimulation pain summation tolerance threshold (mA) median: imipramine 1.25 vs. codeine 1.5 vs. placebo 1.0, p = 0.03 imipramine vs. placebo; p = 0.02 codeine vs. placebo. Pressure pain tolerance threshold (kPa) median: imipramine 117 vs. codeine 91 vs. placebo 25.5, p = 0.04 imipramine vs. placebo; p = 0.02 codeine vs. placebo.	"[T]he tricyclic antidepressant imipramine and the opioid drug codeine both inhibit temporal pain summation on repetitive electrical sural nerve stimulation, whereas only codeine relieves pain in the cold pressor test."	Experimental study. Utility of results clinically unclear.
Zacny 2012 RCT - Experimental Crossover Study	I(5.0)	N = 15 healthy individuals (8 males, 7 females), ages 21-39 years, and some	Placebo vs. 350mg carisoprodol (CARIS) vs. 10mg oxycodone (OXY) vs. 350mg carisoprodol followed 60 minutes later by 10mg oxycodone.	Mean±SEM VAS (range 0-100) coasting ("Spaced out") comparing placebo vs. CARIS 350 vs. OXY vs. CARIS350/OXY 10: 15.3±7.4 vs. 13.3±5.9 vs.	"This is the first study that we are aware of that has shown that carisoprodol and oxycodone, two drugs that are sometimes co-	Experimental study. Data suggest additive CNS impairments between

Industry Sponsored (NIDA Grant DA23969) No COIs declared.		current level of alcohol use. Mean age (±SD) of 27.0 (5.0) years. 7-8 sessions ≥1 week apart.		28.5±8.6 vs. 43.7±9.8; p <0.0001.	prescribed for relief of pain, produce effects when administered "together" (i.e., separated by 60 min) that are of greater magnitude than when they are administered alone. Some of the effects were not benign, and are of concern from both abuse liability and public safety standpoints."	carisoprodol and oxycodone.

Evidence for Post-operative Pain

Search Strategy: PubMed and Google Scholar were searched without limits on publication dates. The following search terms were used: opioids, post-operative and post-surgery. We found 33,078 articles. Of the 33,078 articles found, we reviewed 38 articles and used 27.

Author/Year Study Type Potential Conflict of Interest	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Post-Operative Pain						
Buvanendran 2010 RCT Supported by a Medical School Grant from Pfizer, Inc. Placebos provided by Pfizer.	I(9.0)	N = 240 with osteo-arthritis knee scheduled to undergo elective primary TKA.	Pregabalin 300mg PO 1-2 hours before TKA and for 14 days after TKA (150mg BID x 10d, 75mg BIDx2 days, 50mg BID x 2 days) (n = 120) vs. placebo (n = 120). All spinal epidurals, epidural fentanyl and PCA. All Celecoxib 400mg 1-2 hours before surgery and 200mg PO BID for 3 days. Oral opioids prescribed. Follow-up at 3 and 6 months post-op.	Pregabalin had lower incidences of neuropathic pain, allodynia, and hyperalgesia in the operated leg vs. the placebo group: 0% (0/113) vs. 8.7% (10/115, p = 0.001), (2%, 2/113) vs. (12%, 14/115, p = 0.002), and (8%, 8/113) vs. (20%, 23/115, p = 0.009). At 6 months, incidences: 0% (0/113) vs. 5.2% (6/115, p = 0.014), 0% (0/113) vs. 8% (9/115, p = 0.002), and 2% (2/113) vs. 11% (12/115, p = 0.006). 24 used opioids, 15 in pregabalin and 9 in placebo groups (p = 0.282).	"Perioperative pregabalin administration reduces the incidence of chronic neuropathic pain after TKA, with less opioid consumption and better range of motion during the first 30 days of rehabilitation. However, in the doses tested, it is associated with a higher risk of early postoperative sedation and confusion."	Data suggest reduced chronic pain with pregabalin. Post-op sedation (26%) and confusion (13%) mildly problematic. Data suggest earlier functional recovery in addition to reduced chronic pain.
Chang 2004 RCT Double-blind	I(9.0)	N = 225, aged ≥16 years, scheduled to undergo	Etoricoxib 120 mg PO, (n = 100) vs. Oxycodone/ acetaminophen 10/650 mg PO (n = 100) vs. placebo (n = 25).	Overall mean TOPAR6 scores for etoricoxib 120 mg 1.53 (95%CI, 14.0-16.5) and Oxycodone/ acetaminophen 10/650 mg 12.1 (95%CI, 10.8-	"[T]his study demonstrated that the overall analgesic efficacy over 6 hours of a single dose of	Data suggest Etoricoxib superior to oxycodone/APAP superior to placebo.

Placebo- and active comparator-controlled, Single dose, Single center trials Supported by Merck & Co., Inc. No COIs declared.		extraction of ≥2 third molars, ≥1 partially imbedded in mandibular bone	Primary assessment included, total pain relief over 6 hours (TOPAR6), and other efficacy included pain intensity differences 6 hours (SPID6) and patient global assessment of response to therapy (PGART) at 6 and 24 hours; follow-up 7-10 days after surgery.	13.4), vs. placebo, 4.1 (95%CI, 1.6-6.7). Total pain relief over 6 hours for etoricoxib was more vs. oxycodone/ acetaminophen, p < 0.001.	etoricoxib 120mg was superior to that with a single dose of oxycodone/ acetaminophen 10/650mg in the treatment of acute postsurgical dental pain."	
Musclow 2012 RCT Toronto Authors state no financial disclosures or conflicts of interest	I(8.5)	N = 200 undergoing total hip or knee replacement surgery experience unmanaged pain during post-op physiotherapy sessions 2004-2006	Long-acting MS 30mg PO vs. placebo PO BID for 3 days. All received routine postoperative analgesia, with PCA x 2 days, rofecoxib/celecoxib/ ketorolac/ibuprofen, and oxycodone 5/325mg 1-2 PO Q3hour PRN. 4 days follow-up.	Pain intensity improvement at least two points on 9 to 10 scale, in AM or p = 0.046, and with activity by or p = 0.017, and in PM, or p = 0.049, showed clinically significant improvement. No differences between groups in adverse events, function, and sleep. Higher satisfaction with pain management reported with morphine.	"Thirty milligrams twice per day of long-acting morphine from days 1 to 3 following total hip and total knee replacement surgery provided minimal improvements in pain scores, and more adverse effects in the treatment group."	Data suggest minimal short-term efficacy, and no significant functional gain.
Yeom 2012 RCT Korea No mention of conflict of interest	I(8.5)	N = 40 ages 38–78, undergoing 1-2 level posterior lumbar spinal fusion.	Control group, Fentanyl 0.4µg/kg/ml, n = 20 vs. Ketamine group, 0.4µg/kg/ml and 30µg/kg/ml n = 20; 2-day follow-up.	Numerical Rating Scale or NRS at rest; 5.1±2.1 and 4.2±2.1 vs. 3.6±2.0 and 2.4±1.4 in control for post-anesthesia care or POD 1 and 2. No differences re. postoperative patient-controlled analgesia or PCA or adverse effects between groups.	"[We] conclude that small dose of ketamine (0.5-2.5µg/kg/min) proportional to fentanyl is not only safe, but also lowers postoperative pain intensity in patients undergoing spinal fusion, although the opioid-sparing effects of ketamine were not demonstrated."	Data suggest ketamine associated with modest pain results. No long term outcomes or longer objective data provided.
Comelon 2013 RCT Double-blind Prospective trials	I(8.5)	N = 109 undergoing non-malignant, elective, laparoscopic supra-cervical or	Group O: Oxycodone prolonged-release (PR) 10mg BID x 3 day (n = 45) vs. Group ON: Oxycodone PR 10 mg + naloxone PR 5mg as pre-medication and BID x 3 day (n = 40).	Groups were similar in demographic data/pain scores. In 24-72-hour period, 16% and 23% of patients had NRS >3 in group O and ON, respectively.	"In conclusion, the addition of naloxone PR to oral oxycodone PR, in the present study design of 3-day pain regimen after laparoscopic	Data suggest naloxone did not reduce adverse effects. Trend towards worse pain control with naloxone.

Funded by, Oslo University Hospital. Conflicts of interest: Post-operative pain research group at Oslo University Hospital received an unrestricted grant from Mundipharma AS, producer of both study drugs, before start of the study. No COIs declared.		total hysterectomy.	Primary outcome; numeric rating scores (NRS, I-IV) and secondary outcomes) recorded at 0.5, 1, 2, 3, 4 and 24 hours after end of surgery. Follow up, 8 days after inclusion and surgery.		hysterectomy, does not seem to have significant effects, neither beneficial nor harmful to the post-operative course of these patients."	
Foss 2005 No mention of conflict of interest	I(8.0)	N = 60 with hip fracture surgery. Elderly patients, ≥60 years of age.	Group A, 4 days of continuous epidural 4ml/h infusion of bupivacaine (0.125% and morphine (50µg) (n = 28) vs. Group B, NS. (n = 27). 4 day follow-up.	No differences between groups in improved pain relief, scores for recovery of physical independence.	"Postoperative epidural analgesia after hip fracture surgery provides superior analgesia attenuating pain as a restricting factor during rehabilitation without motor dysfunction."	Study of post-op analgesia and functional recovery outcomes. Absence of improved recovery with pain control may be important finding in light of numerous studies determining which post-op pain control method is most effective.
Pandey 2004 RCT No mention of conflict of interest, no sponsorship	I(8.0)	N = 56 who underwent lumbar discectomy	Gabapentin, 300mg (n = 28) vs. placebo given 2 hours prior to surgery on post-op pain (n = 28); 24-hour follow-up.	VAS pain scores 3.5±2.3 vs. 6.1±1.7 at 0 to 6 hours, and remained significantly different at 18 to 24 hours (1.2±1.3 vs. 2.1±1.2)	"[A] preemptive 300 mg oral dose of gabapentin decreases significantly the incidence of pain postoperatively in patients who undergo lumbar discoidectomy without significant adverse effects."	Placebo controlled study suggesting decreased post-op pain for first 24 hours within use of gabapentin. Data suggest improved post-op analgesia from pre-op oral gabapentin.
Silvanto 2002 RCT Supported in part by Rhone-Poulenc Rorer Corp. and a grant from the Scientific Committee of National Defense, Finland.	I(7.5)	N = 64 patients operated under spinal anesthesia for knee arthro-plasty.	Diclofenac 75mg IV then 150mg/day PO (n= 24) vs. Ketoprofen 100mg IV then 300mg/day PO (n = 24) vs. placebo NS for 3 days (n = 16). All spinals and all PCA with oxycodone.	Ketoprofen group used less oxycodone than placebo in 13-24 hours and 61-72 hours (20.6 vs. 31.1mg) and (5.5 vs. 16.4mg) ($p < 0.05$) respectively. Diclofenac group used less oxycodone than placebo in 25-36 hours, 37-48 hours, and 49-60 hours with values of 12.9 vs. 27.2mg, 9.4 vs. 18.7mg ($p < 0.01$), and 9.7 vs. 19.7mg ($p < 0.05$) respectively. No	"[T]he first day after knee arthroplasty (13-24h), ketoprofen exerted an opioid-sparing effect. After day 1 (25-60h), with the doses used, diclofenac proved to be better than placebo, whereas ketoprofen was not."	Data suggest NSAIDs effective to reduce oxycodone use and decrease pain scores.

				differences in mean VAS scores between NSAID groups.		
Sell 2004 RCT Placebo-controlled, double-blind study Homocentric Study was carried out with the support of Novartis Pharma. No mention of conflict of interest, no sponsorship.	I(7.5)	N = 245 with total hip arthroplasty or THA.	Cholestyramine-bound diclofenac 75mg QD (n = 121) vs. prophylaxis with diclofenac 150 mg/day for 14 days post-op (n = 124).	In diclofenac 150mg, 19% slight heterotopic ossification (Booker 1, none more severe) vs. 75mg which had 17% grade 1 and 4% grade 2 Booker. No clinical difference after 6 months.	"Although the two doses displayed similar efficacy the author recommends the lower dose because of the lower instance of adverse gastrointestinal event (23% vs. 38%, p = 0.02)."	Co-administration of proton pump inhibitors likely resulted in lower side effect profile. No placebo control.
Aqua 2007 RCT Multicenter Double-blind Active and Placebo - parallel group study No industry sponsorship. No COIs declared.	I(7.5)	N = 331 undergoing abdominal surgery that required an incision of ≥3cm.	Oxycodone IR (immediate release) 10mg, 4 to 6 hours after 1st dose, and multiple dose evaluation up to 48 hours after 1st dose (n= 82) vs. Oxycodone IR 20mg, 4 to 6 hours after 1st dose, and multiple dose evaluation up to 48 hours after 1st dose (n = 81) vs. Oxycodone IR 15mg, hours after 1st dose, and multiple dose evaluation up to 48 hours after first dose (n = 83) vs. placebo, hours after 1st dose and multiple dose evaluation up to 48 hours after 1st dose (n = 85). Pain recorded at 15, 30, 45, and 60 minutes and 2, 3, 4, 5, and 6 hours after dose.	At baseline, pain intensity was moderate in 285 or 86.1% and severe in 46 or 13.9% patients. At 1st 6 hours (single dose), IR 20mg more effective than placebo, p <0.05. Average pain intensity lower among patients treated with: oxymorphone IR 10mg, 20mg, or oxycodone IR 15mg vs. placebo (39.7, 35.2, 39.8, and 50.1, respectively, p <0.005).	"In this predominantly female population undergoing abdominal surgery, oxymorphone IR given every 4 to 6 hours for up to 48 hours provided efficacious and tolerable analgesia for moderate to severe pain."	Dropout rates are high, makes interpretation challenging. Data suggest Oxycodone 20mg/>5mg/>10mg.
Jung 2004 RCT Single-center Single-dose Active-controlled, Parallel-group	I(7.0)	N = 128 underwent oral surgery involving bilateral extraction of >2 third molars, one	Tramadol/APAP 75/650mg single PO dose (N = 64) vs. Codeine/APAP/IBU 20/500/400mg single PO dose (N = 64).	Mean (sd) baseline pain scores were 5.92 (1.00) in the Tr/Ac group and 5.75 (0.82) in the Co/Ac/Ib group. PID time-effect during 5 and 6 hour assessments were greater	"In this small and selected group of subjects, the onset of analgesia and analgesic efficacy of Tr/Ac was comparable to that of Co/Ac/Ib."	Data suggest equivalence of these single doses.

Supported by Janssen Korea Ltd., Seoul, Korea. No COIs declared.		of which was at least a partial bony mandibular impaction requiring bone removal, age ≥16.	Measuring primarily onset of analgesia using 2-stopwatch technique, and others include pain intensity (PID), relief, use of supplemental analgesic medication and the patient's overall assessment; 6 hours follow-up.	with Co/Ac/Il compared with Tr/Ac, $p < 0.05$.		
Kuusniemi 2012 RCT Finland, Germany COI: IPOP study (protocol number OXN4505) designed with Mundipharma Oy and conducted by investigators under full sponsorship of Mundipharma Oy. Data gathered by sponsor and evaluated jointly by authors and sponsor. NIS study designed with Mundipharma GmbH, Limburg an der Lahn, Germany, and conducted by investigators under full sponsorship of Mundipharma GmbH. Observations from daily clinical practice for QIP not funded externally. Writing assistance and publication fees for manuscript funded by Mundipharma Oy. Note: Targin®, Targinact®, and Targiniq® are registered trademarks.	I(6.5)	Study 1: IPOP N = 137 – analgesic efficacy of OXN PR compared with prolonged-release oxycodone (OXY PR) in patients with knee arthroplasty. Study 2: NIS N = 80 – OXN PR treatment compared with other opioids during rehab after knee arthroplasty Study 3: QIP N = 44 surgical patients on other opioids switched to OXN PR post-op.	Study 1: n = 63 (OXN PR) n = 64 (OXY PR Patients aged <65 years received 20/10 mg OXN PR or 20mg OXY PR, whereas patients aged ≥65 years received 10/5mg OXN PR or 10 mg OXY PR. Study 2: n = 41 (OXN PR) n = 36 (control group) 10/5 mg OXN PR Study 3: n = 24 (spine surgery) n = 20 (rehabilitation) Structured questionnaire at baseline, at the end of OXN PR treatment and 14 days after end of OXN PR treatment.	Study 1: Overall, 24-hour average pain intensity at rest score decreased by a mean of 1.2 (95% confidence interval [CI] –1.5, –0.9) in OXN PR group and by a mean of 1.1 (95% CI –1.4, –0.8) in OXY PR group. Study 2: Mean overall pain scores pre-operatively were 4.1 in OXN PR group and 4.3 in control group. Study 3: Of 24 patients undergoing cervical spine surgery in QIP, 3 received 5/2.5mg; 13 received 10/5mg; and 8 received 20/10mg OXN PR. Of 20 patients undergoing rehabilitation following orthopaedic joint surgery, 5 received 5/2.5mg; 7 received 10/5mg; and 8 received 20/10mg OXN PR.	"The analgesic efficacies of OXN PR and OXY PR were similar in post-operative pain settings. OXN PR reduced the degree of restriction in relation to patients carrying out physiotherapy compared with other opioids, and improved bowel and bladder function."	Three studies in 1 report. Only first randomized. No significant differences between 2 active treatments. Without placebo or other control, conclusions rather limited.

Barreveld 2013 RCT No industry sponsorship. No COIs declared.	I(6.5)	N = 64 with chronic pain taking opioids undergoing nononcologic surgery.	Ketamine IV hydromorphone PCA plus IV ketamine (0.2 mg/kg/hour) (n = 32) vs. placebo, received hydromorphone PCA plus IV NS (n = 32). Baseline demographic questionnaire, preoperative pain numeric rating scale (NRS), and HADS scale, symptoms check list, and medication side effects questionnaire; 1 day follow-up.	No difference between 2 groups; in length of hospital stay, p = 0.39 between 24-hour postoperative day, opioid use or 24 hours prior to discharge, p = 0.7480 or 0.5584 / preoperative medication side effect / or treatment related adverse events during the first 24 hours. Those given ketamine had improvement in percent change, average pain vs. placebo, p = 0.048, 0.05.	"Our study demonstrates that a postoperative ketamine infusion at 0.2 mg/kg/hour in addition to opioids results in a statistically significant reduction of "average" pain scores in patients undergoing surgery who take opioids for chronic pain."	Data suggest minimal effects of ketamine and modest increase in opioid use.
Gimbel 2001 RCT Multicenter Placebo- and active-controlled Double-blind Parallel-group trials. No industry sponsorship. No COIs declared.	I(6.5)	N = 418 uncomplicated orthopedic surgery requiring open manipulation of bone with periosteal elevation, including bunionectomy, ACL repair, open reduction and internal fixation of long-bone fractures, laminectomy, or osteotomy for acquired or congenital malforma-tions.	Single-dose assessment period (SDAP), 8 hours after 1st dose celecoxib 200mg (n = 141) vs. Hydrocodone/ APAP 10/1000mg (n= 136) vs. placebo, within 24-hour period (n = 141). Multiple-dose period (MDAP), 8 hours after 1st dose of medication, continued ≤5 days; Celecoxib 200mg, plus placebo (n = 185) vs. Hydrocodone/APAP 10/1000mg TID PRN (n = 181). 2 and 11withdrawals during SDAP and MDAP due to adverse events. Pain intensity difference as primary outcome. 8 hour, 5 day follow-ups.	SDAP mean PID scores at1 hour, 7 and 8 hours; significantly favored celecoxib and hydrocodone –acetaminophen, p ≤ 0.016/p <0.001. MDAP mean PID scores at end of each day celecoxib group had significantly superior maximum intensity scores compared with hydrocodone –acetaminophen, p >0.001.	"Over 8 hours, patients with moderate to severe pain after orthopedic surgery experienced comparable analgesia with single doses of celecoxib and hydrocodone/ acetaminophen."	One report, 2 trials. Short term trial suggest celecoxib equivalent to Hydrocodone/APAP for 0-6 hours after dose. Celecoxib superior to both opioid and placebo. Data suggest celecoxib superior to Hydrocodone / APAP.
Nader 2012 RCT No mention of industry sponsorship.	I(6.0)	N = 62 undergoing total knee replacement	Oral analgesics (OOA) (n = 31) vs. continuous femoral nerve analgesia (CFA) (n = 31).	CFA group had lower pain scores, less oral narcotics, and experienced greater knee flexion vs. OOA group. CFA group had higher analgesia management	"CFA for 24 hours following discontinuation of epidural analgesia was associated with lower pain scores,	One year follow-up study. Data suggest greater early functional improvement, e.g., knee flexion in the CFA group vs. oral analgesics at 1-

The authors have no conflict of interest to disclose.			Follow-up at 1, 6, and 12 months after surgery.	satisfaction 9 (8 to 10) vs. OOA group, 7 (6 to 9) (p <0.005).	greater compliance with physical therapy, increased range of motion, reduced opioid analgesia use, and greater patient satisfaction during hospitalization. The increased flexion of the operated joint was still evident at 1 month postoperatively."	month (p = 0.04). More thrombosis in oral group (p = 0.04), though trend to more positive joint aspirates in CFA (p = 0.08).
Rothwell 2011 RCT Before 2004, M.P.R. received honoraria from Napp pharmaceuticals, Roche pharmaceuticals, and Jansen-Cilag for lectures about postoperative pain and postoperative nausea and vomiting to hospitals, general practices, and meetings.	I(6.0)	N = 114 undergoing total hip replacement (THR) age 60-85 willing to undergo spinal anesthesia.	Oral controlled-release oxycodone 20 mg (OOXY, n = 57) v. I.V. patient-controlled analgesia of morphine 1mg bolus, 5 min lockout time, and no loading dose (IVPCA, n = 57) for 3 days or patient wished to discontinue. All received paracetamol and diclofenac; 1 day follow-up.	Time to analgesic discontinuation (hours, mean±SD): OOXY 50.53±17.27 v. IVPCA 56.58±13.24, p = 0.042. Number of additional antiemetic doses (0-24 hours, mean±SD): OOXY 1.11±0.84 v. IVPCA 1.44±0.75, p = 0.03.	"[O]ral controlled- and immediate-release OOXY after THR provides equivalent analgesia to IVPCA with morphine with a similar degree of PONV."	Data suggest equivalency.
Backlund 1997 RCT Double-blind No industry sponsorship. No COIs declared.	I(6.0)	N = 44 American Society of Anesthesiologists physical status I, II, and III, scheduled for elective major abdominal surgery.	Epidural morphine, bolus 0.015mg/kg followed by infusion 0.003mg/kg/hour (n = 13) vs. epidural oxycodone, bolus 0.15 mg/kg followed by infusion 0.03 mg/kg/hour (n= 16) vs. Oxycodone intravenously (IVO) (n = 11). Premeditated with; diazepam 0.15 to 0.2 mg/kg PO ~60 min. before arrival to operating theater.	Right after surgery, mean pain scores higher at rest in Oxycodone or group IV, 0.5±08 or 0.7±1.0, p = NS. At 17 hours, pain scores at coughing were higher in Group IVO, vs. two epidural groups, p <0.05. Incidence of nausea and pruritus equal in all groups.	"In the dosages reported, oxycodone can be used epidurally for acute postoperative pain."	Significant baseline differences in length of operations (214 v 175 v 305 minutes). More respiratory depression in oxycodone group – baseline differences suggest randomizations failure.

			Pain recorded hourly up to 3 hours after surgery. Three patients excluded.			
Wong 1991 RCT Double blind Supported by a grant from Anaquest Inc., Madison, Wisconsin. No COIs declared.	I(6.0)	N = 44 with acute moderate to severe post-operative pain after total knee arthroplasty or unilateral hip arthroplasty.	Pentamorphone 0.08µ/kg IV after surgery (n = 19) vs. Pentamorphone 0.16µ/kg IV after surgery (n = 18) vs. Pentamorphone 0.24µ/kg IV after surgery (n = 17) vs. placebo (n = 18). Time of first dose and total amount of morphine administrated in the first 5, 10, 15, and 60 minutes after.	VAS scores decreased with time in group receiving highest dose of pentamorphone, 0.24µ/kg, p = 0.003. Between-group comparisons; 0.24µg/kg of pentamorphone was more sedated than placebo at 5 and 10 minutes after study drug administration, p = 0.0002 and 0.004, respectively.	"…0.08-0.24 pg / kg of pentamorphone is ineffective in relieving acute pain after major abdominal or orthopedic operations."	Trial of 1 hour duration. Data suggest 0.24µm/kg effective.
Ouellette 1982 RCT Double blind Multiple center Parallel-design trial Buprenorphine used in this, made available by Eaton-Reccol, Inc., Norwich, N.Y. No COIs declared.	I(6.0)	N = 97 postsurgical patients	Buprenorphine 0.3 mg Q3 or more hours PRN up to ≤6ml in any 24 hour period (n = 47) vs. Morphine 10 mg Q3hr. PRN up to max. 6ml in any 24 hour period (n = 50). Drugs administrated every 3 or more hours as need up to maximum of 6ml, in any 24-hour period.	No statistical difference between groups on pain relief/number of injections administrated/adequate analgesia/days 1 and 2 or overall observed interval/or comparison of side effects by patient.	"[B]uprenorphine appears to offer an effective and safe alternative to morphine for patients with acute pain."	Data suggest equal efficacy.
Kastanias 2010 RCT Supported by grants from Krembil Nursing Awards, U. Health Network, Canadian Nurses Foundation, and Nursing Care Partnership Program. No statement of author COIs.	I(5.5)	N = 90 undergoing total knee replacement	(PCOA) individually prescribed short-acting opioid (n = 45) vs. Traditional nurse (RN)-administered oral analgesia (n = 45).	No significant differences between groups, including oral MS equivalents, pain ratings, pain relief, worst pain, least pain, average pain.	"Although the present study did not find significant differences between PCOA and RN-administered oral analgesia, we continue to expand the use of PCOA in our facility because it is in keeping with a patient-centered care philosophy."	Pragmatic trial of short duration. Data suggest PCA not superior to traditional oral administered opioids.
Hayek 2006 RCT	I(5.0)	N = 41 patients aged 40-84	Stimulating catheters (n = 19) vs. Non-stimulating catheters (n = 22); 25	No differences in ropivacaine given to patients with stimulating vs. non-stimulating catheters:	"The use of stimulating catheters in continuous	Data suggest lack of efficacy.

Supported by NIH Grant, Gheens Foundation, Joseph Drown Foundation, and Commonwealth of Kentucky Research Challenge Trust Fund. Arrow International provided stimulating catheters. No COIs disclosed.		years scheduled for unilateral total knee replacement.	recruited for each group, but 6 excluded from data analyses. 2-day follow-up.	8.2mL/h vs. 8.8mL/h respectively (p = 0.26).	femoral nerve blocks for total knee replacement does not offer significant benefits over traditional nonstimulating catheters."	
Kerrick 1993 RCT No mention of conflict of interest, no sponsorship.	I(5.0)	N = 28 undergoing total hip or knee arthroplasty	Amitriptyline 50mg (n = 14) vs. placebo both in conjunction with supplemental PCA (opioid) therapy for 3 days post-op after total knee or hip arthroplasty (n = 14).	No significant pain relief or improvement in mood reported. Amitriptyline group reported significantly greater mean pain scores; on day 1(15:00 hours), p < 0.05/on numerical verbal scale or NVS/on day 2 (15:00 hours) for VAS only, p <0.05. Strong correlation between VAS and NVS pain scores at all times, p, <0.001, ranging from 0.78 to 0.92. Sleep scale/global sense of well being: Amitriptyline group mean scores lower, p <0.025/greater for placebo, p <0.05, on days 1 and 2.	"The data from this pilot study failed to show that amitriptyline had an opioid sparing or potentiating effect, or any appreciable salutary effect on pain or symptoms control, during the acute postoperative period."	Both knee and hip patients included. Small numbers. Data suggest lack of efficacy, but potentially underpowered.
Mok 1981 RCT Supported in part by a grant from Eaton-Reccol, Inc. No other mention of industry sponsorship or COIs.	I(4.5)	N = 98 hospitalized patients with moderate to severe post-op pain	Buprenorphine Group 0.3 mg buprenorphine HCl (n = 49) vs. Morphine Group 10mg (n = 49) Each received only buprenorphine or only morphine in variable dose of 1.0, 1.5 or 2.0ml per injection not to exceed one injection every 3 hours. Study duration 3 days.	No significant difference between test medications with respect to investigators overall evaluation was found. No difference (p = 0.26) in number of injections between 2 test substances. A difference (p = 0.049) found in average number of injections. Buprenorphine patients given more injections per day.	"These data and the reported lack of withdrawal symptoms and the absence of physical dependence liability suggest that buprenorphine may have a role in the management of chronic pain."	No placebo. Short follow-up period; 3-day trial of post-operative pain. Data suggest equal efficacy. Conclusion from these data that buprenorphine may have a role in managing chronic pain appears unwarranted.
Divella 2012 RCT	I(4.5)	N = 260 undergoing THR.	EPI group: epidural anesthesia followed by continuous infusion of levobupivacaine 0.125% and sufentanil 0.7mcg/mL	Mean dynamic VAS scores and SD post-operative there were significant values in EPI group on POD#1 (8/16/24/32 hour: 2.68±1.98/ 1.92±1.69/	"Oral CR oxycodone plus IV paracetamol was as effective as epidural levo-bupivacaine and	Many details sparse. Data suggest equivalency.

No mention of industry sponsorship.			at 7mL/h (n = 130) vs. OXY group: spinal anesthesia and oral CR oxycodone 10mg/q12h plus IV paracetamol 1g/q6h (n = 130). Follow-up at 8, 16, 24, 32, 40, 48, 56, 64, and 72 hours post-op.	1.65±1.49/1.71±1.63, p = 0.001) and in OXY group at POD#3 (72 hours: 0.70±0.98). OXY group had significantly different scores on POD#2 (p = 0.005) and POD#3 (p = 0.001), (40/48/56/64/72 hours: 1.12±1.54/0.87±1.45/0.69±1.26/ 0.46±0.93/ 0.33±0.76).	sufentanil for postoperative pain relief after THR."	
Dahl 1995 RCT Financial support provided by Weifa Pharmaceuticals. JB is affiliated with Weifa Pharm.	I(4.5)	N = 123 patients due for a primary hip arthroplasty in spinal anesthesia.	Ibuprofen group received Ibuprofen 800mg PO (n = 48) vs. Ibuprofen/ codeine group 800mg/60mg PO (n = 50) vs. placebo group (n = 25). All had spinals.	Placebo, ibuprofen, and ibuprofen/codeine groups received 6.8±3.1mg, 4.7±2.0mg, and 4.7±2.5mg ketobemidone, respectively. Placebo 45% more opioids than other treatments (p <0.001), but no differences between ibuprofen and ibuprofen/codeine groups. Placebo group had higher VAS-score after 2 and 4 hours (p <0.05).	"[A] prophylactic dose of 800mg ibuprofen orally has an opioid sparing effect with a tendency of less pain experience during the first hours after hip arthroplasty."	Sparse methods. Data suggest IBU and IBU/ codeine equivalent. Both reduced needs to opioids compared with placebo.
Ittichaikulthol 2010 RCT Thailand No mentions of industry sponsorship or COIs disclosed.	I(4.0)	N = 120 elective total hip or knee arthroplasty.	Group I (control): placebo (n= 40) vs. Group II: celecoxib 400mg PO (n = 40) vs. Group III: parecoxib 40mg IV (n = 40). Medications given 1 hour before surgery. All had access to patient-controlled analgesia (PCA) with intravenous morphine. Follow-up 0, 1, 6, 12, and 24 hours.	Parecoxib group (10.73±3.20mg) and celecoxib (25.28±5.39mg) had lower mean 24 hour morphine consumption vs. placebo (37.50±6.78mg, p <0.00). Total morphine consumption at 24 hours post-op. reduced vs. placebo by parecoxib (71.39%, p <0.01) and celecoxib (32.59%, p <0.01). Parecoxib had lower VNRS score vs. celecoxib and placebo at 1, 6, 12 (p <0.001) but similar at 24 hours (p = 0.121).	"Within 12 hours after total hip and knee arthroplasty, pre-operative administration of parenteral parecoxib 40 mg was more effective than oral celecoxib 400 mg and placebo in terms of morphine consumption and VNRS score."	Short term trial of 1 day. No breakdown or stratification by group assignment. Many details sparse. Less MS used if 1 pre-op dose parecoxib or celecoxib. Lowest was parecoxib.
Lin 2012 RCT Open-label, Active-controlled study No industry sponsorship. No COIs declared.	I(4.0)	N = 62 with post-surgical pain.	Ultracet, 37.5mg tramadol/325mg opioid combined with acetaminophen or APAP (n = 29) vs. Depain-X, 65mg propoxyphene/650mg APAP (n = 33). Withdrawal patients, n = 45.	Ultracet patients had lower mean pain intensity score, p < 0.1 and higher percentage change from baseline, p = 0.0525 and < 0.01.	"Among patients with mild to moderate postoperative wound pain, single-dose Ultracet can provide slightly better analgesic efficacy than Depain-X in terms of onset and duration."	High dropouts. Data suggest Tramadol/APAP minimally superior.

Evidence for Subacute Pain

Author/Year Study Type Potential Conflict of Interest	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Low Back Pain						
Li 2008 RCT Double-blind Supported by grant from Pliva Pharmaceutical Industry Inc. Publication sponsored by AWD-pharma GmbH & Co. CL, JN, ML, and ZW all received research grants from Pliva Inc. MG is an employee of AWD-pharma GmbH & Co. MAU is a scientific consultant for Pliva Inc.	I(6.0)	N = 209, with subacute LBP (duration ≥4 weeks) and at least moderate severity. Ages 18-65 years.	Flupirtine maleate 100mg (n = 105) vs. tramadol 50mg (n= 104) TID for 5-7 days.	Pain intensity before 7.0; 95% CI: 6.5-7.0 and after a week p<0.0001 for both with mean flupirtine 2.8±1.9 (3.0; 95% CI; 2.4-3.1) vs. tramadol 3.0±2.2 (mean; 3.0; 95% CI; 2.6-3.4), p = 0.298. Global effect assessment; flupirtine 63.8% vs. tramadol 64.4%, p = 0.633.	"F]lupirtine…proved to be comparably efficacious with respect to pain relief and improvements in functional capacity to tramadol 50 mg three times daily, but was significantly better tolerated, when administrated to patients with subacute back pain for one week."	No placebo. Allocation unclear, sparse details for baseline comparability, blinding method, compliance. Data suggest similar efficacy at 1-week.

Evidence for Chronic Pain

Search Strategy: Articles were taken from previous ACOEM guidelines.

Author/Year Study Type Potential Conflict of Interest	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Cervical/Thoracic Pain						
Lemming 2005 RCT Crossover Trial No mention of industry sponsorship or COIs.	I(10.0)	N = 33 whiplash associated disorder Grade II in chronic stage.	Morphine (0.3mg/kg) vs. lidocaine (5mg/kg) vs. ketamine (0.3mg/kg) vs. placebo (NS) with one dose, 30 minutes administered for each drug. Pain recorded daily 5 days prior and 5 days post each medication. Each test 1 week apart.	No significant differences among groups for VAS scores 5 days before and 5 days after testing. The 3 drugs showed significant decreases in pain intensities and unpleasantness after start of infusion, p values: 0.001-0.044.	"This study clearly indicates heterogeneity in responses to different pharmacological challenges among individuals with chronic whiplash-associated pain."	Chronic WAD II pain averaged 26 months. Assessments up to 120 minutes with 30-minute infusion time. No further evaluations. A group of "global nonresponders" were 33% of study group. Experimental design of very short duration without clear clinical impact.

Lemming 2007 Crossover Trial No mention of industry sponsorship or COIs.	I(8.0)	N = 21 chronic whiplash associated pain or WAD.	Placebo/placebo vs. placebo/remifentanil vs. ketamine/placebo vs. ketamine/remifentanil. Each evaluation in 4 study sessions 1 week apart in crossover.	Pain intensity decreased over time with 3 groups that had active drugs. KET/REMI had most reduction of local pain, but KET/REMI and P/REMI reduced total pain equally.	"During these short-term infusions, adding ketamine to remifentanil enhanced the effects on chronic whiplash associated pain compared to the single drugs alone."	Excluded patients with history of drug abuse. Cross-over design. Clinical feasibility is limited as both IV medications; no long-term follow-up.
Ma 2008 RCT Supported by Shanghai Sixth People's Hospital Clinical Research grant. States no other COIs.	I(7.5)	N = 116 chronic neck pain with acute pain episodes.	Oxycodone 5-10mg and Q12 hours (n = 58) vs. placebo Q12 hours (n = 58) for 2-4 weeks. Follow-up on withdrawal symptoms performed on days 7 and 14 post-treatment.	Amount of acute pain flares, >3 times a day in Oxy-CR group decreased in Day 3 and 7 vs. pre-treatment and placebo, (p <0.05). 20.7% had continued flare ups. Day 7 and 21 followed by no complaints in Oxy-CR group, (p <0.01). VAS for OXY-CR lower than placebo, (p <0.05-0.01).	"Oxycodone controlled release could be an important optional drug for the management of refractory and frequent acute episodes of chronic neck pain in patients who failed to respond to non-opioid conservative treatment."	Chronic pain with acute flare. Diagnosed with spondylosis of neck. No clear diagnosis. Dosing for 2-4 weeks. Excluded alcohol or drug abuse. Assessments up to 28 days. No long-term prescription or follow up.
Low Back Pain						
Wasan 2005 RCT Crossover Trial No mention of industry sponsorship or COIs. 1 of 2 authors employed by Amgen Corporation.	I(8.5)	N = 60 with "discogenic" (pain ≥1 degenerated, herniated, or torn lumbar disc with≥ Grade III disc degeneration, abnormal morphology, or hyper-intense zone). LBP ≥6 months.	Morphine IV (high dosage n = 20, moderate n = 20, low (n = 20) vs. placebo (n = 20). Patients weaned off opioids for 2 weeks prior to study. Subjects continued all other pain psychiatric medications throughout study period of 2-3 weeks.	Total pain relief calculation (TOTPAR): LOW had 65.1% TOTPAR vs. 41.0% in HIGH, p = 0.026. Placebo analgesia LOW had 7.7% TOTPAR vs. 23.5% in HIGH, p = 0.03. Morphine minus placebo analgesia calculation was 59.2% TOTPAR in LOW vs. 21.7% in HIGH, p = 0.0001.	"[P]sychopathology predicts poor opioid analgesia in patients with chronic low back pain."	Placebo administration suggested high and moderate groups had significantly greater placebo analgesia than low group. Data suggest psychopathology in opioids use significant.
Gross 2008 Crossover Trial Supported by the University of Alberta.	I(8.5)	N = 30 with chronic LBP ≥6 months with or without leg pain, ≥3/10 LBP,	Fentanyl phase (FP) with naloxone (3µg/kg IV) vs. placebo (NS) phase (PP). Patients had 24-hour washout prior to treatments. After 1st treatment, functional	If FP first: Difference in maximum floor-to-waist lift (FP: 28.3 ± 17.3 kg vs. PP: 20.8±20.8kg, p = 0.003), and total work performed (FP: 6167±4169 joules vs. PP: 4733±3147 joules, p = 0.004). If	"Acute opioid administration improves work-related exercise performance in the short term."	Experimental study only with short-term IV administration.

		absence of specific pathology.	strength test performed lasting <30 minutes. A 30-minute washout taken prior to 2nd treatment and associated functional strength test also <30 minutes.	PP first: difference in time to fatigue (FP: 339.8±291.0 seconds vs. PP: 205.2±138.4, p = 0.02), and total work performed (FP: 7572 ± 5773 joules vs. PP: 4758±2771 joules, p = 0.006).		
Peloso 2004 RCT Supported by a grant from Ortho-McNeil Pharmaceutical, Raritan, New Jersey, USA. 2 of 5 authors employees.	I(7.5)	N = 336 with chronic LBP.	Tramadol/acetaminophen (Ultracet® 37.5/325mg, n = 167) vs. placebo (n = 171). Preceding treatment was washout period lasting up to 21 days. Patients evaluated Days 1, 14, 28, 56 and 91 (final visit).	Medications titrated up from 1 HS Day 1 to QID Day 10, then up to 2 tablets QID. Final pain VAS scores favored active medication (47.4 vs. 62.9) as did mean final pain relief scores (1.8 vs. 0.7). Adverse effects: somnolence (16.8% vs. 3.0%), dizziness (18.0% vs. 7.1%), headache (28.1% vs. 21.9%), nausea (25.1% vs. 5.9%), vomiting (11.4% vs. 2.4%), constipation (22.2% vs. 7.7%).	"Tramadol 37.5 mg/APAP 325 mg combination tablets show efficacy in pain reduction, in measures of physical functioning and quality of life, and in overall medication assessments, with a tolerability profile comparable with other opioids used for the treatment of chronic LBP."	Dropout rates high, suggesting problems with both lack of efficacy and adverse effects. Data suggest tramadol/ acetaminophen modestly superior to placebo.
Ruoff 2003 RCT No mention of industry sponsorship or COIs. 4 of 5 authors are employees of Ortho-McNeil Pharmaceutical.	I(7.5)	N = 318 with chronic LBP.	Tramadol/acetaminophen (37.5/325mg, titrated up from 1 QD to 4 QD on Days 1 to 10 and then up to 8 a day, n = 162) vs. placebo (n = 160). Following 3 week washout period, patients received 91 days of treatment.	Roland-Morris scores favored active drug (14.8±4.4 to 10.7±6.3 with tramadol/acetaminophen vs. 14.2±4.6 to 11.6±6.3 with placebo).	"[T]ramadol 37.5 mg/APAP 325 mg combination tablet is an effective therapy for the treatment of chronic lower back pain with a favorable safety profile."	Dropout rates high and related to either insufficient pain relief or adverse drug reactions in both arms. Data suggest tramadol/acetaminophen modestly superior to placebo.
Rashiq 2003 Double-blind Crossover Trial U. of Alberta Hospitals Foundation funded with grant to S.R. First author is PI on study sponsored by Janssen-Ortho Inc, and received honoraria from same for lectures.	I(7.0)	N = 28 with chronic LBP.	All subjects received fentanyl (1mcg/kg IV vs. placebo (naloxone after fentanyl). Randomized to single dose treatments at times (minutes) 0, 20, 30, and 50. Told to guess treatment order at time = 55 minutes. Treatment was preceded by a 24 opioid washout. Data collected between	Mean Sorenson test performance was modestly better in fentanyl group (77±49 seconds vs. 60±42 seconds).	"[I]n addition to relieving pain in CLBP, the administration of 1 mg/kg fentanyl is associated with an improvement in lumbar exercise test performance."	Experimental study. Single administration of medication.

			October 2000 and March 2002.			
Hale 1999 RCT Sponsored by Purdue Pharma L.P., Norwalk, Connecticut.	I(7.0)	N = 47 with chronic moderate-to-severe low back pain.	Controlled-release oxycodone, 10mg/12 hours, (n = 25) vs. Immediate-release oxycodone hydrochloride, 5mg QID4 times/day (n = 22). Up to 10 day titration period. Follow-up time for 4-7 days.	Pain intensity decrease from moderate to severe at baseline. Average daily dose required for stable analgesia was 40.0 (4.2 SE) mg of controlled-release and 38.5 (4.0 SE) mg of immediate-release, not significantly different. Overall pain intensity was 1.2 (0.1 SE) with controlled-release and 1.1 (0.1 SE) with immediate-release oxycodone.	"Controlled-release oxycodone given every 12 hours was comparable with immediate-release oxycodone given four times daily in efficacy and safety, and it provides convenient, twice-daily, around-the-clock treatment for selected patients with persistent back pain that is inadequately controlled by non-opioids or as-needed opioid therapy."	No placebo group. Data suggest comparable efficacy.
Jamison 2013 RCT Secondary Analysis Warnick is employee of Covidien, no other authors declare a conflict of interest. Study supported partly by a grant from Mallinckrodt, a Covidien company.	I(7.0)	N = 459 age 18-75 with >6 months moderate to severe LBP, and taking opioids.	All subjects participated in a screening visit, 2-4 week open-label conversion/ titration phase of opioid therapy (converted to hydromorphone ER using MEQ), and 12 week double-blind treatment (eligible if on stable dose between 12 and 64mg/d for ≥7 days, took average ≤2 tabs rescue med./day, mean NRS score ≤4, no intolerable side effects, and said medication helped pain). Hydromorphone ER (specific patient stabilized dose) vs. placebo (tapering dose of hydromorphone ER over 14 days); 12-week follow-up.	Hospital Anxiety and Depression Scale (HADS) categories: low = HADS <8 (N = 154), moderate = HADS 8-12 (N =155), high = HADS >12 (N = 147). Discontinued study during conversion and titration phase: greater negative effect (HADS = 10.74±5.34) vs. randomized to treatment (HADS = 9.49±4.49, p = 0.01); Low HADS (34.4% discontinued) vs. Moderate HADS (40.0% discontinued) vs. High HADS (50.3%), p = 0.019. Discontinuations during titration/ conversion phase: Moderate and High HADS groups rated opioid as least favorable on Patient Global Assessment (PGA) – Low = 3.17± 1.02, Moderate = 3.68±0.74, High = 3.93±0.71, p <0.001. Patients randomized: hydromorphone ER had 2x improvement vs. placebo in pain intensity ratings (9.0% vs. 24.6%) and at-home diary ratings (17.9%	"[T]he results suggest that high levels of negative affect have a significant impact on a trial of opioid therapy."	Secondary analysis, Hale 2010. Data suggest negative effect, maybe associated with more dropout and less benefits.

				vs. 35.1%, p <0.001). Pain intensity scores mean in-clinic rating: Low (4.67±2.42) vs. Moderate (5.13±2.17) vs. High (5.40±2.36), p = 0.03. Pain intensity scores mean at-home diary: Low (4.58±2.17) vs. Moderate (5.18± 2.14) vs. High (5.19±2.20), p = 0.02. Placebo: Low negative effect group showed greatest increase in average pain scores (in-clinic, 1.96±1.69) over whole trial vs. High negative effect group (1.05±1.27), p = 0.02. Roland-Morris Disability Scale: Low (10.68±6.25) vs. Moderate (12.04±6.40) vs. High (13.65±6.33), p <0.001. Subjective Opioid Withdrawal Scale (SOWS): Low (4.39±7.78) vs. Moderate (5.92±6.38) vs. High (6.32±6.63), p = 0.05.		
Hale 2013 RCT Kutch affiliated with Cytel Inc; Hale served as consultant or on advisory board for Cephalon, Covidien, Neuromed, and Purdue Pharma and served on speakers' bureaus for Covidien and Purdue Pharma; Nalamachu served as consultant on an advisory board or on speakers' bureau for and received research grants from Covidien, Endo Pharmaceuticals, and ProStrakan. Study supported by Neuromed Pharmaceuticals, Inc,	I(7.0)	N = 459 ages 18-75 years with moderate to severe chronic LBP ≥20 days/ month for ≥ 3 hours/day, for ≥6 months. Patients required to have: non-neuropathic (class 1 and 2) or neuropathic (class 3, 4, 5, or 6) LBP based on Quebec Task Force Classification of Spinal Disorders;	During conversion, converted to dose of OROS hydromorphone about 75% of equianalgesic dose of prior MEQ. Lowest starting dose OROS hydro-morphone ER 12 mg/day and highest 48 mg/day; PO QD total daily doses of 12, 24, 32, 40,48 or 64mg. OROS hydromorphone ER dosage titrated upward as frequently as Q 3 days to next dosage; decreases allowed only once and not below 12mg/day. Conversion and titration phase 2-4 weeks with ≤5 visits. Entered double-blind phase (fixed dose of OROS hydromorphone ER 12	179 discontinued during conversion and titration phase. 60% reached stabilized dose within 4 weeks. 43% began conversion and titration phase at 12 mg dose and 22.1% ended with 64 mg dose. Mean NRS score: decreased from 6.6±0.1 at screening to 4.3±0.1 at final visit of conversion and titration phase. Mean Patient Global Assessment (PGA) score: improved from 3.6±0.04 at visit 1 to 3.0±0.05 at the final visit. In those achieved stable dose: Mean change NRS score was -3.2(0.01) vs. -0.7±0.2) for dropouts, p<0.001. Mean PGA score: decreased in patients achieving stable dose but increased from 3.6±0.1 at visit 1 to 3.80.01 at termination visit in patients discontinued, p <0.001. Patients achieving steady state: mean change Roland-Morris	"[T]he detailed analysis of results from this conversion and titration phase confirm the findings of previous studies evaluating the efficacy and safety of OROS hydromorphone ER."	High rates of adverse effects and dropouts. Another report of Hale 2010.

Mallinckrodt Inc, and Covidien company. Study declares no conflicts of interest.		and daily opioid requirement of ≥60mg MEQ, but ≤320 MEQ within 2 months prior to study.	weeks or placebo, 10 weeks) if NRS score during last 7 consecutive days was ≤4 and met stable dosing criteria within 4 week timeframe; 12 week follow-up.	Disability Questionnaire (RDQ) of -4.3±0.03 vs. -0.4±0.3 for dropouts, p <0.001. 55% of patients experienced at least 1 adverse event: most commonly reported – constipation, nausea, somnolence, headache, and vomiting.		
Hale 2007 RCT See also Peniston 2009, 2010; Gould 2009 Research funded by Endo Pharmaceuticals, Inc.	I(6.5)	N = 250 randomized, with moderate to severe chronic LBP and opioid-experienced.	Oxymorphone extended release, in 2 equal doses once every 12 hours (n = 70) vs. placebo every 12 hours in 2 equal doses (n = 72)/12-week follow-up.	Increase from baseline pain (at randomization) to final visit 31.6 mm for placebo vs. 8.7mm with OPANA ER (p <0.0001). Placebo approximately 8-fold more likely than OPANA ER to discontinue due to lack of efficacy (p <0.001). Discontinuations from adverse events 10% placebo vs. 11% OPANA ER. Opioid-related adverse events with constipation (6%), somnolence (3%), and nausea (3%).	"In a 12-week, double-blind, randomized, placebo-controlled trial in opioid-experienced patients with chronic, moderate to severe LBP, OPANA ER provided efficacious, long-term analgesia and was generally well-tolerated."	Multiple etiology of back pain included some trauma. All currently on opioids chronically for LBP. Data suggest Oxymorphone ER may be an option for treatment in opioid experienced patients when compared to placebo. No long term follow-up.
Müller 1998 RCT Crossover 7-day trial Funding from bene Arzneimittel GmbH. No COIs declared.	I(6.5)	N = 55 with refractory chronic back pain for at least 3 months.	Codeine/paracetamol 30/500mg 8-hourly for 7 days (n = 54) vs. tramadol 50mg 8-hourly for 7 days (n= 52). Cross-over on day 8. 1 week follow-up.	80% of patients found tramadol effective vs. 81% codeine/ paracetamol effective in relieving back pain. 69% codeine/paracetamol vs. 81% tramadol tolerated well. VAS scores for quality of sleep and pain were similar, (no p value reported).	"Tramadol is at least as safe and efficacious as the reference product in the treatment of patients suffering refractory chronic back pain, with the test out-scoring the reference in respect of tolerability and patients preference."	Data suggest comparable results in this short 7-day trial.
Cloutier 2013 RCT Crossover Study was supported by a research grant from Purdue Pharma. No COIs declared.	I(6.5)	N = 83 adults (≥18 years), men and non-pregnant women with LBP of moderate or greater intensity for prior 3+ months.	At least moderate pain after 2-7 day washout period. Oxycodone/CR naloxone 10mg/5mg Q12 hours vs. placebo. Patient titrated at weekly to 20mg/10mg, 30mg/15mg, or up to 40mg/20mg Q12 hours. After 4 weeks in 1st phase, again received	Medication doses not different between groups. Rescue dose (tabs/day) mean±SD: CR oxycodone/CR naloxone (2.6±3.1) vs. placebo (4.3±3.5), p = 0.0003. Treatment effectiveness: CR oxycodone/CR naloxone (1.4±1.0) vs. placebo (0.9±1.0), p = 0.022. Treatment preference (%): patient (20% no preference)	"In patients who had previously been treated with opioids or were scheduled for opioid treatment, on the primary measure of analgesic efficacy, pain control was significantly better in the CR	Data suggest modest efficacy (crossover) of oxycodone.

			initial dose of 10mg/5mg CR oxycodone/CR naloxone or placebo Q12 hour and titrated. Rescue analgesia: acetaminophen plus codeine 300mg/30 mg Q4-6 hours. If completed both double-blind phases, eligible to receive CR oxycodone/CR naloxone for 6 months open-label extension.	– CR oxycodone/CR naloxone (n = 56) vs. placebo (n = 24), p = 0.013. Global Impression of Change (GIC) scores: patient – CR oxycodone/CR naloxone (3.2±1.4) vs. placebo (3.9±1.5), p = 0.0102; baseline following treatment with CR oxycodone/CR naloxone)/4.0±2.9, p = 0.0190. Total pain and disability index scores: 42.0±13.2/34.3±15.6 (p <0.0264 improvement from baseline CR oxycodone/CR naloxone)/37.5±15.2 (p ≤0.0142) following placebo treatment), p = 0.0511.	oxycodone/CR naloxone treatment phase compared with the placebo phase in patients adherent to the protocol, including their taking of blinded study medications."	
Chu 2012 RCT NIH K-award supported. No COIs disclosed.	I(6.0)	N = 103 with moderate to severe nonmalignant LBP, with a VAS ≥40/100 and eligible for opioid therapy.	Sustained-release morphine 15mg (n = 48) vs. placebo (n = 55); 1-month using sustained-release morphine or weight-matched placebo capsules. Patients were asked to complete an online follow-up survey approximately 1 year after study participation.	Among the morphine group, average VAS pain scores were significantly improved (p < 0.001), Roland-Morris Disability Index scores improved (p < 0.001), but Beck's Depression scores did not improve (p = 0.32) from baseline. Among the placebo group VAS pain scores improved (p < 0.01), but disability scores did not improve (p = 0.37) as well as Beck's Depression scores (p = 0.67) from baseline.	"Although often successful in acute settings, long-term use of opioids may be accompanied by waning levels of analgesic response not readily attributable to advancing underlying disease, necessitating dose escalation to manage pain…Our results suggest that opioid-naïve, chronic low-back pain patients maintained oral morphine therapy for 1 month developed tolerance to opioids but did not develop opioid-induced hyperalgesia."	Data suggested modest development of hyperalgesia.
Allan 2005 Non-blinded RCT	I(5.5)	N = 680 with chronic LBP.	Transdermal fentanyl (titrated 25µg/hour increments Q72 hrs, n = 338) vs. sustained-release oral morphine	LBP at rest favored TDF (severe back pain at rest 9% vs. 12%) as did nocturnal pain (10% vs. 16%).	"TDF and SRM provided equivalent levels of pain relief, but TDF was	No clear baseline characteristics to predict treatment responsiveness, but suggest 1-month trial

Supported by Janssen Pharmaceutical (protocol no. FEN-INT-26).			(30mg increased by 30% to 50% every 12 hours, n = 342). Treatment continued for 13 months.		associated with less constipation."	sufficient to determine treatment response. Employment status most influential factor predicting at least 30% reduction in pain. Data suggest modest efficacy.
Katz 2007 RCT Placebo – controlled Study supported by Endo Pharmaceuticals Inc. Katz serves as consultant for Endo Pharmaceuticals Inc and Ahdieh, Ma, van der Hoop, and Kerwin are employees. No COIs declared.	I(5.5)	N = 205 opioid-naïve (<5mg/day oxycodone or equivalent for 14 days before screening), ≥10 years old, initial VAS pain ≥50mm, and moderate to severe chronic LBP daily for at least several hours/day for ≥3 months.	Open-label dose-titration period: oxymorphone ER 5 mg PO Q12 hours for 2 days, then titrated at 5-10mg Q12 hours every 3-7 days until dose stabilization. Stable dose: both tolerability and efficacy (pain ≤40mm on VAS) for 3-5 consecutive days. Dose-stabilized patients randomized into 12-week double-blind treatment. Stabilized dose of oxymorphone ER, every 12 hours (n = 105) vs. placebo every 12 hours (n = 100). 12 week follow-up.	Average pain intensity for titration completers: pain intensity decreased from 69.4mm to 22.7mm, p <0.0001. Completion of randomized trial: oxymorphone (67.6%) vs. placebo (47.0%), p <0.001. Efficacy (LS mean±SE) change from baseline: placebo (26.9±2.4) vs. oxymorphone ER (10.0±2.4), p <0.0001. Clinically meaningful improvement from screening to final visit (≥30% VAS reduction): oxymorphone 93.0% vs. placebo 72.3%, p = 0.002. Clinically meaningful improvement from screening to final visit (≥50% reduction in pain intensity): oxymorphone 85.9% vs. placebo 55.3%, p <0.001. Dosage of rescue medication over first 4 days: oxymorphone 3.4±5.7mg vs. placebo 8.0±7.4mg, p<0.001.	"Stabilized doses of oxymorphone ER were generally safe and effective over a 12-week double-blind treatment period in opioid-naïve patients with CLBP."	Open label dose titration phase. High dropouts. Data suggest modestly lower pain scores.
Steiner 2011 RCT Industry Sponsored (Purdue Pharma, LP). Industry COI (Drs. Steiner, Munera, Ripa, and Landau are employees of Purdue. Dr. Hale served as consultant to Purdue, and was PI). No mention of other COIs.	I(5.5)	N = 662, ≥18 years, ≥3 months LBP, with or without lower extremity radiation, taking 30-80 MEQ, ≥4 days/week, for ≥30 days before screening visit.	Buprenorphine transdermal system (BTSD) 20µg/hour (n = 219) vs. immediate-release oxycodone (40mg/day) (n = 221) vs. BTSD 5µg/hour (n = 222). 12-week trial with visits at 1, 2, 4, 8, and 12 weeks.	Average pain in prior 24 hours was lower for BTDS 20 vs. BTDS 5 (p <0.001). Treatment difference of 0.75 in favor of oxycodone 40mg/day vs. BTDS 5 (p <0.001).	"This active-controlled superiority study demonstrated the superiority of BTDS 20 treatment compared with BTDS 5 for the treatment of moderate to severe low back pain in patients requiring treatment with opioid medications."	Trial stopped early by pharmaceutical company. Required opioid use at baseline. Run-in phase. 43% dropouts in run-in. 34% dropouts in RCT. Higher dropouts in BTDs vs. oxycodone (13% vs. 7% for adverse effects).
Miller 2013	I(5.0)	N = 660 opioid-	Opioid taper phase for 14 days, then 21 day	SF-36v2: BTDS 20 significant advantage over BTDS 5 for	"These data suggest that opioid-	Second study of Steiner, 2011. Enrolled

RCT Paper sponsored by Purdue Pharma. Miller and Yarlas full-time employees of QualityMetric, Inc. Wen, Dain, Lynch, and Ripa full-time employees of Purdue Pharma. Brennan paid consultant for Purdue Pharma. No other COIs declared.		experienced moderate to severe chronic LBP patients ages ≥ 18 years.	open-label (OL) run-in for tolerability and responsive-ness to Buprenorphine transdermal system (BTDS) 20. BTDS 20 (n = 219) vs. BTDS 5 (n = 221) vs. Oxycodone IR 40mg/day (OxyIR) (n = 220). Quality of life (QoL) assessed at weeks 4, 8, and 12 during double-blind phase. After 12 weeks, all invited to participate in 52-week open label extension phase with QoL assessed at weeks 4, 8, 12, 16, 20, 24, and 52.	Role-Physical (mean 41.2 BTDS 20 vs. 38.6 BTDS 5) and Bodily Pain (mean 41.3 vs. 39.1) scales, and overall Physical Component Summary (PCS) (mean 38.3 vs. 36.1), p <0.01. Mean PCS varies by 0.2 points over 52 weeks, range 37.5-37.7, and MCS by 0.9 points, range 53.0-53.9).	experienced moderate-to-severe CLBP patients receiving BTDS 20 exhibited better QoL than patients receiving BTDS 5."	opioid using population. High dropout in extension phase too. Data suggest modestly less pain with 20µg (micro) vs. 5µg.
Schnitzer 2000 RCT Supported by Ortho-McNeil Pharmaceutical, Raritan, NJ.	I(4.5)	N = 380 with chronic LBP.	Tramadol (up to 400mg a day (n = 127) vs. equivalent amount of placebo medication (n = 127); 3-week washout period, followed by 3-week open label, run-in phase and 4-week randomized placebo controlled double blind trial. "About" 4 weeks follow-up.	Mean±SD VAS score comparing tramadol vs. placebo: 3.5±2.79 vs. 5.1±2.98; p ≤0.0001. RDQ score: 8.8±6.2 vs. 10.2±6.2; p ≤0.0001.	"[T]ramadol is effective in maintaining control of low back pain among people who tolerate tramadol and perceive a benefit."	Open-label phase prior to RCT. Dropout rate in open-label phase high due to adverse drug reaction and inadequate pain relief, as was subsequent dropout rate in RCT.
Low Back Pain: Opioids vs. Other Opioids vs. Placebo						
Buynak 2010 RCT Supported by Johnson & Johnson Pharmaceutical Research & Development, L.L.C. First author received funding support and remaining 8 authors	I(7.5)	N = 981 with ≥3 months moderate-severe LBP. Had to have taken analgesics for ≥3months prior to study.	Tapentadol ER 100 to 250mg twice daily (n = 318) vs. oxycodone CR (controlled release) 20 to 50mg daily (n = 328) vs. placebo (n = 319). After 3-7 day washout of all analgesics, patients underwent 3-week titration period, 12-week maintenance period. Follow-up 4 days post	High dropout rates across all groups (tapentadol 48%; oxycodone 60%; placebo 54%). Pain improvement from baseline significant for tapentadol ER vs. placebo (p = 0.004), but not for oxycodone vs. placebo (p = 0.090). Adverse events in all groups with ≥ 1 adverse event were tapentadol 75.5%; oxycodone 84.8%; 59.6%.	"Treatment with tapentadol ER 100-250 mg b.i.d. resulted in significantly better relief of chronic low back pain over 15 weeks than placebo administration."	Dropout rates 47.8-59.5%. MD/patient adjusted doses. Highest dropouts in oxycodone. Both medications modestly effective compared with placebo.

are current/former industry employees.			treatment; 12 week follow-up.			
Hale 2005 RCT Sponsored by Endo Pharmaceuticals Inc, Chadds Ford, PA, and Penwest Pharmaceuticals Co, Danbury, CT.	I(7.5)	N = 330 with ≥2 months chronic LBP and with opioid experience.	Oxycodone 155mg a day every 12 hours in the early morning and in the evening (n = 80) vs. Oxymorphone 79.4mg a day every 12 hours in the early morning and in the evening (n = 80) vs. placebo every 12 hours in early morning and in evening (n = 75). Before randomization, patient randomized to double blind dose titration; Extended release (ER) oxymorphone 10-110mg every 12 hours for 7-14 days (n = 166) vs. Controlled release (CR) oxycodone 20-220mg every 12 hours for 7-14 days (n = 164); 18 days double blind treatment and up to 3.5-4.5 weeks follow-up.	ER oxymorphone vs. placebo and CR oxycodone vs. placebo mean VAS differences at study end greater with placebo, -18.21 (95% CI, -25.83 to -10.58; p = 0.0001) vs. -18.55 (95% CI, -26.12 to-10.98; p = 0.0001). Mean percent change in pain intensity at study end greater in placebo, -27.69 (95% CI, -45.96 to -9.41; p = 00.0032) vs. -36.36 (95% CI, -54.51 to -18.21; p = 0.0001). Less rescue medication with oxymorphone ER p = 0.0068, p = 0.0024.	"[B]oth oxymorphone ER and oxycodone CR provide significant analgesia with minimal need for rescue medication and comparable adverse event profiles."	High dropouts. Data suggest modest pain reductions. No major functional benefits reported.
Webster 2006 Phase III Trial Authors employed by Lifetree Clinical Research and Pain Therapeutics.	I(7.5)	N = 719 with chronic LBP.	Oxycodone QID (n = 206) vs. Oxytrex QID (4µg naltrexone/day, n = 206) vs. Oxytrex BID (2µg naltrexone/day, n = 206) vs. placebo (n = 101). Patients entered 4-10 day washout before	Dropouts high (54%). Most discontinuations in active treatment due to adverse effects; most placebo discontinuations due to inadequate pain relief. Pain scores (baseline/12 weeks): placebo (7.7±1.4 to 5.2±3.0),	"[B]y formulating 1 µg naltrexone per tablet into the oxycodone, oxytrex provided equivalent analgesia in a twice-daily dose regimen to oxycodone alone	Patients included a mix of opioid users and non-users. Psychological aspects not addressed other than few exclusions (e.g., no substance abuse in past 5 years).

			randomization. Over 1-6 weeks, titrated daily doses. Final titrated dose (max 80mg/day) used as treatment for 12 weeks. Post-treatment follow-up daily for 4 days.	oxycodone (7.6±1.4 to 4.0±2.5), oxytrex/naltrexone QID (7.3±1.4 to 4.2±2.6), oxytrex /naltrexone BID (7.6±1.3 to 4.3±2.6).	administered in 4 daily doses."	Very high dropouts. Data suggest modestly greater pain score reductions with opioids compared to placebo.
Vorsanger 2008 RCT Double-blind Supported by Biovail Corporation, Mississauga, Canada, and by Ortho-McNeil Janssen Scientific Affairs, LLC, Raritan, NJ.	I(7.5)	N = 386 with chronic LBP, ≥6 months.	Tramadol ER 300 mg 3 active tablets daily (n = 128) vs. Tramadol ER 200mg 2 active and 1 placebo tablet daily (n = 129) vs. placebo received 3 placebo tablets daily (n = 129). 3 week open-label tramadol ER run-in period. Following treatment, patients discontinued study medication and treated with nonopioid analgesics. 12-week study follow-up.	VAS during double-blind period for ER 300 mg (+5.2 mm, p = 0.009 vs. ER 200 mg (+7.8mm, p = 0.052) vs. placebo 12.2 mm. ER 300-mg group 76% vs. 200-mg 61% vs. placebo 57% experienced adverse events.	"[This] double-blind study with an open-label run-in demonstrated the analgesic efficacy and tolerability of tramadol ER in the treatment of chronic low back pain in patients who obtained clinical benefits or tolerated initial treatment with tramadol ER."	Study completed on populations that tolerated tramadol, 38% washed out. Data suggest pain reduced with Tramadol 300mg ER, although clinical significance appears uncertain (VAS 30.5 vs. 40.3).
Hale 2010 RCT Double-blind Supported by Neuromed Pharmaceuticals, additional funding for editorial support for this manuscript provided by Neuromed and Covidien Pharmaceuticals.	I(7.0)	N = 268 with LBP for 6 months.	Hydromorphone ER once-daily (n = 134) vs. matching placebo (n = 134). After a 2-4 week titration phase, patients were randomized to a 12-week double blind treatment phase.	Weekly diary NRS scores baseline-12 weeks and 12 weekend; (p <0.001) and (0.2U vs. placebo 1.6 units). At 12-weeks PGA scores/reduction in pain intensity; (p <0.001) / (80 ER vs. 57 placebo vs. 56 ER reported ≥30% pain reduction and 32 placebo vs. ER 30% reported ≥50% pain reduction, p = 0.01 or 50% or greater (p <0.01) reduction in pain vs. placebo.	"Once-daily hydromorphone ER (12-64 mg) demonstrated significant pain relief in opioid tolerant patients with moderate-to-severe low back pain."	Highly select, high-dose opioid-tolerant patients enrolled, limiting generalizability. Trial design was placebo withdrawal of therapeutic opioid. Details on compliance, observer blinding unclear. Withdrawal rates high although study design targeted for this outcome. Data suggest modest efficacy for pain ratings and somewhat greater for Roland Morris Disability Questionnaires. Overall, 24.0% completion rate from initial enrollment

						despite targeting opioid tolerant significantly limits generalizability.
Gordon 2010a RCT, Double-blind Crossover Trial Funded by Purdue Pharma, Pickering, Ontario, Canada. No conflicts of interest with regard to the content disclosed. 5 authors are/were employees.	I(7.0)	N = 79 with LBP with mean duration 10.6 years, at least moderate intensity.	Buprenorphine Transdermal System (BTDS) (weekly, 10/20mg per hour patch (max. 40mg per hour)) (n = 37 Phase I, n = 38 Phase III) vs. placebo (matching patch); crossed over after 4 weeks, for 4 more weeks (n = 42, 23). 2-7 day washout before randomization. All patches worn for 6-8 days. Follow-up total of 8 weeks (each treatment phase 4 weeks).	BTDS vs. placebo; study/rescue medication/VAS pain/PSQ/PDI/ QBPDS/SF-36/Effectiveness; (26.5 (12.9)/3.6 (3.4) vs. 33.6(10.9)/3.9(3.2) mg/h/tablets, p = 0.006)/(on both VAS (44.6(21.4) vs. 52.4(24.0) mm, p = 0.005) and ordinal scale 2.0(0.7) vs. 2.2(0.8), p=0.016) / (37.3%, p <0.001 vs. 18.9%, p = 0.004) / (16.8% (p = 0.003) vs. 11.9% (p = 0.033)) / (19.3% (p <0.001) vs. 14.0% (p = 0.001)) / (P range <0.001-0.017 vs. <0.001-0.025)/(and effectiveness 1.18 (1.1) vs. 1.0(1.1), p = 0.016).	"In this randomized, double-blind crossover phase of this study, pain control was significantly better during receipt of BTDS compared with placebo in the adult patients with moderate to severe chronic low back pain who had previously been treated with opioids."	Data suggest modest improvement in VAS scores, although clinical significance unclear. No difference in pain rescue medication.
Gordon 2010b RCT, Double-blind Supported by a research grant from Purdue Pharma, Canada. 4 authors employed by Purdue Pharma.	I(7.0)	N = 79 with at least moderate LBP severity, < 6 weeks.	BTDS in (5/10/20mg/h patches) titrated weekly vs. placebo (matching patches). Each treatment phase was four weeks. Patients could then participate in a 6 month open-label evaluation.	BTDS vs. placebo; VAS pain 5/20mg/h/PDI/QBPDS/BTDS dose for ITT/SF-36; (17.2mm/21.8mm vs. 14.7mm/15.6mm)/ (p = 0.0002 vs. p = 0.0001)/ (p = 0.0014 vs. = 0.0055 vs. baseline p = 0.2995)/ (14.3±6.3 vs. 16.85±5.5 mg/h, p = 0.0174) at 4 weeks/no statistical significance.	"Pain control was significantly better after four weeks of treatment with active BTDS than with placebo, even when active codeine plus acetaminophen was available to be taken as often as required."	Same as Gordon 2010a.
Gould 2009 RCT Supported by Endo Pharmaceuticals Inc. Three of the authors (M.P.J., A.R.G., and B.S.G.) receive royalties from industry-sponsored use of the Pain Quality Assessment Scale, but do not receive royalties from nonsponsored use.	I(6.5)	N = 140 with chronic LBP.	Oxymorphone ER 60mg/day (20-260mg/day) vs. placebo for 12 weeks measured on PQAS (paroxysmal, surface, deep pain) scale.	PQAS P<0.0022 decrease found in 12 of 20 PQAS items, and p <0.05 for 2 of remaining 3 items. ER and placebo significant time effect, for 18 of 20 PQAS items and 3 PQAS scores.	"[O]xymorphone ER has different effects on different pain qualities, and supports the use of pain quality measures, such as the PQAS, for detecting these effects."	Secondary analysis of Hale 2007.

Peniston 2010 RCT Endo Pharmaceuticals sponsored the two studies and financially supported the publication. 2 of 3 authors are employees.	I(6.5)	N = 348, with chronic LBP, for ≥3 months.	Upload-Naïve stabilized Oxymorphone ER at 10mg/day) vs. experienced (5mg ER as needed); 12-week randomized, double-blind, placebo controlled phase.	Naïve vs. experienced-dose/VAS/ AEs; (85 [62] mg vs. 39 [27] mg, p <0.001; 95% CI, mean difference, -55 to -36)/(p = 0.002; 95% CI,-6 to -2) /(P=0.99); Hydrocodone group vs. oxycodone experienced VAS/age <65/ER/AE; (p = 0.69)/(p = 0.03)/(p = 0.006, 95% CI, -60 to -10)/(no difference).	"These findings build on results from a previous analysis for the double-blind periods of the same clinical trials 26, which found that majority of adult succeed with titration to a generally well tolerated dose of oxymorphone ER will experience durable, effective analgesia regardless of patient age, sex, or history of prior opioid use."	Ad-hoc analysis of 2 RCTs. Approximately 60% were tolerated.
Peniston 2009 RCT Double-blind Endo Pharmaceuticals Inc sponsored the two studies analyzed and contributed financial and statistical support to the publication. One of 2 authors is an employee.	I(6.5)	N = 348 with moderate to severe LBP	Oxymorphone ER (n= 175) vs. placebo (n = 172) stabilization at ER previous opioid users 87.2 (60.4) vs. naïve 40.0 (25.8). 12-week randomized, double-blind, placebo controlled phase.	Pain at baseline and12 weeks/VAS in efficacy analysis ER(N = 174) vs. (n = 169)/LS/adverse event; (74.3% (130/175) moderate, 25.7% (45/175) severe vs. 77.3% (133/172), 22.7% (39/172) and 69.0% (120/174) vs. 38.5% (65/169), p = 0.001)/(ER similar vs. 20.6(0.85) baseline, 12 week 32.7(3.32)mm, p <0.001)/ (12.3 (2.8) mm, p< 0.001)/(similar).	"In this enriched population of responders, oxymorphone ER provided effective analgesia and was generally well tolerated, independent of patients' age, sex, or previous opioid use."	Greater dropouts for adverse effects with Hydromorphone. Greater dropouts for lack of efficacy for placebo.
Etropoliski 2010 RCT - Crossover Sponsored by Johnson and Johnson Pharmaceutical Research and Development, L.L.C. Authors are employees.	I(6.0)	N = 88 with chronic LBP.	Tapentadol IR vs. ER tablets. 2-period (2 weeks each). Study consisted of screening period (≤21 days, with all prior analgesic medication discontinued during the last 3-7 days); an open label flexible dose tapentadol IR treatment period (21 days); 2 randomized double-blind fixed dose treatment crossover periods (14 days each)	Mean pain intensity scores virtually identical at each follow-up period.	"Approximately equivalent TDDs of tapentadol IR and tapentadol ER provided equivalent analgesic efficacy for the relief of moderate to severe chronic LBP."	No placebo. Approximately 10% dropouts with ADRs. However, had both washout period and open label pre-treatment that resulted in initial 49.7% withdrawals. Data suggest equal (in)efficacy.

			and a follow-up period (10-14 days).			
Kalso 2007 RCT Funded by Janssen Pharmaceutical, the manufacturer of transdermal fentanyl.	I(5.5)	N = 680 with LBP.	Slow Release Morphine (n = 370) vs. Transdermal Fentanyl (n = 310) for 13-months; >100µg/h TDF or >390mg/day SRM. 13 month randomized trial.	VAS/SF-36/;74% TDF and 70% SRM) / (28,3) and (30,1)); baseline 30% pain reduction due to; employment / use of high dose variable; ($\chi2$ = 11.06, p = 0.0259) / ($\chi2$ = 3.04, p = 0.0811); at least 30% & 50% relief was higher in higher dose group 70% vs. 54%, p = 0.043 and 44% vs. 39% no significance.	"Strong opioid treatment can be beneficial for some patients with severe low back pain."	Secondary analysis of Allan 2005. Using primary outcome measures of pain relief ≥30% at any point in the trial. Data suggest 1 month trial period sufficient to determine response likelihood at this patient population using strong opioids.
Vondrackova 2008 RCT Sponsored and designed by Mundipharma Research GmbH and Co. KG. 7 of 11 authors are employees.	I(5.0)	N = 464 with moderate-severe chronic non-malignant LBP	Oxycodone PR (n = 151) vs. Oxycodone PR/ naloxone PR (n = 154) vs. placebo (n = 158). 12 weeks with 12 months extension.	Overall incidence of adverse events similar across all groups (total 53.8% of patients enrolled). Placebo group had higher brief pain intensity scale scores vs. oxycodone PR (p = 0.0012) and oxycodone PR/ naloxone PR (p = 0.158). Both treatment groups had better scores on sleep subscale (p <0.01). Rescue medication was also higher in placebo group vs. both treatment groups (p < 0.001).	"For both the full analysis and per-protocol populations, the appearance of pain events was significantly rarer under oxycodone PR/naloxone PR compared to placebo; combination therapy reduced the risk of pain events to 58% (p <0.0001 and p = 0.0014, respectively).	Baseline exclusion of those on <10mg/day oxycodone produced bias and limits generalizability. 38.2% initial dropouts in opioid taper and run-in phases. Data suggest oxycodone and combination both equivalent for pain relief and superior to placebo.
Hip, Knee, or Spine OA						
Silverfield 2002 RCT No mention of industry sponsorship or COIs. However, 3 of 4 authors employed by Ortho-McNeil Pharmaceutical, Inc.	I(8.5)	N = 308 with hip or knee OA.	Tramadol/acetaminophen (37.5/325mg or 75/650, n = 197) vs. placebo (N = 111) 1-2 QID for 10 days.	Discontinuation from adverse effects was tramadol/acetaminophen 12.7% vs. 5.4% placebo. Pain intensity scores (baseline/final): Tramadol/ acetaminophen (2.4/1.3) vs. placebo (2.4/1.6), p <0.001. Patients' overall assessments (very good and good): Tramadol (80.0%) vs. placebo (56.4%), p <0.001.	"[A]ddition of tramadol/ acetaminophen to NSAID or COX-2-selective inhibitor therapy was well tolerated and effective in the treatment of OA flare pain."	Short-term trial of 10 days of addition of tramadol for OA flare in addition to NSAID suggests modest efficacy.
Caldwell 1999 RCT Sponsored by Purdue Pharma L.P. One	I(8.0)	N = 107 with spine or knee OA.	Oxycodone controlled release 10mg q 12 hours (n = 34) vs. Oxycodone plus acetaminophen 5/325mg TID (n = 37) vs. placebo (n = 36).	Mean global pain intensity scores increased from open label to DB-RCT [mean (SE)]: placebo +1.0 (0.13) vs. controlled release oxycodone 0.44 (0.13) vs. oxycodone-ASAP	"Controlled release oxycodone q12h and immediate release oxycodone-APAP qid, added to NSAID, were	Most (60%) taking opioids previously. Dropout rates very high with 35.9% lost during initial open label titration phase;

author employed by Purdue Pharma.			All on NSAID. Open label titration run-in for 30 days then 30 day RCT. Double dummy. 30 day follow-up.	0.49 (0.11), p <0.004 comparing active treatments vs. placebo, NS between active treatments. Overall, adverse reactions included 50% somnolence rates in oxycodone group during titration.	superior to placebo for reducing OA pain and improving quality of sleep. The active treatments provided comparable pain control and sleep quality. Controlled release oxycodone was associated with a lower incidence of some side effects."	additional 33.6% lost during trial (total 57.5% dropouts). Suggests equivalency of 2 opioids. Modest efficacy vs. placebo, results also only directly applicable to patients previously treated with opioids.
Fleischmann 2001 RCT Funding provided by research grant from Ortho-McNeil Pharmaceutical, Raritan, New Jersey (Study #CAPSS-051). 2 authors employed by Ortho-McNeil Pharmaceutical.	I(7.5)	N = 129 with knee OA.	Titrated doses of tramadol 1-2 50 mg tablets QID (n = 63) vs. placebo for 91 days; 10-day washout period (n = 66). After a 7-day titration period, patients were permitted to 400mg/d as needed for 84 days. Follow-up visits at days 14, 28, 56 and 91 days.	Final pain intensity scores: tramadol 2.10±1.06 vs. 2.48±1.13 placebo, p = 0.082. Patient overall assessment tramadol 0.10±1.41 vs. placebo -0.44±1.3, p = 0.038. Dropout rates were high (41.3% tramadol vs. 65.2% placebo).	"Tramadol may be useful as monotherapy in the treatment of joint pain associated with OA."	High dropout rate (41.3% tramadol vs. 65.2% placebo), limits strength of conclusions; may limit generalizability. Data statistically negative for main outcome, but positive for others suggesting modest efficacy.
Langford 2006 RCT Supported by funds from Janssen-Cilag (protocol FEN-EMA-1). All but one author received honoraria from industries for speaking, advisory board activities, etc.	I(7.5)	N = 416, ≥40 years old with hip or knee OA requiring arthroplasty; mean daily VAS score ≥50 at start and end of 7-day pre-treatment and inadequate control on "weak" opioids	Transdermal fentanyl (TDF, 25µg per hour, titrated up to 100µg per hour with 4 patches) (n = 202) vs. placebo (n = 197); 6 weeks treatment; allowed metoclopramide, after a 1-week pretreatment run-in phase. 6 week follow-up.	Mean±SEM VAS score change from baseline to last visit comparing placebo vs. fentanyl: -17.9±1.9 vs. -23.6±1.8; p = 0.0025.	"TDF can reduce pain and improve function in patients with knee or hip OA."	Results generalizability limited to pre-arthroplasty patients. High dropouts (52.5%) despite requirement for opioids treatment for study eligibility. High adverse effects in TDF group. Pain change from baseline benefits shown at Weeks 1-4, but differences with placebo disappeared at Weeks 5 and 6 per graph, though other data suggest modest efficacy.
Malonne 2004 RCT	I(7.5)	N = 230 with hip or knee OA rated ≥35mm on 100mm	Tramadol LP (n = 111) 200mg QD vs. placebo (n = 119) for 14 days. The treatments	Mean pain decrease 2.43 vs. 1.55 cm, p <0.01. Improvement before Day 7 comparing tramadol vs. placebo: 88.2% vs. 65.2%; p = 0.021. Mean time to	"[T]ramadol LP 200 mg was significantly more effective than placebo in alleviating pain in	Short-term study. Modest improvement over placebo. Approximately 2.5-fold

No mention of industry sponsorship or COIs. However, 4 of 5 are apparently industry employees.		Huskisson VAS; symptoms ≥6 months, requiring regular analgesics or NSAIDs for ≥1 month.	consisted of 4 visits: -7, 0, 7, and 14 days.	report improvement: 3 vs. 6 days; p <0.001. Reports of adverse events: 45% vs. 19.3%; p <0.001.	patients with osteoarthritis of the hip or knee. It appeared to be relatively well tolerated for an opioid compound."	adverse effects; 21.6% dropouts in tramadol.
Afilalo 2010 RCT Funded by Johnson and Johnson Pharmaceutical Research and Development, L.L.C.M. No conflict of interest stated that is directly relevant to the content of this study; however, 9 of 10 authors are industry employees.	I(7.5)	N = 1030 patients >40 years of age with knee OA. For a 3-week titration period followed by a 12-week maintenance period.	Tapentadol extended release (ER) (n =346) vs. Oxycodone controlled release (CR) (n = 345) vs. placebo (n = 339) for a 3-week titration period. 12 week follow-up.	High dropout rates for all groups: tapentadol (n = 163; 47%), oxycodone Cr (n = 224; 65%), and placebo (n = 134; 40%). Percentage of patients reporting "minimal change" in overall status from baseline: 24% in placebo, 21% in tapentadol ER, and 26.5% in oxycodone CR.	"…[B]oth tapentadol ER and oxycodone CR provided effective relief of moderate to severe osteoarthritis knee pain…In addition to showing clinically meaningful improvements in pain intensity compared with placebo, tapentadol ER had a better tolerability profile than oxycodone CR, as shown by significantly lower incidences of nausea, vomiting, and constipation."	Large sample size. High dropouts all groups, but lowest in placebo (40%). Data suggest tapentadol minimally better than oxycodone which is minimally better than placebo. Mean pain intensity at 15 weeks of approximately 4.6 vs. 4.8 vs. 5.1.
Lerner 2012 RCT 2nd Report See also Afilalo 2010 Sponsored by Janssen Scientific Affairs, LLC. No relationship/ conditions/circumstances that present potential conflict of interest stated however 4 of 7 authors are employees.	I(7.5)	N = 758 with knee OA, aged 40-65.	Tapentadol ER (n = 249) vs. Oxycodone CR (n = 249) vs. placebo (n = 260). Five study phases: screening (≤14 days), washout (discontinue all analgesics 3-7 days), titration (3 weeks), maintenance (12 weeks), and follow-up (assessments 4 days after treatment and 10 to 14 days phone calls after last dose).	Tapentadol ER mean reduction in pain (p = 0.001) vs. oxycodone CR (p = 0.438). PCS score improved for tapentadol (p <0.001) and for oxycodone (p <0.001). WOMAC improved for tapentadol (p <0.001) vs. oxycodone (p = 0.10) Estimated mean productivity improved for both tapentadol (p = 0.001) vs. oxycodone (p <0.001). Mean cost savings per subject per year were $1960 for tapentadol vs. $1510 for placebo vs. $1400 for oxycodone.	"In addition to identifying differences in at-work productivity associated with analgesic treatment options for managing chronic pain, this study demonstrated that imputation is a tool for advancing research on health and work productivity."	Secondary analysis of Afilalo 2010. Data suggest modest efficacy compared with placebo and better pain relief with tapentadol.
Burch 2007	I(7.0)	N = 1,028 age 40-80	Tramadol Contramid OAD (n = 432) increased	Mean±SD absolute improvement comparing placebo	"Tramadol Contramid OAD	Open label (66% with adverse effect) followed

RCT Corresponding author from Labopharm, and other research jobs in author list.		years with knee OA and taking NSAIDs, COX-2 inhibitors, or tramadol regularly past 30 days	gradually by 100mg to 200-300mg vs. placebo for 12 weeks maintenance period (n = 213). Visits were at 21, 42, 63, and 84 days. Titration followed by 7-day taper.	vs. tramadol: 2.29±1.97 vs. 3.03±2.12. Difference in absolute improvement between tramadol and placebo; p <0.0001.	given once daily is an efficacious and safe treatment for pain due to OA."	by DB RCT. High placebo dropouts. Data suggest modest pain reduction and high adverse effects despite open label phase.
Katz 2010 Crossover RCT Supported by King Pharmaceuticals, Inc, Bridgewater, NJ. 3 of 4 authors are employees and other associated with Analgesic Research.	I(7.0)	N = 113 with hip or knee OA	ERMS-ALO-01 (MS/naltrexone) (n = 35): sequence 1 vs. ALO-01-ERMS (N = 37): sequence 2. 5-period cross-over. Washout period. Period 1: titrated with extended-release MS (ERMS), ranging 20-160 mg BID. Period 2: 14 day active therapy of ERMS or ALO-01. Period 3: Open Label ERMS. Period 4: Cross over to other active treatment. Period 5: Open label ERMS BID for 7 days. Follow-up phone call 7 days after period 5.	No significant differences between ERMS and ALO-01 with respect to pharmacokinetics, safety, and efficacy.	"[T]reatment of patients with OA of the hip or knee with ALO-01 results in morphine exposure, efficacy, and safety similar to marketed ERMS."	Data suggest comparability.
Pavelka 1998 Crossover Trial Sponsored by Grünenthal GmbH, Aachen, Germany. 2 of 5 authors employees.	I(7.0)	N = 60 with hip or knee OA	Tramadol 50-100mg up to TID (n = 54) vs. diclofenac 25-50mg (n = 54) up to TID for 4 weeks each treatment. One group received tramadol for 4 weeks followed by diclofenac for 4 weeks or visa versa. 1 week washout period between medications. Doses titrated.	Mean tramadol dose 164.8±54.1mg; mean diclofenac dose 86.9±21.4mg; 3 in each group terminated. Adverse events greater during tramadol treatment (20.0% vs. 3.3%, p = 0.0056). No patient treatment preference (46.7% tramadol vs. 45.0% diclofenac, p = 0.85). Functionality scores (WOMAC) improved in tramadol group 39.6±16.0 to 32.0±17.4 vs. diclofenac 40.0±17.2 to 30.1±17.0 with no significant difference between groups.	"OA patients' response to analgesic treatment was highly individual and the response to one drug was not predictive of that to another drug. As functional scored improved (lower WOMAC scores) on analgesic vs. NSAID, pain rather than inflammation may be the most important aspect of treatment. A significant	Data suggest tramadol equivalent to diclofenac on average. Study suggests some preferred different medications and results not predictable.

					proportion of patients were not treated satisfactorily with diclofenac or tramadol alone."	
Markenson 2005 RCT Financial support from Purdue Pharma P.L.	I(7.0)	N = 107 with moderate to severe OA (ACR; hip 18%, knee 30.8%, spine 45%), taking scheduled NSAID or APAP at least 2 prior weeks or oral opioid therapy ≤60mg oxycodone a day	CR oxycodone 10mg (n = 56) vs. placebo (n = 51). Q12 hours for 90 days. Dose titrated. Follow ups on days 15, 30, 45, 60, and 90.	Least square means±SE for observed average pain intensity at Day 90: 6.0±0.4 (placebo) vs. 4.9±0.3 (O = oxycodone); p = 0.024. Stiffness and difficulty in physical function and in composite score observed in CR oxycodone group (48.7± 6 3.2, 45.4±6 2.6, and 46.6±6 2.7, respectively, vs. 68.9±3.5, 58.6±2.9, and 62.2±3.0, respectively, for placebo; p <0.001).	"Treatment with controlled-release oxycodone of patients with osteoarthritis with persistent moderate to severe pain uncontrolled by standard therapy resulted in significant pain control and improvements in physical functioning."	Mixed OA joints. May have enrolled if under opioid treatment, thus data may not be applicable to population not under treatment. Allowed adjusted doses. Large dropout rate (66%), mostly ineffective in placebo and adverse effects in active treatment. 41% of active treatment finished trial.
Matsumoto 2005 RCT Supported by Endo Pharmaceuticals Inc., Chadds Ford, Pennsylvania, and Penwest Pharmaceuticals Co., Danbury, Connecticut.	I(7.0)	N = 489 with hip or knee OA, >40 years old, at least Grade 2 Kellgren-Lawrence scale, prior treatment with acetaminophen, NSAID, COX-2, or opioid for ≥75 of 90 prior days	Oxymorphone ER 20mg (n = 121) vs. Oxymorphone ER 40mg (n = 121) vs. Oxycodone controlled release 20mg (n = 125) vs. placebo (n = 124). 6 months follow-up.	Arthritis pain intensity week 3 oxymorphone ER least squares mean difference (LSMD) from placebo -9.0 (95% CI -16.2 to -1.8; p = 0.015). Secondary efficacy analysis with improvements at Week 4 (LSMD from placebo, -10.3 [95% CI: -17.7 to -2.8]; p = 0.007) and with oxymorphone ER 20mg at Week 3 (LSMD from placebo, -7.7 [95% CI: -15.0 to -0.4]; p = 0.039) and Week 4 (LSMD from placebo, -7.5 [95% CI: -15.0 to 0.0]; p = 0.050). WOMAC scores favored active treatment. Patient's global assessments at Week 4: placebo, -19.5 vs. oxycodone CR 20mg -25.4 vs. oxymorphone ER 20mg -23.2 vs. oxymorphone ER 40mg -28.6.	"In this short-term study, oxymorphone ER was superior to placebo for relieving pain and improving function in patients with moderate to severe chronic OA pain, and is an alternative to other sustained-release opioids."	Short-term study only. Modestly lower pain and improved function with active treatment, but high dropouts (45.2%), mostly adverse effects in medicated groups.
Florete 2008 2 RCTs, 2nd report combined analyses	I(7.0)	N = 1,608 ≥18yrs with x-ray confirmed ACR	Study A: Tramadol ER 100 vs. 200 vs. 300 vs. 400mg vs. placebo. Study B: Tramadol ER	All tramadol ER groups improved in sleep quality vs. placebo at Week 1; p ≤0.022 in final visit for all tramadol ER	"In this post hoc analysis, a reduction in pain was associated with	Two trials combined in 1 report with only post-hoc analyses. Main outcome was sleep

Study sponsored by Biovail Corporation, Mississauga, Ontario, Canada. Editorial support provided by Nancy Bella, PharmD, and was funded by Ortho-McNeil Janssen Scientific Affairs, LLC. Authors are apparently employees.		functional Class I or II knee or hip OA	100 vs. 200 vs. 300mg vs. placebo; both were 12 week studies, 12 weeks follow-up.	groups (p ≤0.022) (mostly graphic data). For morning awakening due to pain, improvement started at Week 1 thru to final visit for tramadol ER 200 and 300mg dosage (all p ≤ 0.017); Week 3 and continuing to final visit for tramadol ER 100mg dosage (all p ≤0.046). Awakening at night, falling asleep also improved.	a significant reduction in (pain-related sleep disturbances) due to OA."	disturbance; however, study is short- to intermediate-term. Data suggest modest improvement in short term. High dropouts.
Gana 2006 RCT Study supported by Biovail Laboratories International SRL. Medical writing assistance on behalf of PriCara, Unit of Ortho-McNeail Inc.	I(7.0)	N = 1,020 with ACR functional Class I-III knee or hip OA who took acetaminoph en, NSAID, COX-2, or opioid for at least 75 of prior 90 days.	Tramadol ER 100, 200, 300, or 400mg QD vs. placebo. Titration over up to 15 days for 400mg dose; 12 weeks treatment, and follow-up at weeks 1, 2, 3, 6, 9, 12, and 13 weeks.	Mean±SE WOMAC Index for physical function (0-1700) comparing placebo vs. tramadol 100 vs. 200 vs. 300 vs. 400mg.Tramadol ER 200 and 300 mg were more effective than placebo (P≤ 0.050) for subject global assessment of disease activity and pain intensity of non-index joints.	"Tramadol ER 100-300 mg once daily was associated with significant improvement in pain intensity and physical function, and was well tolerated, despite the use of a fixed-dose study design not reflective of usual clinical practice. Tramadol ER is a useful treatment option for patients with osteoarthritis pain."	High dropouts (44.8%). Overall global assessment trended in favor of treatment (p = 0.079). Data suggest modest efficacy, particularly 100mg vs. placebo with minimal incremental gain with higher doses, but more adverse effects. No long-term follow-up.
Parr 1989 RCT No mention of industry sponsorship or conflict of interest. However, 2 of 4 authors apparently employed by Ciba-Geigy Pharmaceuticals.	I(6.5)	N = 846 mostly hip or knee OA, ankle and wrist.	Diclofenac sodium slow release 100mg QD (n = 373) vs. Dextropropoxyphene 180mg plus paracetamol 1.95gm QD (n = 382). 4 week follow-up.	Pain ratings (change in VAS): diclofenac -27.0 vs. dextropropoxyphene plus paracetamol -22.7, p <0.05 (8% greater reduction in diclofenac). Physical mobility scores: -10.8 vs. -7.4 (p <0.01) (13% better with diclofenac). Work interference less in diclofenac (3 vs. 11, p <0.05), and time lost (3 vs. 16, p <0.05). Dizziness, lightheadedness less for diclofenac (14 vs. 30, p <0.05), as was CNS symptoms (48 vs. 93, p <0.01). Abdominal pain higher with diclofenac (40 vs. 18, p <0.01) and diarrhea (14 vs. 2, p <0.01). Overall GI effects	"Pain as measured by a visual analogue scale (VAS) showed 8% greater pain reduction with DSR as compared with D&P (P<0.05). Physical mobility as measured by the (Nottingham Health Profile) improved by 13% more with DSR as compared with D&P (P<0.05)."	No regular NSAID use prior 6 months. Dropouts 15.3% diclofenac vs. 17.0%. Suggests greater efficacy of diclofenac vs. dextropropoxyphene plus acetaminophen. Benefits suggested for working populations from diclofenac including lower incidence of problems at work and lost work time.

				not different (63 vs. 60); comparable dropouts.		
Lloyd 1992 RCT Support provided by Sanofi Winthrop Ltd. Corresponding author employed by Napp Laboratories Ltd.	I(6.5)	N = 86 with severe hip OA	Controlled-release dihydrocodeine 60mg to 120mg BID (n = 43) vs. Dextro-propoxyphene/ paracetamol 32.5 to 325mg 2 tablets TID-QID (n = 43). 2 week follow-up.	Average daily pain scores Week 2: dihydrocodeine 39.2±5.3 vs. dextropropoxyphene 39.8±4.6 (NS). Pain on hip ROM better in hydrocodeine group. Adverse effects worse with dihydrocodeine and more dropouts (total dropout rate 33.7%) Overall adverse effects: dihydrocodeine 102AEs/ 43 patients (2.4/patient) vs. dextropropoxyphene (84/43) (2.0/patient).	"[A]fter 2-weeks' treatment CR dihydrocodeine provided superior analgesia to dextropropoxyphene/ paracetamol with no difference in side-effects."	Short-term study described as double blind, but different dosing regimens raise questions about blinding success. Data suggest short-term equivalency by most measures, but higher dropouts for dihydro-codeine (43% vs. 21%) and more adverse effects (39.5% vs. 9.3% of dropouts).
Kean 2009 2 RCTs in 1 report Analysis funded by Labopharm Inc., and 1 of 3 authors an employee.	I(6.5)	N = 685 females with moderate-to-severe OA pain	100mg Tramadol Contramid® OAD (n = 130) vs. 200mg Tramadol Contramid® OAD (n = 131) vs. 300mg Tramadol Contramid® OAD (n = 144) vs. placebo (n = 280). Titrated dose in run-in. Follow-up for 12 weeks.	Tramadol 87.7% vs. placebo 75.7% found overall pain relief effective or very effective. WOMAC pain scores from week 0 to 12 improvement for 100mg vs. 200mg vs. 300mg vs. placebo: 58.8% vs. 53.0% vs. 58.9% vs. 45.2% (p = 0.018, p = 0.175, p = 0.023 vs. placebo). Mean WOMAC physical function improvement score 100mg vs. 200mg vs. 300mg vs. placebo: 56.9% vs. 54.0% vs. 53.4% vs. 41.9% (p = 0.009, p = 0.034, p = 0.043 vs. placebo).	"The efficacy and safety of Tramadol Contramid® OAD in women with pain due to OA of the knee were demonstrated in this analysis that further supports its recommended use as an alternate treatment to NSAIDs and strong opioids."	Short- to intermediate-term study. Data suggest modest efficacy for pain vs. placebo. High dropouts (54.9%), mostly adverse effects except placebo. Data suggest minimal efficacy and modest differences between doses.
Emkey 2004 RCT Supported by Ortho-McNeil Pharmaceuticals Inc, Raritan, New Jersey. 4 of 5 authors employees.	I(6.5)	N = 307 with moderate or severe knee or hip OA.	Tramadol/acetaminophen vs. placebo up to 4 tablets a day 10 days, then up to 8 tablets a day for duration as added therapy to celecoxib or rofecoxib for 91 days.	Mean VAS scores were (baseline/final) tramadol 69.0±12.5/41.5±26.0 vs. placebo 69.5±13.2/48.3± 26.6. Discontinuations due to lack of efficacy higher in the placebo group (17% vs. 8.5%).	"Tramadol 37.5mg/APAP 325 mg combination tablets were effective and safe as add-on therapy with COX-2 NSAID for treatment of OA pain."	Data suggest modest efficacy of tramadol/ acetaminophen vs. placebo. Overall dropouts 26.1% equal in both groups, but more insufficient pain relief in placebo (66.7% dropouts) and adverse events in active treatment (48.8% dropouts).

Kivitz 2006 Randomized, Double-blind, Placebo-Controlled, Dose-Ranging, Phase 3 Trial Study supported by Endo Pharmaceuticals Inc., Chadds Ford, Pennsylvania, and Penwest Pharmaceuticals Co., Danbury, Connecticut. No COIs declared.	I(6.5)	N = 370 with chronic, moderate to severe osteoarthritis pain in hip/knee.	Oxymorphone ER 10mg (n = 95, 61 completed 2-7 day washout of analgesics) vs. Oxymorphone ER 40mg (n = 93, 35 completed washout) vs. Oxymorphone ER 50mg (n = 91, 37 completed washout) vs. placebo, (n = 91, 65 completed washout). All Q12 hours during weeks 1-2. Follow-up for 2 weeks.	Oxymorphone ER 40 mg ($p \leq 0.025$) and 50 mg $p \leq 0.001$) produced significant results than placebo for pain. Oxymorphone ER 10 mg produced significant results than placebo for pain (-83.6; $p \leq 0.025$).	"In these patients with chronic, moderate to severe pain related to OA of the hip or knee, oxymorphone ER administered twice daily for 2 weeks produced dose-related reductions in arthritis pain intensity and improvements in physical function."	High dropouts – data suggest Oxymorphone 40 and 50mg mostly superior to 10mg or placebo.
Vojtaššák 2011 RCT Study funded by Janssen Cilag Medical Affairs EMEA, a division of Janssen Pharmaceutica NV, Beerse, Belgium.	I(6.0)	N = 288 patients with moderate to severe pain from osteoarthritis of knee or hip.	OROS hydromorphone (n = 139) vs. placebo (n = 149). Followed for 16 weeks.	There was no difference between placebo and hydromorphone in efficacy (-0.2365 95% CI -0.5357 to 0.0627). Scores on the Brief Pain Inventory was not significantly different between the two groups. More subjects dropped out of the hydromorphone group compared to placebo (25.9% vs. 4.7%).	"The study did not meet the primary objective of showing superiority of OROS hydromorphone compared with placebo in its analgesic effect induced with subjects with moderate-to-severe OA of the hip or knee."	No significant benefit hydromorphone over placebo at any time point. In stratified analyses, some differences if not on NSAID. If no NSAID, no statistical benefits.
Roth 2000 RCT Sponsored by Purdue Pharma LP, Norwalk, Connecticut. 1 of 8 authors a Purdue employee.	I(6.0)	N = 133 with moderate to severe spine, knee or other OA	Oxycodone controlled release 10mg Q12 hour vs. 20mg Q12 hours vs. placebo for 14 days; 6 month open label extension and optional 12 month extension.	Mean pain intensities (baseline/14 days, interpretation of graphic data): oxycodone 10mg (2.5/1.9) vs. oxycodone 20mg (2.5/1.6) vs. placebo (2.4/2.2), $p < 0.05$ compared with placebo.	"Around-the-clock controlled-release oxycodone therapy seemed to be effective and safe for patients with chronic, moderate to severe, osteoarthritis-related pain."	Short-term trial. Overall dropouts 47.4% (81.5% of placebo dropouts ineffective, 60.5% oxycodone dropouts with adverse events). Somnolence in 25-27%, dizziness 20-30%, nausea in 27-41% of active treatment groups. Data suggest modest efficacy. In long-term open-label extension, 10-21% required dose titration each visit. Dose appeared to trend upwards modestly over 72 weeks.

Schnitzer 1999 RCT Sponsored by ortho-McNeil Pharmaceutical Inc., and 2 of 3 employees.	I(6.0)	N = 236 with knee OA	Tramadol 200mg a day vs. placebo over 8 weeks with 5 weeks open label run-in. All treated with naproxen 500mg BID and those with marked relief excluded.	In open-label, tramadol reduced VAS pain scores by 19mm in naproxen non-responders vs. 5mm in responders, p <0.05. Maximum effective naproxen dose for naproxen responders, 221 for tramadol vs. 407 placebo, p = 0.021. For naproxen non-responders, mean effective doses: 419 vs. 396mg, p = 0.71.	"In patients with painful OA of the knee responding to naproxen 1,000mg a day, the addition of tramadol 200mg/day allows a significant reduction in the dosage of naproxen without comprising pain relief."	Overall dropouts in active treatment 19.3%. Main utility of data may be in treatment of patients not responsive to naproxen.
Roth 1998 RCT Supported by Ortho-McNeil Pharmaceutical Inc.	I(6.0)	N = 63 with OA break-through pain	Tramadol 50mg 1-2 Q 4-6 hour PRN vs. placebo. Open label run-in for 1 day, then 13 day RCT. Study was 2 weeks total.	Patient assessments (excellent/very good): tramadol (11/20 = 55%) vs. placebo (5/20 = 25%). Mean resting pain scores at end: tramadol 0.85±0.32 vs. placebo 1.32±0.33, p = 0.46. Cumulative continuation rates 13 days: tramadol 84% vs. 53% (graphic data). Adverse effects in somnolence in tramadol 25% vs. 14%, nausea 35% vs. 14%, vertigo 20% vs. 5%.	"Tramadol may have a role as adjunctive treatment for breakthrough pain in patients receiving NSAID therapy for musculoskeletal pain attributed to OA."	20.6% discontinued open-label from adverse effects. Only 36.5% (23/63) of original study population completed RCT. Data suggest limited efficacy for breakthrough pain reduction in OA flares, but dropouts very high.
Peloso 2000 RCT 2 of 7 authors are employees of Purdue Frederick; otherwise, no mention of industry sponsorship or conflict of interest.	I(6.0)	N = 66 with hip and/or knee OA	Control-released codeine vs. placebo. Dose titrated from 100mg/day up to 400mg/day for 4 weeks.	WOMAC pain scale 44.8% improved (263.5/145.4) in codeine vs. 12.3% (252.4/ 221.3) controls (p = 0.0004). Rescue medication with acetaminophen averaged 4.2 codeine vs. 9.2 controls. Patient clinical effectiveness CR codeine 2.1±0.9 vs. 0.9±1.0, p = 0.0001.	"Single entity controlled release codeine is an effective treatment for pain due to OA of the hip or knee."	Total 39.2% codeine withdrew vs. 32.7%; 75% codeine withdrawals due to adverse effects; 16.2% of placebo withdrawals due to inadequate pain control.
Fishman 2007 RCT Study funded by Labopharm, and 3 of 10 authors are employees.	I(6.0)	N = 552 age 40-75 with knee OA and required WOMAC OA index pain subscale score of >150mm	Four groups: Tramadol Contramid OAD 100 mg QD (n = 103) vs. 200mg (n = 107) vs. 300 mg (n = 105) vs. placebo (n = 224). During 6 day run-in, dose titrated by 100 mg increments every 2-3 days until randomized dose reached. Treated with randomized dose for 12 weeks.	WOMAC pain score % improved from baseline: 100mg (41.6±50.2, [31.5; 51.6] CI), 200mg (42.8±46.4, [33.9; 51.6] CI), 300mg (46.0±39.9, [38.2; 53.7] CI), and placebo (32.3±48.2, [25.9; 38.6] CI). For difference in improvement between active and placebo estimate (mean), 95% CI, and p-value: tramadol Contramid groups 100mg (9.50, [-1.60; 20.60] CI, p = 0.0933), 200mg	"This study shows the efficacy and safety of Tramadol Contramid OAD 200 mg and 300 mg in patients with moderate or severe pain of the knee due to OA."	High dropouts (55.3%). Data suggest slight benefits for pain with only 300mg statistically significant.

				(10.81, [-0.02; 21.64] CI, p = 0.0504) and 300mg (13.41, [2.49; 24.33] CI, p = 0.0162). Responder analysis-WOMAC pain score (30% improvement from baseline): Tramadol Contramid OAD 100 mg (58%, p = 0.2236), 200mg (65%; p = 0.0095) and 300mg (65 %; p = 0.0104) vs. placebo (50%).		
James 2010 RCT Double-Blind Double-Dummy Funded by Napp Pharmaceuticals Limited, UK, and 1 of 3 authors an employee.	I(6.0)	N = 238 patients with moderate to severe pain caused by OA of the hip(s) and/or knee(s).	After titration period up to 21 days, randomly allocated to 7-day, low-dose transdermal buprenorphine patch (BuTrans®) (TBP, n = 118) or sublingual buprenorphine tablets (SBT, n = 120) for ≤28 days.	No differences between groups per Box Scale-11 Pain Scores and sleep disturbance. TBP patients had less nausea (p = 0.035), dizziness (p = 0.026) and vomiting (p = 0.039).	"This study has shown that it provides effective analgesia for this period with an improved tolerability profile in terms of nausea, dizziness, and vomiting, than sublingual buprenorphine tablets."	Substantial dropout. Data suggest minimal differences.
Rauck 2013 Randomized, Double-blind, Placebo-Controlled, Fixed-dose Supported by Johnson & Johnson PRD, and Mallinckrodt Inc., a Covidien company. No COIs declared.	I(6.0)	N = 990 with osteoarthritis pain in the hip/knee with pain score ≥5.	OROS Hydromorphone ER 8mg (n = 319, 157 completed QD for 1st week of titration) vs. OROS Hydromorphone ER 16mg, dose increased from 8 to 16mg (n = 330, 128 completed) vs. placebo, matching 8 and 16mg, (n = 332, 187 completed). Follow-up for 12 weeks.	Hydromorphone ER 16mg associated with improvements for analgesia than placebo (p = 0.0009), and pain, p = 0.01.	"OROS hydromorphone ER failed to achieve statistical significance for the primary endpoint using the prespecified imputation method (BOCF), likely due to the high discontinuation rate associated with the fixed-dose design."	High dropouts – study negative for primary, but positive for secondary outcomes. Suggests modest short term to intermediate efficacy.
Zautra 2005 RCT Study funded by Purdue Pharma LP, Stamford, Connecticut.	I(5.5)	N = 107 with OA as defined by ACR guidelines, moderate to severe pain.	CR oxycodone 10mg (n = 55) vs. placebo Q 12 hours (n = 49). Follow-up on days 15, 30, 45, 60, and 90.	Discontinued from study: 38/51(75%) placebo vs. 33/56 (59%) CR oxycodone. Discontinuation due to reported lack of efficacy: 34/51 (67%) placebo, 9/56 (16%) CR oxycodone (p <0.001). Ratings of acceptability of pain medication higher for CR oxycodone vs. placebo (3.4 vs. 2.2; p <0.001). Coping outcomes efficacy favored oxycodone 0.46, SE0.17, p <0.007.	"[C]ontrolled-release oxycodone treatment accounted for improvements in coping with pain beyond that of placebo controls. This medication may be most beneficial to osteoarthritis patients when	Many details sparse. Arthrosis joint(s) not defined. Allowed up to 60mg/day prior oxycodone in study. High dropouts in oxycodone group (41%) mostly adverse effects. Data suggest modest benefit on efficacy beliefs and coping but with high adverse effects.

					incorporated as part of a multi-disciplinary approach to pain management."	
Babul 2004 RCT Study was managed by SCIREX Corporation, Horsham, PA. Authors are employees of research centers. Lead author employed by TheraQuest.	I(5.5)	N = 246 with functional Class I-III primary knee OA meeting ACR diagnostic criteria; age >50, morning stiffness <30 minutes in duration, and/ or crepitus, warranted acetaminoph en, COX-2, NSAIDs, tramadol, or opioids at least 75 of 90 days prior to study, baseline VAS ≥40mm.	Tramadol ER initiated at 100mg QD and increased to 200mg QD by end of 1 week with further increases to 300-400mg QD (n = 124) vs. placebo (n = 122). 12 week follow-up.	WOMAC pain subscale, LS mean change greater for tramadol ER vs. placebo (change from baseline over 12 weeks: 120.1 vs. 69.0 mm, LS mean difference 51.1mm; p <0.001). WOMAC physical function scale: 407.0 vs. 208.5; p <0.001.	"Treatment with tramadol ER results in statistically significant and clinically important and sustained improvements in pain, stiffness, physical function, global status, and sleep in patients with chronic pain. A once-a-day formulation of tramadol has the potential to provide patients increased control over the management of their pain, fewer interruptions in sleep and improved compliance."	Two to 7 day washout before RCT; 49.6% dropouts. Data suggest modest benefit and high adverse effects.
Caldwell 2002 RCT 1 author employed by Ligan Pharmaceuticals and 2nd employed by Elan Pharmaceutical Research Corp. No other mention of industry sponsorship or COIs.	I(5.0)	N = 295 with moderate to severe hip and/or knee OA.	Extended release morphine 30mg QAM (n = 73) vs. ER morphine 30mg QPM (n = 73) vs. morphine controlled release (MS Contin) 15mg BID (n = 76) vs. placebo (n = 73). 4 week follow-up. Double dummy.	Reductions in WOMAC OA index pain by 17% with morphine ER QAM dose vs. 20% QPM vs. 18% MS-controlled release vs. 4% placebo (not different between 3 active treatments). ER morphine had better quality of sleep. Dropouts high at 40% of active treatments, with similar dropout rates across groups, except placebo with more due to lack of efficacy and fewer from adverse effects. Somnolence in 12-16%, dizziness in 10-12% of active treatment patients.	"Controlled release oxycodone q12h and immediate release oxycodone-APAP qid, added to NSAID, were superior to placebo for reducing OA pain and improving quality of sleep. The active treatments provided comparable pain control and sleep quality. Controlled release oxycodone was associated with a lower incidence of some side effects."	Data suggest modest efficacy. 39.6% (88/222) of active treatment patients dropped out, with 60.2% (53/88) of those due to adverse effects. A subsequent randomized open label trial of 181 of patients who completed compared QAM and QPM regimens and 52.5% of those patients withdrew with 33.1% experiencing adverse effects.

Munera 2010 RCT 3 of 4 authors employees of Purdue Pharma. No other mention of industry sponsorship or COIs.	I(5.0)	N = 315 with OA; 155 completed study.	Placebo Transdermal System (TDS) (n = 163) vs. Buprenorphine Transdermal System (BTDS) (n = 152). Initially received 5ug/h and could titrate dosages to 10ug/hour or 20ug/hour as needed, study lasted 35 days.	Results of the primary efficacy analysis (% successful) indicated 44% success in BTDS vs. 32% placebo TDS, p = 0.036. BTDS group had better mean patient satisfaction score (p = 0.046).	"In this randomized, placebo-controlled, double-blinded, parallel group study of patients with moderate to severe pain due to OA of the knee or hip who had not achieved adequate control with NSAID's alone, a greater percentage of patients treated with BTDS experienced treatment success compared with those treated with placebo."	High dropout rate. Data suggest modest efficacy vs. placebo.
Hartrick 2009 RCT Study sponsored by Johnson & Johnson Pharmaceutical Research & Development and Grunenthal GmbH. Two authors employed by Johnson & Johnson/Janseen, and 2 employed by Grünenthal GmbH.	I(4.5)	N = 666 candidates for primary joint replacement surgery as a result of end-stage degenerative joint disease.	Randomized into 4 groups: Tapentadol Immediate-Release 50mg (TIR50, n = 161), Tapentadol Immediate-Release 75 mg (TIR75, n = 169), Oxycodone HCl Immediate-Release 10 mg (OIR10, n = 172), or the Placebo Group (PG, n = 172). Study 10 days duration	Total pain relief (Day 2 [TIR50: 82.0±52.04 vs. placebo: 54.5±45.83, p <0.001; TIR75: 80.3±45.87 vs. placebo: 54.5±45.83, p <0.001; OIR10: 86.7±52.03 vs. placebo: 54.5±45.83, p <0.001], Day 5 [TIR50: 202.2±122.32 vs. placebo: 142.9±107.49, p <0.001; TIR75: 207.6±108.48 vs. placebo: 142.9± 107.49, p <0.001; OIR10: 216.0± 116.85 vs. placebo: 142.9±107.49, p < 0.001], Day 10 [TIR50: 376.6± 228.37 vs. placebo: 259.0±201.21, p < 0.001; TIR75: 384.5±211.09 vs. placebo: 259.0±201.21, p <0.001; OIR10: 391.9±212.55 vs. placebo: 259.0±201.21, p <0.001]), and Sum of total pain and pain intensity difference (Day 2 [TIR50: 164.0±123.12 vs. placebo: 100.0±108.96, p <0.001; TIR75: 164.0±116.87 vs. Placebo: 100.0± 108.96, p <0.001; OIR10: 178.1± 128.20 vs. placebo: 100.0±108.96, p <0.001], Day 5 [TIR50: 434.4±	"[T]apentadol IR 50 and 75 mg were effective in providing relief from moderate to severe pain caused by end-stage joint disease, with efficacy noninferior to that of oxycodone HCl IR 10 mg and significantly better gastrointestinal tolerability."	Data suggest modest efficacy of tapentadol compared with placebo and not inferior to oxycodone.

				333.04 vs. placebo: 274.3±265.80, p <0.001; TIR75: 434.1±306.99 vs. placebo: 274.3±265.80, p <0.001; OIR10: 462.6±307.26 vs. placebo: 274.3±265.80, p <0.001], Day 10 [TIR50: 853.5±640.36 vs. placebo: 506.8±510.26, p <0.001; TIR75: 817.6±595.96 vs. placebo: 506.8±510.26, p <0.001; OIR10: 853.7±573.10 vs. placebo: 506.8± 510.26, p <0.001]). No significant differences between TIR50, TIR75, and OIR10.		
Likar 1997 RCT Study sponsored by Stiftung-u. Förderungsgesellschaft der Universität Salzburg and Forschungsinstitut Gastein-Tauernregion. No mention of conflict of interest.	I(4.5)	N = 23 with knee OA (ARA)	Intra-articular Morphine/Intervenous NS (Group A) (n = 13) first received simultaneous injections of 1mg morphine HCl in 5mL of NS intra-articularly and 5mL NS IV. After 7 days, crossed over to 5mL NS intra-articularly and 1mg of morphine HCl in 5mL NS IV. Intra-articular Saline/Intravenous Morphine (Group B) (n=10) received reverse treatment sequencing. Study duration of 9 days.	Comparison for mean pain intensity based on Phase I data alone because of carryover effect. Difference in mean pain intensity between group A and Group B (p <0.05). Mean NRS Scores in Group A were significantly lower than baseline values (p <0.05). No changes from baseline values in Group B before 2nd injection (p = 0.25, ANOVA). Difference between Group A and B VAS scores both at rest and during movement (p <0.05). VAS scores in Group A lower than baseline values (p <0.05, ANOVA). No changes from baseline values in Group B before 2nd injection (p = 0.48). No difference between MPQ of Groups A and B (p = 0.59).	"This study shows that the injection of 1 mg of morphine but not saline into the painful arthritic knee joint of patients suffering from chronic osteoarthritis results in significant relief of their pain."	Experimental study with small sample size. Data suggest superiority of morphine over saline over short timeframe of 2 days.
Rosenthal 2004 RCT Study sponsored by Ortho-McNeil Pharmaceutical, Inc., and 4 of 5 authors employees.	I(4.5)	N = 113 ages ≥65 with painful osteoarthritis (OA) flare	Tramadol/Acetaminophen (Tramadol/APAP, n = 69) permitted to take 1-2 tablets of Tramadol 37.5mg/APAP 325mg up to QID (maximum of 8 tablets) vs. placebo (n = 44) group took up to 8 tabs of matching placebo; 10 day study.	Average daily pain intensity (p = 0.034) and average daily pain relief score (p = 0.010) improve days 1-5 with Tramadol APAP plus NSAIDs. Average pain intensity (p = 0.012) and pain relief (p = 0.019) scores were improved on days 1-10. Significance also for WOMAC overall score (p = 0.011), pain (p = 0.005) and physical function (p = 0.027) subscores. Sixteen	"In this study, tramadol/APAP combination tablets were effective in treating acute painful flares of OA in an elderly population."	Subset analysis of larger study, only analyzing those 65+ years old.

				tramadol/APAP and 4 placebo patients reported adverse events; most common were nausea, vomiting and dizziness. Sixteen withdrew, all but one because of adverse events.		
Fancourt 1984 RCT No mention of industry sponsorship or conflict of interest.	I(4.0)	N = 60 with chronic pain due to rheumatoid arthritis and osteoarthritis.	Meptazinol 200mg every 3 to 6 hours (as required) (n = 30) vs. placebo (n = 30) for a period of 72 hours total.	Three patients in placebo dropped out; data from 57 patients included. Change in pain intensity improved in Meptazinol vs. placebo for spontaneous pain ($p < 0.05$), pain on pressure ($p < 0.05$), pain on passive movements ($p < 0.01$), pain severity by facial expression ($p < 0.01$), and pain by degree of activity ($p < 0.05$). No differences for side-effects.	"[T]his study has demonstrated that 200mg Meptazinol 3 to 6 hourly produced significantly better analgesia than placebo and was well tolerated by patients with chronic pain. The incidence of side-effects was not significantly different between the two groups."	Short follow up period. Data suggest efficacy over short timeframe.
Karlsson 2009 Randomized, Open Label, Controlled, Parallel-Group, Noninferiority study Sponsored and designed by Mundipharma AB, Goteborg, Sweden, and was conducted by qualified investigators. No COIs declared.	I (4.0)	N = 135 with chronic, moderate to severe hip/knee OA.	Low-dose 7 day buprenorphine patches (5, 10, and 20µgram/hour for 12 weeks) (n = 69, 55 completed) vs. Tramadol BID (75, 100, 150, 200, 400mg for 12 weeks) (n = 66, 45 completed).	Seven (7) day buprenorphine patches ($p = 0.039$) vs. tramadol ($p = 0.020$) for pain relief. 70.3 % preferred patch Qweek at 95% CI, 62-78) (FAS); in PPAS, 64.0% preferred a once-weekly patch (95% CI, 54-74).	"In these patients with chronic, moderate to severe OA pain of the hip and/or knee, 7-day low-dose buprenorphine patches effective in providing pain relief and well tolerated. The 7-day buprenorphine patches were non-inferior to prolonged-release tramadol tablets."	Data suggest comparable efficacy. High drop outs in tramadol.
Other						
Mullican 2001 RCT Study supported by R.W. Johnson Pharmaceutical Research Institute and Ortho-McNeil Pharmaceutical, Inc.	I(8.0)	N = 462 with mild-moderate chronic LBP, osteoarthritis pain, or both.	Tramadol/acetaminophen 37.5mg/325mg (TRAM/APAP) (n = 309) vs. Codeine/APAP 30mg/300mg (n = 153) over 4 weeks.	Dropouts for both groups were 20% (n = 61) in TRAM/APAP and 21% (n = 32) for the COD/APAP group. Mean total pain relief scores similar at days 1, 8, 15, and 22. Efficacy scores comparable: Day 1 difference (95% CI, -0.2 [-1.42 to 1.02]), Day 8 (0.3 [-0.9 to 1.55]), Day 15 (0.7 [-0.63 to 2.03]), Day 22	"A tramadol/APAP (37.5mg/325mg) combination capsule provided equal pain relief from chronic nonmalignant low back pain, OA pain, or both by 30 minutes after each dose. Patient reports	Large sample. No placebo; 79.8% completed study. Data suggest comparable efficacy.

				(0.3 [-1.07 to 1.67]). Somnolence (24 vs. 17%), constipation (21 vs. 11%). Similar efficacy for LBP and OA.	of pain relief and pain intensity were comparable for the 2 products, as were patient and investigator assessments of efficacy."	
de Craen 2001 RCT 2x2 design with 4 groups. No mention of industry sponsorship or conflict of interest.	I(8.0)	N = 112 patients with chronic pain.	Four groups. Positive attitude group given positive information from physician regarding expected analgesic effect. Neutral group received neutral information. Positive: single dose 50mg tramadol (n = 28) vs. placebo (n = 27). Neutral: single dose 50mg tramadol (n= 28) vs. placebo (n = 29). Study duration of 24 hours.	Adverse events in those receiving tramadol was 64% and for placebo 36%. Difference in analgesic effect (0.1cm difference 0.6cm to 0.5cm) not statistically significant between expectancy groups (95% CI; -0.7cm to 1.0cm).	"[E]xperimentally-induced expectancy, expressed by means of verbal statements by physician, did not influence the analgesic effect of tramadol relative to placebo in chronic pain patients. Moreover, we could not demonstrate a significant analgesic effect of a single dose tramadol at all, regardless of expectancy group."	Underpowered based on authors sample size calculation, 2x2 design challenging. Data do not support superiority of a single dose of Tramadol.
Hale 2009 RCT Study sponsored by Johnson & Johnson Pharmaceutical Research & Development, LLC and Grünenthal GmbH, with 4 of 5 authors as industry employees.	I(7.5)	N = 878 with ≥3mo LBP or knee or hip OA.	Randomization 4:1. Immediate Release Tapentadol 50-100mg Q4-6hrs PRN, max. 600mg QD (IRT, n = 679) vs. Immediate Release Oxycodone 10-15mg Q4-6hrs PRN, max. 90mg QD (IRO, n = 170); 90 days treatment with 3 days of follow-up.	Odds ratio showed patients treated with IRT less likely than IRO to report nausea (0.542, p <0.001), vomiting (0.458, p <0.001), composite of nausea and/or vomiting (0.458, p <0.001), and constipation (0.396, p <0.001).	"[A] flexible dosing schedule of oral tapentadol IR (50 or 100 mg), administered for up to 90 days, provides effective analgesia with an improved gastrointestinal tolerability profile compared with oxycodone IR (10 or 15 mg) for the management of low back pain or OA pain of the hip or knee."	High dropouts 42 vs. 49. Data suggest comparable efficacy, but lower adverse effects with tapentadol.
Watson 1998 RCT Cross-over	I(7.5)	N = 50 with neuralgia or painful	Controlled-release oxycodone 10mg vs. placebo Q12 hours for 4 weeks. Then crossover	Patients reported greater daily pain relief with oxycodone compared to placebo (2.9 +/- 1.1 vs. 1.9+/- 1.0; p = 0.0001).	"…Despite the higher incidence of adverse effects, patients rated the	Many details sparse. Methods to blind unclear. High dropout rates. Data suggest

Supported by grant from Purdue Frederick. 1 of 2 authors employed.		diabetic neuropathy.	for another 4 weeks, no washout period between treatments.	Weekly pain intensity scores on VAS was lower in the oxycodone than placebo steady pain (34 +/- 26 vs. 55 +/- 27; p = 0.0001), brief pain (22 +/- 24 vs. 42 +/- 32; p = 0.0001), skin pain (32 +/- 27 vs. 50 +/- 30; p = 0.0004).	overall benefit of oxycodone, based on both pain relief and adverse effects, as significantly greater than placebo, and a substantially greater number of patients (67% vs. 11%) expressed masked preference for oxycodone over placebo."	lower pain ratings with oxycodone than placebo.
Portenoy 2007 RCT Supported by grant from Purdue Pharma, L.P and CIMA Labs. One author member of Cephalon Speakers Bureau.	I(6.5)	N = 123 began and then N = 77 randomized with breakthrough chronic cancer pain.	Post titration, randomized patients received 1 of 18 dose sequence combinations of 7 Fentanyl Buccal and 3 Placebo tablets. All 10 tablets had to be taken within 21 days, no more than 4 per day; 3 week follow-up for double-blind phase.	For breakthrough pain, FBT had greater pain relief for up to 120 minutes (p <0.02).	"FBT was efficacious and well tolerated in the treatment of BTP in opioid-treated patients with chronic low back pain."	Open-label phase prior to blinding. Initial washouts (all reasons) 46/123 (37.4%). High rate of adverse drug reactions (65%). Beginning to end removed large proportion of initially eligible population 68 complete/139 = 48.9% completed. Heterogeneous group of patients.
Naliboff 2011 RCT Study sponsored by Department of Veterans Affairs, Health Services Research and Development.	I(6.5)	N = 135 with chronic nonmalignant chronic pain for at least 6-months.	Stable dose opioid (n= 73) vs. Escalating dose opioid (n = 57). Both groups received nonopioid interventions anti-depressants and non-pharmacological coping skills. Study duration 1 year.	A significant month x treatment group interaction (p = 0.018) effect due to the escalating dose group increased pain relief of about 21% compared to 2% in stable dose. No difference between groups for Oswestry Disability Index (ODI) scores.	"[T]he results show a significantly greater rate of increase in opioid medication dosages in the Escalating Dose group as compared with the Stable Dose group…Because a large percentage of patients in both groups showed evidence of serious opioid misuse or noncompliance, this study clearly indicates careful monitoring of opioid treated patients is	High dropouts overall; 27% misused or were non-compliant regarding opioid use. Morphine equivalent doses increased significantly greater in escalating dose arm than stable dose, however, both increased.

					required regardless of escalation strategy."	
Hanna 2008 RCT Sponsored by Mundipharma Research Limited, and 1 of 3 authors an employee.	I(6.5)	N = 338 with moderate to severe neuropathy despite maximum tolerated dose of gabapentin	Oxycodone (TG, n = 163) prolonged-release tablets or matched placebo (CG, n = 165) oxycodone tablets Q12 hours. Study duration 12 weeks.	Significant difference between groups for mean change in BS-11 pain scores at period 2 [Day 15-28] (TG: 1.7±2.14 vs. CG: 0.9±1.73, 0.001 < p <0.01), period 3 [Days 29 - 42] (TG: 2.0 ± 2.49 vs. CG: 1.2 ± 2.06, 0.001 < p <0.01), period 4 [Days 43 - 56] (TG: 2.0±2.49 vs. CG: 1.2±2.06, 0.001 < p < 0.01), period 5 [Days 57-70] (TG: 2.1± 2.52 vs. CG: 1.4 ± 2.30, 0.001 < p < 0.01), and period 6 [Days 71 - 84] (TG: 2.1±2.61 vs. CG: 1.5±2.38, 0.001 < p <0.01).	"[C]o-administration of the prolonged-release oxycodone and existing gabapentin therapy has a clinically meaningful effect in painful diabetic neuropathy."	Multicenter study with 70 locations in Europe and Australia. Data suggest modest differences in pain.
Wild 2010 RCT Sponsored by Johnson & Johnson Pharmaceutical Services LLC and Global Development, Grünenthal GmbH.	I(6.0)	N = 1117 with ≥3 month moderate to severe knee or hip pain or low back pain of nonmalignant origin.	Tapentadol extended-release (ER) 100 to 250mg BID (n = 894) vs. oxycodone HCl controlled-release (CR) 20 to 50mg QD (n = 223). Study duration of 52 weeks.	Overall 85.7% (n = 766) in tapentadol ER group and 90.6% (n = 202) in oxycodone group experienced adverse event. Only 46.2% (n = 413) and 35.0% (n = 78) completed study in tapentadol ER and oxycodone CR groups.	"[T]apentadol ER (100 to 250 mg bid) relieved moderate to severe chronic low back pain or hip or knee osteoarthritis pain. The stability of both the mean of the average TDDs along with the steadiness of the analgesic scores over time throughout the study supports that there was no acquired tolerance."	Open label ≥3 month knee, hip or low back pain. Variable dosing. Tapentadol tended to have modestly lower pain ratings and adverse effects.
Cruciani 2012 RCT: Double-blind Study funded by Knoll Pharmaceuticals and Covidien. Dr. Cruciani is member of Speaker Bureau for Covidien. Dr. Katz was consultant for Knoll Pharmaceuticals,	I(6.0)	N = 113 ≥18 year, with chronic noncancer pain or cancer pain treated with opioid or transdermal fentanyl. Total MEQ	Stabilization of prior opioid: ≤7 days after consent. Open-label hydromorphone IR conversion and titration: ≤14 days. Hydromorphone IR 5 times/day at stable dose in last 2 days of open-label phase (n = 39) vs. Hydromorphone ER QD	Mean±SD daily dose of fixed scheduled doses: hydromorphone ER half-dose (16.6±8.0) mg vs. full-dose hydromorphone ER group (39.0±14.1) mg vs. hydromorphone IR (37.3±15.0); there was increase in breakthrough medication use from baseline to endpoint (full-dose, p = 0.027; half-dose, p	"In a randomized, double-blind trial, the same total daily dose of immediate-release hydromorphone and once-daily osmotic-controlled extended-release hydro-morphone had comparable effects."	High dropouts in opioid stabilization phase but not in RCT. Data suggest comparable efficacy.

Alza, Neuromed, and is consultant for Covidien. Dr. Portenoy participated in single advisory meetings sponsored by Neuromed and Covidien to discuss drug evaluated in study. No COIs declared.		was 80-300mg; transdermal fentanyl – dose between 25 and 175 µg/hr.	at stabilization dose (n = 34) vs. Once-daily hydro-morphone ER at ½ of stabilization dose (n = 40) for 7 days. All took study medication 5 times/day and given hydromorphone IR at 15-30% of stabilization dose for breakthrough pain. 7 day follow-up.	<0.001; hydromorphone IR, p = 0.001). Change in pain relief, pain intensity and sleep interference from baseline to endpoint. Pain relief: hydromorphone ER (NS) vs. ½ hydromorphone ER (-9.0±16.9, p = 0.002 within group) vs. hydromorphone IR (NS). Pain intensity: hydromorphone ER (NS) vs. ½ hydromorphone ER (.7±1.7, p = 0.017 within group) vs. hydromorphone IR (NS). Sleep interference: NS.		
Freeman 2007 RCT States no funds received for this work. No industry sponsorship or COIs disclosed.	I(5.5)	N = 313 adults with painful diabetic peripheral neuropathy (DPN).	Tramadol/Acetaminophen (Tram/APAP, n = 160) group treated with either 37/5mg tramadol/325mg acetaminophen tablets vs. Placebo (n = 153) with placebo tablets. Both groups had titration period of 10-days and 56-day maintenance period.	Differences between groups for worst pain in last week (Tram/APAP = -2.9±2.82 vs. Placebo = -1.7±2.57, p = 0.001), change in the lease pain in the last week (Tram/APAP = -2.4±2.40 vs. Placebo = -1.4±2.47, p < 0.001), change in average pain the past week (Tram/APAP = -2.5±2.61 vs. Placebo = -1.7±2.40, p = 0.004), change in pain right now (Tram/APAP = -2.6±2.61 vs. Placebo = -1.6±2.94, p <0.001), pain relief final week (Tram/APAP = 55.4±31.00 vs. Placebo = 37.7± 33.42, p < 0.001), change in sensory pain (Tram/APAP = -7.7±8.01 vs. Placebo = -4.2±2.33, p = 0.008), Change in total pain (Tram/APAP = -9.9±10.74 vs. Placebo: -5.4±9.85, p = 0.013), Change in present pain index (Tram/APAP: -1.1±1.11 vs. Placebo: -0.6±1.11, p < 0.001), change in mood/vigor (Tram/APAP: 0.19±0.785 vs. Placebo: 0.02±0.768, p = 0.007), change in SF-36 - Bodily Pain (Tram/APAP: 18.5±20.69 vs. Placebo: 10.5±18.94, p < 0.001), change in SF-36 – Social Functioning (Tram/APAP: 12.5±	"In this multicenter clinical study of patients with painful DPN, tramadol/APAP therapy for approximately 9 weeks was associated with significantly greater pain relief and improvement in several secondary measures of analgesia, quality of life, mood, and function as compared to placebo."	Lumbar fusion patient population. Cost effectiveness study in UK.

				27.35 vs. Placebo: 6.5±22.88, p = 0.012), and change in SF-36 – Health transition (Tran/APAP: -14.6 ±25.31 vs. Placebo: -4.5±22.79, p < 0.001).		
Jadad 1992 RCT Cross-over Funding support of authors included Cancer Research Campaign, European Community and Elizabeth Clark Charitable Trust. No other mention of industry sponsorship or COIs.	I(5.5)	N = 13 with chronic pain of malignant or non-malignant origin, or had poor pain relief on existing or previous opioid regimens.	Morphine 10mg (M10) vs. Morphine 30mg (M30). After treatment period, patients crossed over to other treatment. Study duration 4 months.	Twelve patients responded consistently to morphine; 10 showed good responses (6 nociceptive, 4 neuropathic). Those with neuropathic pain had high maximum pain relief scores (neuropathic: 97±5mm vs. nociceptive: 94±10, p = 0.048), and shorter times to maximum score (neuropathic: 2±1 hours vs. nociceptive: 4±2 hours, p = 0.01).	"This PCA method is a quick and efficient tool to determine the consistency of analgesic response. Such consistency can guide the clinician as to whether continued or higher-dose opioid treatment will produce good analgesia. An inconsistent response points to the use of other pain-relieving strategies."	Experimental study with PCA device with small number of patients. Details sparse. No significant differences in relief whether nociceptive or neuropathic pain.
Peat 1999 RCT Cross-over One author employed by Nycomed Pharma.	I(5.0)	N = 47 with chronic stable pain.	Repro-Dose morphine (RDM) once daily vs. MS continuous (MST) twice daily. Study duration of 15 days.	Mean (95% CI) pain intensity scores identical for MST and RDM 1.2 (1.0-1.4). Pain scores and escape analgesia similar between groups. Successes and failures within intent-to-treat (ITT) and per protocol (PP) populations not significantly different between groups (p >0.05). Adverse events not statistically different between groups.	"[M]orphine administered as RDM in a single evening dose gives analgesic efficacy which is similar or superior to that provided by the same daily dose administered in equal divided doses as MST."	No placebo. Data suggest equivalent (in)efficacy.
de la Iglesia 2012 RCT Crossover (report of 2 studies) COIs: Pace, Huang, Stern, and Richards affiliated with QRxPharma Inc. No COIs declared.	I(5.0)	N = 44 with chronic noncancer pain; male or female in-patients, ages 18-70 years, with chronic (>6 months)	Morphine (M) vs. morphine/oxycodone: 3:2 ratio in study A; 1:2 ratio in study B by weight (MOX) for ≤7 days before crossover for another 7 days. No washout between treatments. Study A: Morphine (5mg/ml) (n = 21) vs.	No significant difference between groups for VAS scores from baseline to steady-state in either study. Morphine equivalent dose (MED) for achieving steady state of pain control: MOXs lower than morphine alone (additional 40.5mg, study A, p <0.006; or 20.5mg, study B, p <0.003) needed compared to MOX. Cognitive functions, trial making	"[T]wo different combination ratios of morphine and oxycodone produce analgesic synergy and AE attenuation in patients with chronic noncancer pain."	Data suggest comparable efficiency.

			morphine/oxycodone combination (3:2 ratio morphine HCl/oxycodone HCl – 1.5mg/ml and 1mg/ml). Study B: Morphine HCl (5 mg/ml) (n = 23) vs. morphine/oxycodone combination (1:2 ratio; 0.75 mg/ml and 1.5mg/ml).	test B (TMT) B study A: morphine pretreatment (89.2±58.1) vs. steady state (74.8±45.8), p <0.005; MOX pretreatment (92.3±52.0) vs. steady state (71.8±47.3), p <0.005. Incidence of adverse effects (N): study B – constipation: morphine (15) vs. MOX (7), p = 0.025.		
Watson 2003 RCT Crossover Industry Sponsored (Research grant from Purdue Pharma). No mention of COIs.	I(5.0)	N = 45 patients with diabetic neuropathy with moderate or greater pain for at least 3 months. Mean age 63.0±9.4 years.	Oral controlled–release (CR) oxycodone 10mg n = 22) vs. Active placebo 0.25, 0.5, 0.75 or 1mg tablets (n = 23). 4 weeks of treatment until crossover.	CR oxycodone resulted in lower mean daily pain (21.8±20.7 vs. 48.6±26.6mm VAS), p = 0.0001; steady pain (23.5±23.0 vs. 47.6±30.7mm VAS); brief pain (21.8±23.5 vs. 46.7±30.8mm VAS); skin pain (14.3±20.4 vs. 43.2±31.3 mm VAS), and total pain and disability (16.8±15.6 vs. 25.2±16.7; p = 0.004).	"CR oxycodone is effective and safe for the management of painful diabetic neuropathy and improves QOL."	Patients not well described. High dropouts. Oxycodone associated with lower pain ratings.
Binsfeld 2010 RCT Study sponsored by Janssen-Cilag Medical Affairs EMEA, a division of Janssen Pharmaceutica NV, with 2 of 5 authors as employees.	I(4.5)	N = 504 with chronic non-cancer pain.	OROS® hydromorphone 8mg once daily (n = 254) vs. sustained release (SR) oxycodone 20mg (10mg 2/daily) (n = 250). Study duration of 24 weeks.	Both groups had high dropout rates (n = 139; 45%) for the hydromorphone group and (n = 142; 43%) for oxycodone. Almost all subjects (n = 502; 99.6%) reported taking concomitant medications throughout the study for additional pain relief. Both groups had similar pain relief from baseline to end of treatment. Most subjects (81% for hydromorphone, 85% for oxycodone) experienced at least 1 adverse event.	"This study demonstrated that once-daily OROS hydromorphone was a noninferior treatment to twice-daily SR oxycodone for subjects with chronic moderate to severe noncancer pain in terms of the "pain right now" score on the BPI. Both treatments reduced pain by at least 2.8 points on the 11-point BPI scale, which is a clinically relevant change."	Open-label, noninferiority trial. Data suggest equal (in)efficacy.
Hamann 2007 RCT	I(4.5)	N = 15 adults with history of unrelieved chronic non-	Naltrexone 100µg Q12 hour (Group A, n = 3) vs. Naltrexone 10 µg Q12 hour (Group B, n = 7) vs.	Peak pain intensity difference (PID) score: day 1 highest in Group A vs. Groups B and C, p <0.05. Day 2 PID scores: Group	"[P]atients with CNMP who received oral naltrexone 100 µg	Phase I, pilot study, and small sample size. Data suggest possible non-significant benefits.

Study supported by Pain Therapeutics, Inc. No COIs declared.		malignant pain (CNMP); chronic refractory pain and history of inadequate pain relief after ≥2 different opioids; baseline VAS score ≥5	Placebo Q12 hour (Group C, n = 5). All patients continued constant intrathecal morphine infusion at same dose during 7-day study period. Assessments TID.	A significantly higher ($p < 0.05$) than Groups B and C ($p < 0.05$). Day 3 PID scores: Group A higher scores than Groups B or C, $p<0.05$.	twice daily in conjunction with continuous intrathecal morphine infusions tended to demonstrate the greatest improvement in daily pain scores as compared to patients receiving placebo or naltrexone 10 µg twice daily."	
Weiss 2011 RCT Study sponsored by National Institute on Drug Abuse (NIDA) Clinical Trials Network Grants. Multiple conflicts among authors re. industry consultancy, research grants, and compensated speakers.	I(4.5)	2 phase study; phase 1: N = 653 with prescription opioid dependence given brief treatment; unsuccessful patients then randomized in phase 2. Phase 2: N = 360 with prescription opioid dependence who did not have success in phase 1.	All patients received buprenorphine-naloxone stabilization followed by 4-week taper and 8-weeks of follow-up, then randomized into: standard medical management (SMM) (n = 180) vs. SMM plus individual opioid dependence counseling (SMM +ODC) (n = 180).	Seventy (38.9%) of 180 in SMM + ODC group abstained completely from opioid use from weeks 9-12 of phase 2 compared to 61 (33.9%) patients in SMM only group ($p = 0.25$). Rate of complete abstinence from opioid use was higher for week 12 compared to week 24 (36.4% vs. 6.7%; $p < 0.001$). In phase 1, most patients had one or more adverse events (n = 542; 83.0%). In phase 2, most patients (n = 216; 60%) experienced one or more adverse events. There was no significant difference between the two groups in successful outcomes and opioid use.	"…[T]he rate of unsuccessful outcomes after buprenorphine-naloxone taper, even after a 12-week treatment, was high, exceeding 90%. In contrast, patients stabilized with buprenorphine-naloxone treatment had considerably better opioid use outcomes than did those who had been tapered off the medication."	Opioid-dependent patients. Counseling found to be ineffective for reducing failures. Outcomes unrelated to chronic pain.
Farrar 2010 RCT Study sponsored by Cephalon Inc., 2 of 4 authors were employees and other 2 received compensation from Cephalon.	I(4.0)	N = 148 opioid-tolerant adults with non-cancer related chronic pain and breakthrough pain.	Fentanyl buccal tablet (FBT) (n = 79) vs. placebo (n = 79). Study duration 12 weeks.	Study began with a titration period, in which only 105 had success (71%). Then 104 (70%) entered 12-week study trial, but 81 completed (55%). Change in pain intensity was statistically significant ($p<0.0001$) FBT compared to placebo (7.7 [SD 6.2] vs. 4.6 [4.7]). Adverse events were reported by 101 of 148 patients (68%).	"…The results of each of three RCT assessment periods favored the use of FBT over placebo across a range of efficacy measures, with statistical separation from placebo as early as 5 minutes post dose. The response to FBT was	Details sparse. Opioid tolerant patients included, requiring at least 60mg Morphine/day. Of 199 screened and 140 enrolled, only 81 completed. Data suggest lower pain with fentanyl in this highly selected population.

					maintained over time, with efficacy after 4, 8, and 12 weeks of treatment."	
Jones 2011 RCT Funded by a NIDA grant. All authors have received support from Reckitt-Benckiser Pharmaceuticals and Schering-Plough Corporation. Additional COIs include Johnson & Johnson Pharmaceutical Research & Development, Endo Pharmaceuticals, and Avigen.	I(4.0)	N = 18 patients with chronic, non-malignant pain who met the DSM-IV criteria for opioid abuse.	Randomized to be maintained on various levels of Buprenorphine/ Naloxone (Bup/Nx, 2/0.5, 8/2, and 16/4mg/day) throughout study and receive various doses of Oxycodone (0, 10, 20, 40, and 60mg/70kg) throughout study. Study duration of 7 weeks.	Effects of Bup/Nx (mg) dose: Differences between dosage amounts with in Latency to withdraw hand from cold water (2/0.5: 43.72±12.47 sec vs. 8/2: 59.72±15.73 sec vs. 16/4: 55.44± 14.39 sec, p <0.05; 2/0.5: 43.72± 12.47 sec vs. 8/2: 59.72±15.73 sec, p < 0.05), Latency to feel pain in cold water (2/05: 32.00±12.78 sec vs. 8/2: 46.39±14.89 sec vs. 16/4: 40.83 ±13.10 sec, p <0.05; 2/05: 32.00± 12.78 sec vs. 8/2: 46.39±14.89 sec, p <0.05); however, CPT MPQ was not significantly different. Effects of Oxycodone (mg) dose: There was a significant difference between dosage amounts with respect to Latency to withdraw hand from cold water (0: 52.96±8.13 sec vs. 10: 53.88±8.08 sec vs. 20: 62.32±8.58 sec vs. 40: 63.70±8.56 sec vs. 60: 63.78±8.09 sec, p < 0.01; 0: 52.96± 8.13 sec vs. 20: 62.32±8.58 sec, p <0.05; 0: 52.96±8.13 sec vs. 40: 63.70 ±8.56 sec, p <0.05; 0: 52.96±8.13 sec vs. 60: 63.78±8.09 sec, p <0.05); however, latency to feel pain from cold water and CPT MPQ not significant.	"These data suggest that sublingual Bup/Nx has the potential as an analgesic medication and further research should investigate its use in treating patients with chronic pain who abuse opioids."	Experimental study. Not enough information to clearly describe randomization. Details sparse, small sample size (n = 18).

Richarz 2013 RCT Industry Sponsor (Funding for this support was provided by Mallinckrodt Inc., a Covidien company, Hazelwood, MO.) Industry COI (Dr. Richarz disclose as employee of Janssen Global Services LLC and a stockholder in Johnson & Johnson. Dr. Sandra Waechter as an employee of Janssen-Cilag and stockholder in Johnson & Johnson. Dr. Rainer Sabatowski disclosed as consultant for Cephalon Inc. and Grunenthal and has received payment for lectures from Merck Sharp & Dohme Limited. Dr. Heinrich Binsfeld Disclosed as consultant for Janssen-Cilag, has served as expert witness, and received payment for lectures from Janssen-Cilag, Pfizer Inc, AWD Pharma Dresden GmbH, and Grunenthal.)	I(4.0)	N = 112 with chronic non-cancer pain (pain occurring ≥ 20 d/month for >3 months) in need of continuous opioids. Opioid-naïve patients, patients receiving treatment with weak opioids, taking ≤ 60 mg MEQ, and those using transdermal fentanyl 25µg/hour or transdermal buprenorphine 35µg/hour.	Hydromorphone extended-release (OROS hydromorphone ER) QD (n = 60) vs. oxycodone controlled release (CR) BID (n = 52). 28 week study.	OROS hydromorphone ER, mean (SEM) overall pain severity decreased from 6.3 (0.1) at baseline to 3.9 (0.2) at week 52.	"Overall, the results of this long-term, 28-week extension phase indicate that OROS hydromorphone ER and oxycodone CR are effective and well tolerated in patients with chronic noncancer pain."	Secondary study to Binsfeld 2010. Open label trial. Large center dropout from initial trial. Data suggest comparable outcomes.
Sittl 2003 RCT Study sponsored by Grünenthal GmbH.	I(4.0)	N = 157 patients with severe chronic pain.	Buprenorphine 20, 30, and 40mg vs. placebo. Study duration 15 days.	The percentage of reduction of additional oral opioid analgesic during study period was significantly lower in buprenorphine group compared to placebo (p <0.05). Patient-	"Buprenorphine TDS was superior to placebo in reducing consumption of additional oral analgesic	Includes pain due to cancer and other disorders. Responders were 36.6%, 47.5% and 33.3% vs. 16.2% placebo responses,

				related degree of pain relief was not significantly different between all groups. Duration of sleep at night was not significantly different between groups.	medication in the form of sublingual buprenorphine tablets. Patients treated with buprenorphine TDS reduced their use of rescue analgesia by 56.7% compared with the prestudy period."	suggesting modest efficacy.
Wilder-Smith 2001 Open-label, Randomized, Parallel Group study Study supported by research funds from GruÈnenthal AG, Switzerland and GruÈnenthal GmbH, Germany. No COIs declared.	I(4.0)	N = 90 age 20-75 with osteoarthritis.	Dihydrocodeine, 60mg BID Q12 hour (n = 29) vs. Tramadol, 100 mg BID: (n = 28) vs. control, NSAIDs only (n = 30). All patients received metoclopramide 10mg for first 4 days. 1 month follow-up.	Tramadol produced lower pain results (p = 0.04). Pain scores (on verbal rating scale 1-4) during movement were lower with tramadol on day 5 (p = 0.05) and decreased pain scores with both treatments on all days compared to baseline (p = 0.0001). Total titrated doses (scheduled and rescued): Tramadol; (day 1) 209 (198±220) mg and 203 (191±206) mg for (day 28) Dihydrocodeine; (day 1) 129 (122±136) mg and 130 (121±134) mg (day 28). Side effects: Drowsiness - Dihydrocodeine (n = 8) vs. Tramadol (n = 15).	"[S]tandard doses of slow-release formulations of dihydrocodeine (Codicontin) 60 mg bid and tramadol (Tramal retard) 100 mg bid provided good analgesia with minor toxicity in conjunction with NSAID's in strong pain due to osteoarthritis."	Variable doses – greater drowsiness with and greater N/V with Tramadol. NSAID arm was not randomized; neither arm blinded.
Wu 2008 RCT/cross-over Funded by NIH. Two authors have industry COIs including speakers for industry.	I(4.0)	N = 60 with persistent post amputation lasting 6-months or more.	Participants randomized into one of three treatment arms. Crossover to all 3 arms with 1-week washout between. Morphine SR 15mg sustain-released (n = 50) vs. mexiletine 75mg (n = 42) vs. placebo (n = 43). Duration of each treatment period 8 weeks, consisting of 4 week titration, 2 week maintenance, and 2 week taper phase	Average change in pain intensity from baseline for placebo -1.4 (95%CI -2.2 to -0.6), -1.5 (-2.2 to -0.9) for mexiletine, and -2.8 (-3.4 to -2.3) for morphine, (p <0.0001) vs. baseline for all three groups. Opioid use had significantly higher mean self-reported pain relief compared to placebo (p <0.001) and mexiletine (p <0.0001).	"[S]ustained-release morphine was significantly superior to both mexiletine and placebo in the treatment of post-amputation pains. Treatment with morphine resulted in significantly lower pain scores and greater mean percentage pain relief."	Post-amputation pain. Morphine improved pain vs. mexiletine, but no improvement in function.

			followed by 1 week washout.				

Evidence for Discontinuation and Tapering of Opioids

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Sullivan 2016 (score=6.5)	Opioid Tapering	RCT	Supported by grant R34DA033384 to Mark D. Sullivan from the National Institute on Drug Abuse, which had no influence on study design, collection, analysis and interpretation of data, the writing of the report, or the decision to submit the article for publication. M.D.S. reports consulting with Chrono Therapeutics. The remaining authors have no conflicts of interest to declare.	N=35 with CNCP, defined as pain on more than half of the days in the past 6 months; use of opioid medication on more than half of the previous 90 days; willingness to taper opioid dose by at least 50% (or to 120 mg MED, whichever was less); daily MED 50+ mg.	Mean (SD) age: 54.4 (10.1) years. 25 females, 10 males.	22-week taper support intervention (psychiatric consultation, psychiatric medication med. if indicated, opioid dose tapering, and 18 weekly meetings with a physician assistant to educate, explore motivation for tapering and CBT-based learning pain self-management skills) (N=18) vs. usual care (N=17).	Baseline and 22 and 34 weeks.	At 22 weeks, adjusted mean (SD) daily morphine-equivalent opioid tapering Group 111.94 (153.63) vs. Usual care 169.85 (201.31), p=0.09. At 34 weeks: 99.51 (151.99) vs. 138.24 (155.85), p=0.34.	"This taper support intervention is feasible and shows promise in reducing opioid dose while not increasing pain severity or interference"	Pilot study. Usual care bias. Both groups improved at 22 weeks, although the taper support group trended towards greater improvements in most measures and sig. improvements in pain interference, self-efficacy and opioid problem perception suggesting efficacy of this taper interventions.

Evidence for Breakthrough Pain

Name/Year Location Potential Conflict of Interest	Score	Study Design	Exposure	Population. Age range. Dropout Rate. Case Definition	Results	Conclusion	Comments
Simpson 2007 RCT	I(5.5)	N = 129; men and women	N = 103 (dose-titration phase) (100, 200, 400,	Effective measures; pain relief (PR) greater after	Primary efficacy measure (SPID) greater in those episodes	"In these opioid-tolerant patients with chronic neuropathic pain who	Most common adverse events typical of opioids –

New York, Pennsylvania, Florida		aged 18 to 80 years who were opioid tolerant; had a >3-month history of chronic persistent neuropathic pain associated with diabetic peripheral neuropathy, post-herpetic neuralgia, traumatic injury, or complex regional pain syndrome; and reported having episodes of break-through pain (BTP).	600, 800µg doses of FBT to be used in identifying a dose that controlled their BTP) N=102 (received at least one dose of FBT and were evaluated for tolerability) N=79 (entered the double-blind phase).	administration of FBT vs. placebo or 0.324 (0.056) 10 minutes after the dose, and at all points thereafter, p < 0.001. Safety and tolerance; no clinically meaningful changes in laboratory values, vital signs, or physical examination findings related to study treatment.	treated with FBT vs. placebo, p <0.001. ≥33% improvement in pain from baseline in greater proportion of BTP episodes treated with FBT vs. placebo from 10 minutes (9% vs. 3%) through 2 hours (66% vs. 37%).	identified an effective FBT dose, FBT had a rapid onset of action and was effective and well tolerated in the treatment of BTP."	nausea, dizziness, somnolence, vomiting, and occurred more often during dose-titration phase. Population highly heterogeneous, thus allowable conclusions regarding application to any single diagnostic entity are necessarily weak. Even though opioid-tolerant patients selected to minimize adverse effects anticipated from use of fentanyl, overall rate of 63% adverse drug reactions high.
Portenoy 2006 United States Supported by a grant to primary author's department from Cephalon, Inc, West Chester. 4 of 6 other authors (Drs. Simon, Brennan, Taylor, Shoemaker)	III	Survey from 9 pain programs	Chronic non-cancer pain. 51% LBP, 8% neck pin, 5% fibromyalgia. February to April 2004.	N= 228 with baseline "controlled" chronic non-cancer pain. N= 168 (74%) with "excruciating breakthrough pain."	No significant difference in use of medication for patients with or without breakthrough pain.	"[B]reakthrough pain is highly prevalent and varied in patients with chronic noncancer pain. Further studies are warranted to determine whether the clinical impact and therapeutic challenges posed by this phenomenon are comparable to the cancer population."	470 ineligible of 717, mostly uncontrolled baseline pain. As no differences in medication use, study raises question regarding conceptual significance of break-through pain.

Cephalon consultants.							
Fine 2010 United States Study sponsored by Cephalon, Inc. Dr. Fine served as an advisory board member and consultant for Cephalon, Inc. Dr. Rathmell served as a medical advisory board member for Cephalon, Inc. Drs. Messina and Xie are employees of Cephalon, Inc.	II	Open-label study.	Fentanyl buccal tablets for 18 months.	N = 646, age 18-80, with chronic non-cancer pain. Opioid tolerant, with "around-the-clock" opioids at ≥60mg/d morphine; 57% LBP, 10% traumatic injury, 6% OA, 5% CRPS, 5% H/A, 4% DM neuropathy.	Worst pain past 24 hours 7.3 decreased to 7.1. Pain at its least, average pain and current pain also showed minimal changes. Interference with activities reportedly improved.	FBT was associated with "self-reported functional improvement observed in most of the opioid-tolerant patients with BTP in association with chronic noncancer pain."	11.3% dropouts mostly ADR or ineffective. 74% psychiatric comorbidity (not defined). Reports of improved function; no objective measures. "Little" change in pain ratings.
Højsted 2006 Denmark No mention of industry sponsorship or COIs	II	Consecutive case series. Multi-disciplinary pain center	3 months treatment in pain program. Assessed at initial referral time and again after 3 months of treatment.	N = 33, age 26-74. Disc prolapse (n= 9), LBP (n = 5), unspecified MSD (n = 4), neurogenic post-operative pain (n = 3), tetra/paraplegia (n = 2), pain after spine fracture (n = 2), ulcerative colitis (n = 2).	Prevalence of BTP decreased from 90% to 70.4%. Precipitating factors fell approximately 50% for many questions (e.g., walking, standing, sitting, and lifting).	"BTP in chronic non-malignant pain patients seems to be surprisingly frequent and severe… Average pain intensity was associated with anxiety and depression."	Modest sample size. Excluded psychiatric disease. Data suggested reduced BTP over 3 months of treatment. Reported incapacities high.

Evidence for the Use of Intrathecal Drug Delivery Systems

Author/Year Study Type Potential Conflict of Interest	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Rauck 2006 RCT Supported by Elan Pharmaceuticals Inc.	I(9.0)	N = 220 with severe chronic pain	Ziconotide starting dose of 0.1µg/hour (2.4µg/day) gradually titrated upward by 0.05-0.10µg/hour (1.2-2.4µg/day), n = 112, vs. placebo, n = 108, over 3 weeks. Participants had 3-week weaning from all IT drugs, 1 week stabilization period, and 3 week treatment period.	VAS improvements from baseline to Week 3: 14.7% ziconotide vs. 7.2% placebo (p = 0.0026). Global McGill scores changed -3.2 vs. -0.6 (p = 0.026). Enjoyment of life subscale: significant improvement ziconotide 42.2% vs. 27.4% placebo (p = 0.019). Higher rates in ziconotide were dizziness (47.3 vs. 13.0%); confusion (17.9 vs. 4.6%); abnormal gait (15.2 vs. 1.9%); memory impairment) 11.6 vs. 0.9%).	"Slow titration of ziconotide, a nonopioid analgesic, to a low maximum dose resulted in significant improvement in pain and was better tolerated than in two previous controlled trials that used a faster titration to a higher mean dose."	Adverse effects in 93% of ziconotide. Data suggest modestly better than placebo.
Raffaeli 2006 RCT No mention of industry sponsorship or COIs.	I(8.0)	N = 144 with chronic pain	0.015mg morphine (n = 25) vs. 0.03mg morphine (n = 30) vs. 0.06mg morphine (n = 31) vs. 0.25mg morphine (n = 33) vs. placebo (n = 25) NS injection in interspinous ligament with follow-up at 2, 4, and 24 hours. Single dose injection study.	Clinically significant pain relief observed in all patients receiving intrathecal morphine but only 6 patients (25%) of control group.	"[T]he onset and incidence of minor opioid-related side-effects after intrathecal morphine administration do not depend on its dose."	Ultra-short-term experimental study of 24 hours to evaluate adverse effects.

Evidence for Oral Agents, Comparative Trials of Opioids v. Non-opioids

Search Strategy: Articles from this section were included from several previous ACOEM chapters such as Ankle/Foot, Low Back Pain, Hip, Knee, and Chronic Pain.

Author/Year Study Type Potential Conflict of Interest	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Oral Agents, Comparative Trials of Opioids vs. Non-Opioids						
Khoromi 2007 Crossover Trial MS Contin placebo tablets gift from Purdue Pharma. Supported by intramural grant from the National Institute of Dental and Craniofacial Research.	I(8.0)	N = 55 with chronic lumbar radiculopathy at least 3 months duration	Sustained-release morphine 15-90mg, (n = 15) vs. Nortriptyline 25-100mg, (n = 13) vs. Combined morphine and nortriptyline (n = 13) vs. active placebo – benztropine 0.25-1mg (n = 14). For 5 weeks, followed by 2 weeks maintenance then 2 weeks dose tapering.	Average leg pain in 28 patients who completed study was (baseline, placebo, morphine, nortriptyline, combination): 4.9±2.4, 3.7±2.7, 3.4±2.8, 3.0±2.7, 3.4±2.5.	"[O]pioids, tricyclic antidepressants, and their combination may be relatively ineffective in the treatment of lumbar radicular pain."	Study suggests no significant benefits of morphine, nortriptyline, or a combination of them for radicular pain. May be underpowered.
O'Donnell 2009 RCT Study and editorial support sponsored by Pfizer Inc. MF Berger, D McCabe, P Bhadra and Spalding are/were full-time Pfizer employees. JB O'Donnell and EF Ekman are consultants to Pfizer. EF Ekman has received research grants from Pfizer.	I(7.5)	N = 796 with chronic LBP	Celecoxib 200mg 1/2 (n = 404/398) vs. tramadol HCl 50mg 1/2 (n = 392/404). 6 weeks follow-up.	Discontinuation in Study 1/2 groups, in tramadol vs. celecoxib (30.6% vs. 14.4%) / (25.8% vs. 13.6%), respectively. At week 6 study in ITT, ≥ 30% improvement from baseline, NRS scale Celecoxib vs. tramadol, study 1/2; (p<0.001/ P=0.008).Safety outcomes: HCl vs. Celecoxib tolerance Studies 1 & 2; 13.4% and 10.6% vs. 1.2% and 1.0% , P<0.0001.	"Overall, celecoxib 20 mg bid was more effective than tramadol HCl 50 mg qid in the treatment of CLBP, with fewer AEs reported."	Data suggested more people responded (>30% improvement in pain score from baseline to 6 weeks) positively to Celecoxib, although overall numbers were similar (63% vs. 50%). More withdrawals from adverse effects with tramadol.

Parr 1989 RCT No mention of industry sponsorship or COIs.	I(6.5)	N = 846 mostly hip or knee OA	Diclofenac sodium slow release 100mg QD (n = 373) vs. dextropropoxyphene 180mg plus paracetamol 1.95gm QD for 4 weeks (n = 382). 4 week follow-up.	Pain ratings (change in VAS): diclofenac -27.0 vs. dextropropoxyphene plus paracetamol -22.7, p <0.05 (8% greater reduction in diclofenac). Physical mobility scores: -10.8 vs. -7.4 (p <0.01) (13% better with diclofenac). Work interference less in diclofenac (3 vs. 11, p <0.05), and time lost (3 vs. 16, p <0.05). Dizziness, lightheadedness less for diclofenac (14 vs. 30, p <0.05), as was CNS symptoms (48 vs. 93, p <0.01). Abdominal pain higher with diclofenac (40 vs. 18, p <0.01); diarrhea (14 vs. 2, p <0.01). Overall GI effects not different (63 vs. 60); comparable dropouts.	"Pain as measured by a visual analogue scale (VAS) showed 8% greater pain reduction with DSR as compared with D&P (P<0.05). Physical mobility as measured by the (Nottingham Health Profile) improved by 13% more with DSR as compared with D&P (P<0.05)."	No regular NSAID use prior 6 months. Dropouts 15.3% diclofenac vs. 17.0%. Suggests greater efficacy of diclofenac vs. dextropropoxyphene plus acetaminophen. Benefits suggested for working populations from diclofenac including lower incidence of problems at work and lost work time.
Moulin 1996 RCT - Crossover Supported by grants from Medical Research Council of Canada and Purdue Frederick.	I(6.0)	N = 46 with chronic non-cancer pain.	Morphine SR up to 60mg BID vs. Benztropine up to 1mg BID for 3 weeks titrations and then for 6 week evaluations. Pain intensity, pain relief, and drug liking rated weekly and psychological features, functional status, and cognition assessed at baseline and end of each evaluation. Followed by 2 week washout.	N = 46 completed dose titration and study. Mean daily morphine 83.5 mg and benztropine 1.7 mg. Reduced pain intensity VAS with morphine vs. placebo in period I (p = 0.01) and that group better in crossover analysis of sum of pain intensity differences from baseline (p = 0.02).	"In patients with treatment-resistant chronic regional pain of soft-tissue or musculoskeletal origin, nine weeks of oral morphine in doses up to 120 mg daily may confer analgesic benefit with a low risk of addiction but is unlikely to yield psychological or functional improvement."	Short-term trial suggesting morphine lowers pain ratings modestly. Data suggest lack of functional improvement.
Harke 2001 Two consecutive RCTs No mention of industry sponsorship or COIs.	I(6.0)	N = 43 with spinal cord stimulators (SCSs) and prior documented "permanent pain relief without any pain medication" to SCS for neuropathic	200mg TID of carbamazepine (CMZ) (600mg, n = 19) vs. placebo (n = 19) in Phase I for 8 days, and sustained-release morphine (30mg TID) (90 mg, n = 20) vs. placebo (n = 15) for Phase II 8 days after a 7 day CMZ elimination interval.	Those with recurrence of pain with SCS deactivated included. 40 adverse drug reactions in CMZ group vs. 5 in placebo. 5/22 CMZ patients vs. 3/21 on placebo switched SCS on within 4 hours considered non-responders. 12 in CMZ accepted pain increase of up to 5.9±2.1 for 89 hours vs. 7.7±1.6 for 45 hours.	"The efficacy of CMZ in neuropathic pain was significant."	Experimental trial with small numbers and short durations. SCS patients with various diagnoses. No stratified analyses by diagnosis. All had SCS in place because of failed medical management. Much higher adverse event profile in morphine group vs. placebo.

		pain syndromes included in Phase I and 36 later entered Phase II				Suggests carbamazepine effective in this subgroup over 14 days.
Jamison 1998 RCT Supported by grant from Roxane Laboratories Inc. No other COIs disclosed.	I(5.5)	N = 36 with chronic LBP	Naproxen 250 mg up to QID (n = 12) vs. oxycodone 5mg up to QID (n = 13) vs. titrated-dose oxycodone, and sustained-release MS (n = 11). Participants had 4-week washout period, 16 weeks treatment, 12 weeks tapering, and 1 month posttreatment washout period.	More anxiety in oxycodone group in washout phase and more adverse drug reactions in opioid groups ($p < 0.05$, $F = 4.27$). Significant differences seen in all groups using MANOVA for pain, mood, activity, and number of hours asleep.	"[O]pioid therapy alleviates pain and improves mood, but does not consistently affect activity level. Chronic opioid therapy seems to benefit some patients without significant risk of abuse. Further study is needed to identify those qualities that predict a positive outcome of chronic opioid therapy."	Conclusions on risk of abuse from RCT with 36 patients likely underpowered. Data suggest naproxen 250mg up to QID is as effective as opioids with less adverse events.
Zacny 2012 RCT Experimental Crossover Study NIDA Grant DA23969 No COIs declared.	I(5.0)	N = 15 healthy individuals (8 males, 7 females), ages 21-39, some current level of alcohol use. Mean age (±SD) 27.0±5.0 years. 7-8 sessions at least 1 week apart.	Placebo vs. carisoprodol 350mg (CARIS) vs. oxycodone 10mg (OXY) vs. carisoprodol 350mg followed 60 minutes by oxycodone 10mg.	Mean ± SEM VAS (range 0-100) coasting ("Spaced out") comparing Placebo vs. CARIS 350 vs. OXY vs. CARIS350/OXY 10: 15.3±7.4 vs. 13.3±5.9 vs. 28.5±8.6 vs. 43.7±9.8; $p < 0.0001$.	"This is the first study that we are aware of that has shown that carisoprodol and oxycodone, two drugs that are sometimes co-prescribed for relief of pain, produce effects when administered "together" (i.e., separated by 60 min) that are of greater magnitude than when they are administered alone. Some of the effects were not benign, and are of concern from both abuse liability and public safety standpoints."	Experimental study data. Data suggest additive CNS impairments with carisoprodol plus oxycodone.
Siddall 2000 RCT Crossover	I(4.5)	N = 15 with neuropathic pain after	Clonidine 50-100µg vs. morphine 0.2-1mg vs. NS. After administration, if pain relief or side	Mixture of morphine and clonidine had pain reductions vs. NS ($p = 0.0084$). Both morphine and clonidine on their own did	"[I]ntrathecal administration of morphine and clonidine appears to	Small sample size (N = 15). Many method weaknesses as details sparse. Data suggest

Supported, in part, by National Health and Medical Research Council of Australia.		spinal cord injury.	effects, patients received mixture of clonidine and morphine. Catheter remained in situ for up to 6 days.	not have significant improvements vs. saline.	provide good relief of pain for a proportion of patients with neuropathic pain after SCI who are unresponsive to other interventions."	potential short-term improvement of pain with clonidine plus MS.
Frank 2008 RCT Supported by grant from Cambridge Laboratories. BF's salary was provided as a part of the research grant.	I(4.5)	N = 96 with chronic neuropathic pain.	Crossover design of 14 week duration. All patients received one drug first for 6 weeks, 2 weeks washout period, and then the other for 6 weeks. Synthetic nabilone 250mcg (n= 48) followed by dihydrocodeine vs. dihydrocodeine 30mg (n = 48) followed by nabilone.	64 completed study and were analyzed. Dihydrocodeine was better analgesic than nabilone 6.0mm on VAS scale (95% CI 1.4 to 10.5; p = 0.01). Bodily pain was decreased in dihydrocodeine compared to nabilone -5.7 (-10.9 to -0.5; p = 0.03).	"The weak opioid, dihydrocodeine, was a statistically better treatment for chronic neuropathic pain than nabilone. More patients had clinically significant pain relief from dihydrocodeine, although a small number of patients responded well to nabilone. The side effects of both treatments were generally mild and in the expected range."	Trial of synthetic cannabinoid. Data suggest inferiority to opioid.

Comparison for Additive Value

Search Strategy: PubMed, EBSCO, Cochrane Review, and Google Scholar were searched without limits on publication dates. The following search terms were used: opioids, chronic pain, complex regional pain syndrome, neuropathic pain, radicular pain, peripheral pain, and chronic persistent pain to find 26,890 articles. Of the 26,890 articles, we reviewed 174 articles and included one article.

Author/Year Study Type Potential Conflict of Interest	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Comparison for Additive Value						
Keskinbora 2007 RCT No mention of industry sponsorship or COIs.	I(4.5)	N = 75 (29 females, 46 males, 63 completed study) with sufficient relief of nociceptive, but not neuro-pathic,	Two groups. GO Group (n = 31) treated with Gabapentin plus opioid. OO Group (n = 32) treated with opioid alone. GO Group patients already receiving opioid given gabapentin as adjuvant. Initial doses for	Significant difference in absolute decrease of burning pain (GO Group: -7.39±2.86 vs. OO Group: -5.78 ± 2.35, p = 0.018) and shooting pain (GO Group: -6.77±3.37 vs. OO Group: -4.66±2.80, p = 0.009). Significant difference in numbers	"[G]abapentin with opioid in combined regimens reduced burning and paroxysmal shooting pain, attenuated allodynia earlier, and provided a means to remain at the same	Multiple methodological weaknesses. Very short term trial. Some in GO group already on an opioid. Data suggest modest improvements with gabapentin added.

		component of cancer pain while receiving ongoing opioid, pain intensity ≥4, and Karnofsky score of >60.	GO Group were 100mg TID for those ≥60 years old and 300mg TID for those <60years. Evaluated at Day 4 and Day 13. Follow-ups days 4 and 13.	of patients reporting an adverse event (GO Group: 9 vs. OO Group: 19, p = 0.015).	WHO treatment ladder step."	

Injection Comparisons

Search Strategy: PubMed, EBSCO, Cochrane Review, and Google Scholar were searched without limits on publication dates. The following search terms were used: opioids, chronic pain, complex regional pain syndrome, neuropathic pain, radicular pain, peripheral pain, and chronic persistent pain to find 26,890 articles. Of the 26,890 articles, we reviewed 174 articles and included 4 articles.

Author/Year Study Type Potential Conflict of Interest	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Injections/IV Comparisons						
Backlund 1997 RCT Double-blind No industry sponsorship. No COIs declared.	I(6.0)	N = 44 American Society of Anesthesiologists physical status I, II, and III, scheduled for elective major abdominal surgery.	Epidural morphine, bolus 0.015mg/kg followed by infusion 0.003mg/kg/hour (n = 13) vs. Epidural oxycodone, bolus 0.15mg/kg followed by infusion 0.03mg/kg/hour (n = 16) vs. Oxycodone intravenously (IVO) (n = 11). Premeditated with; diazepam 0.15 to 0.2 mg/kg PO ~60 minutes before arrival to operating theater. Pain recorded hourly up to 3 hours after surgery. Three patients excluded. Blood samples were drawn 30 minutes, 1, 2, 3, 4, 8, and 24 hours after opioid infusion.	Right after surgery, mean pain scores higher at rest in Oxycodone or group IV, 0.5±08 or 0.7 ± 1.0, p = ns. At 17 hours, pain scores at coughing were higher in Group IVO, vs. two epidural groups, p < 0.05. Incidence of nausea and pruritus equal in all groups.	"In the dosages reported, oxycodone can be used epidurally for acute postoperative pain."	Significant baseline differences in length of operations (214 v 175 v 305 minutes). More respiratory depression in oxycodone group – baseline differences suggest randomizations failure.

Sörensen 1996 Non-randomized crossover experiment No mention of industry sponsorship or COIs.	I(5.5)	N = 40 with chronic LBP >2 years, unable to work >1 year. Mean age 39 years. All with DDD and facet OA, but no specific diagnoses such as radiculo-pathy.	Day 1: placebo (10ml NS given IV 2x) then syringe loaded with 50mg morphine (delivering 1mg MS/kg/hour). Days 2 and 4: no placebo used infusion twice. Patients then given 5mg lidocaine/kg IV over 30 minutes. Day 3: lumbar epidural catheter inserted containing 500ml NS given IV. First 10ml given 2 times separated by 10 minute interval. Followed by 1µ/kg fentanyl in 10ml NS. Total test procedure lasts 4 days.	Intravenous opioid infusion: 18 were morphine responders, 21 nonresponders, and 1 placebo responder. IV infusion of lidocaine: 12 were lidocaine responders, 27 nonresponders, 1 patient missed test. Diagnostic epidural opioid blockade: 17 patients were fentanyl-responders, 11 local anaesthetic responders, 2 placebo responders, 10 nonresponders.	"This approach may prove useful as a guide for further patient evaluation and as a basis for choice of a suitable treatment strategy."	Non-randomized experiment. Wide variation in posthoc classifications. No definitive linkage with a meaningful treatment-related outcome.
Rowbotham 1991 RCT Crossover Supported by US PHS grants, and a gift to the UCSF Foundation from Dr. Harry Hind.	I(4.5)	N = 19 with postherpetic neuralgia lasting >3 months.	One of 6 possible infusion orders for 3 different treatment sessions: lidocaine-morphine-placebo Sessions 48-hours apart and randomized to different treatment each time; 3-session study. Patients kept for 2 hour observation post infusion.	Lidocaine and morphine had decreased pain rating vs. placebo ($p = 0.02$ and $p = 0.04$). Pain relief ratings were significant in morphine vs. placebo ($p = 0.01$), but not for lidocaine vs. placebo ($p = 0.06$).	"[B]oth IV lidocaine and IV morphine reduce pain of PHN. We found no correlation between degree of preinfusion allodynia and relief from any drug."	Small sample size (N = 19). Study of limited value for long-term management as study used IVs.
Keskinbora 2009 RCT No mention of industry sponsorship or COIs.	I(4.5)	N = 50 referred to pain clinic from cardiovascular surgery clinic	Morphine and local anesthetic (combination, 0.125% bupivacaine + 0mg morphine in 20mL Saline) or local anesthetic alone (bupivacaine, 0.125% bupivacaine in 20mL Saline). After 1st period of trial, 24-hour washout period. Following washout, patients treated with opposite treatment. Following this period, patients asking which treatment was better and were treated long-term with this treatment. Last phase began with	Difference between treatments with respect to Resting Numerical Rating Scale Scores (8 hours [Bupivacaine: 3±1.1 vs. Combination: 2.0±0.7, $p < 0.0001$], 12 hours [Bupivacaine: 3± 0.6 vs. Combination: 2±0.8, $p < 0.0001$]), Numerical Rating Scale scores during activity (8 hours [Bupivacaine: 4±12 vs. Combination: 2±0.5, $p < 0.0001$], 12 hours [Bupivacaine: 3±0.6 vs. Combination: 3±0.6, $p < 0.0001$]), Duration of analgesia (Combination: 12 ± 2 hours vs. Bupivacaine: 9±1, $p < 0.001$), Side Effects (Bupivacaine: 0% vs. Combination: 30%, p <	"[I]n PVD, a peripherally administered bupivacaine and morphine combination provided better and longer analgesia compared to bupivacaine alone."	All patients post-sympathectomy, short follow up time. Methodological weaknesses limit conclusions.

			initiation of most satisfying treatment which included 24 hours in hospital follow-up and week follow-up after discharge.	0.001), Resure Analgesic (IV lornoxicam 8mg, Bupivacaine: 65% vs. Combination: 13%, p < 0.001), and Patient Preference (Bupivacaine: 70% vs. Combination: 30%, p = 0.008).		

Evidence for All Adverse Events

Name/Year Location Potential Conflict of Interest	Score	Study Design	Exposure	Population. Age range. Dropout Rate. Case Definition	Results	Conclusion	Comments
Adverse Events							
Gomes 2011 Ontario, Canada Supported by a grant from Ontario Ministry of Health and Long-Term Care (MOHLTC) Drug Innovation Fund and Institute for the Clinical Evaluative Sciences (ICES), a nonprofit sponsored by Ontario MOHLTC	II	Population-based nested case-control study. Eligible for drug plan (e.g., unemployed, disabled, high drug costs vs. income, home care, long-term Rx facility). Age >65 excluded in this study.	August 1, 1997, through December 31, 2006 (113-month study). Included codeine phosphate, MS, oxycodone, hydromorphone, meperidine, or transdermal fentanyl.	From 607,156 people aged 15 to 64 years with at least 1 opioid Rx for nonmalignant pain. Patients who died of opioid-related causes (n = 498) vs. matched controls (n = 1714).	Prescribed daily opioid doses of 200 mg of morphine (OR=2.88, 95% CI 1.79-4.63) had higher risk of opioid-related mortality vs. receiving <20 mg/d (OR=1.32, 95% CI 0.94-1.84). With 50-99 mg/d of morphine, OR=1.92, 95% CI 1.30-2.85 and 100-199 mg/d of morphine OR=2.04, 95% CI 1.28-3.24).	"Among patients receiving opioids for nonmalignant pain, the daily dose is strongly associated with opioid-related mortality, particularly at doses exceeding thresholds recommended in recent clinical guidelines."	Data suggest higher mortality with higher opioid doses. No zero use group for comparison, instead low dose comparison, downward biasing risk estimates compared with no use. Generalizability may be limited as study based on a public drug plan.
Eriksen 2006 Denmark No mention of sponsored organization or COIs.	II	Population-based, cross sectional, national random sample. Interviews with questionnaires.	2000 Danish Health and Morbidity Survey. Opioids use increased in Denmark from 3400,00 EADDs/million in 1984 to 2,523,00 EADDs/million in 2002.	N = 10,066 age ≥16. Participants considered to have chronic pain if chronic/long-lasting pain lasting >6 months. Those who had chronic pain constituted pain group (PG). Those without chronic pain constituted control group (CG).	12% of PG used opioids; 3% used strong opioids; 9% 'weak' opioids. Prevalence of opioid use 20% in PG group moderate/severe or very severe pain vs. 3% non/very mild or mild pain. (OR: 8.37, p < 0.01) Prevalence for opioid use for those who reported fair, bad, or really bad self-perceived health was 18%, vs. 4% rating	"[O]ur research, both in the general population and in patients referred to our pain center, suggests reasons for concern… caution should be used with long-term opioid treatment of pain, at least until there is better evidence on efficacy and outcomes."	Data suggest opioid use greater in physically inactive, those with worse self-perceived health, unemployment.

					health as really good or good (OR: 5.21, p < 0.01). Opioids associated with not physically active (OR: 1.55, p < 0.01), not employed (OR: 0.37, p < 0.01), and using health care system in prior 3 months (OR: 2.52, p < 0.01).		
MacLaren 2006 No mention of sponsored organization or COIs.	III	Longitudinal Consecutive Case Series	Patients who completed multi-disciplinary treatment for chronic pain secondary to work-related injuries between 2001 and 2003.	N = 146 who completed multi-disciplinary treatment for chronic pain secondary to work-related injuries between 2001 and 2003.	No differences between opioid users and non-users per McGill pain questionnaire, Pain disability index, Beck depression index, measures of physical capacity, measures of return to work (p > 0.05).	"Although further exploration is warranted, results of the current study suggest that opioid use during rehabilitation does not necessarily preclude treatment success."	No association between opioid use and outcome of rehabilitation. Modest sample size for this purpose. No difference in RTW (72.1% vs. 75.8%).
Hartung 2007 Oregon, USA No mention of sponsored organization or COIs.	III	Retrospective observational database study. Medicaid claims database study in Oregon State.	Prescription of long-acting opioid (LAO) at least 28 days' supply between January 1, 2000, and December 31, 2004.	N = 5684 had 1+ LAO Rx. Transdermal fentanyl (n = 1546; 70.6 ± 18.1 years) vs. Methadone (n = 974; 51.1 ± 15.4 years) vs. ER oxycodone (n = 1866; 57.4 ± 17.9 years) vs. ER morphine (n = 1298; 58.5 ± 17.0 years).	Oxycodone group less likely to have ED or hospitalization for opioid-related adverse events vs. morphine (95% CI: 0.26 to 0.77; p = 0.004). Oxycodone less likely to die vs. morphine (95% CI: 0.54 to 0.94 p = 0.018). Methadone or oxycodone less likely to be hospitalized vs. morphine (95% CI: 0.68 to 0.99; p = 0.043 or 95% CI: 0.66 to 0.91; p = 0.002). Oxycodone less likely to have constipation vs. morphine (95% CI: 0.35 to 1.00; p = 0.049).	"Our results support a modest safety advantage with ER oxycodone compared with ER morphine. Among subjects with noncancer pain, fentanyl and methadone were associated with an increased risk of an adverse event compared with ER morphine. Additional studies are needed to confirm our findings and further clarify risks associated with different LAOs."	Medicaid database study. Non-randomized method limits the conclusions of any advantage of one opioid as the baseline groups were highly non-comparable.
Krebs 2011 USA	III	Retrospective database study	Department of Veterans affair health care	Patients with chronic pain who received	3347 (3.4%) died. Raw death rates higher in morphine than	"[N]o evidence of excess all-cause mortality among VA	VA database study, with large sample size. Baseline data suggest

No mention of sponsored organization. 1 of 6 authors consulted for Abbott and Cephalon.			databases, January 1, 2000 and December 31, 2007	methadone (N = 28,554; age 56 ±12) and long-acting morphine (N = 79,938; age 59 ± 3).	methadone during 30-days medical exposure. Propensity-adjusted mortality lower for methadone vs. morphine (HR = 0.56, 95% CI = 0.51, 0.62). Risk of death lower in methadone vs. morphine (HR = 0.36, 95% CI = 0.26, 0.49). Mortality lower in methadone in all quintiles except 5th (HR = 0.92, 95% CI = 0.74, 1.16).	patients who received methadone compared with those who received long-acting morphine. Randomized trials and prospective observational research are needed to better understand the relative safety of long-acting opioids."	groups appear mostly comparable, however, lack of randomization limits conclusions that methadone is less risky than morphine; both associated with deaths. Data suggest methadone associated with psychiatric and substance use disorders.
Cheng 2013 Utah, USA	II	Population-based consecutive case series of fatalities	Prescription opioid use	Data from Utah Department of Health, Office of Medical Examiner, Utah Labor Commission, and Prescription Pain Medication Dataset (PPM) about sudden and unexpected deaths for Utah, scene-of-death investigation, autopsy, toxicology tests, unintentional or undetermined drug overdose, work-related injuries, and work-related diseases. Unintentional and/or undetermined drug-poisoning deaths in Utah from October 26, 2008 to October 25, 2009: 432. Next-of-kin interviews administered: 385.	.254/385 (66%) had 1+ opioid in system. 221/254 (87%) had only non-illicit drugs and 13% had combination of illicit/non-illicit drugs. 145/254, (57%) had 1+ prior WC claim(s). Of 254 deaths, 2nd and 3rd most common medications in toxicology tests were benzodiazepines (34%) and histamine-1 antagonist (18%). Demographics: more likely to be ages 25-54, 98% white, married, 19% had <HS degree, 64% unemployed, 52% Latter-day Sainth, faith, OR = 5 for smoking, OR = 3 for alcohol, higher marijuana (50%) and cocaine (30%), half received prior treatment for substance abuse, majority still using an illicit drug 2 months	"There is an elevated risk of opioid-related death among workers with: a psychiatric disorder, current or prior substance abuse problem (including prescription pain medicine, illicit drugs, tobacco, and alcohol), lack of religious support, poor education, and an unmarried status. These data suggest that a detailed history and screening for these risk, is needed to help identify patients who have an increased potential to abuse or misuse the opioid in the course of accessing the workers compensation system."	Population-based study. Data suggest strong risks of opioid related death for psychiatric disorders, prior substance use, tobacco, unemployment, markers of social detachment, benzodiazepines, and diphenhydramine. 57% had a prior WC claim.

					before death (mostly marijuana), half previously diagnosed with mental illness.		
Addiction							
Von Korff 2008 N. California and Washington State, USA Supported by a NIDA grant. No other support or COIs mentioned.	III	Empirically based classification of opioids.	1997 - 1998 1999 - 2000 2001 - 2003	Long-term Opioid Therapy (episodes lasting longer than 90 days) vs. Group Health Cooperative vs. Defacto Long-Term Opioid Therapy at a different time period used to determine opioid use episodes for non-cancer pain and defines thresholds for transition into Defacto Long-term Opioid Therapy.	Short-acting less potent opioids most frequently prescribed for 74% and 65% for all long-term episodes. Overall, acute episodes comprised ~80% of total opioid use episodes. Over 50% of MEQs were for long-term/higher dose episodes (<1.5% of all opioid use episodes) with mean duration ~1000 days, and mean ~55mg/day.	"Defacto Long-term Opioid Therapy was characterized by considerable diversity in medications, dosage, and frequency of use."	Large, population observational database study. Risk of addiction not well quantified. Highest opioid use concentrated among a small minority.
Depression/Anxiety							
Manchikanti 2006 Kentucky, USA Funding provided by Ambulatory Surgery Center and Pain Management Center in Kentucky.	II	Consecutive case series	Enrollment in an interventional pain management setting May 2004 to October 2004.	N = 500 consecutive patients taking prescribed opioids for pain management through a private practice.	Higher illicit drug use <45 years (25% vs. 13% vs 0% over 65). Greater % illicit drug use in females (31% vs. 15%). Opioid abuse and illicit drug use more common if motor vehicle accident-pain (16% and 24%). Males covered by Medicare had higher opioid abuse than those without (11% vs. 3%). 51% with past history of drug use were current illicit drug users. 28% of opioid abusers were also illicit drug users.	"Opioid abuse and illicit drug use were seen in 9% and 16% of patients, though, less commonly than previously reported." Illicit drug use more common in patients less than 45, and in patients after motor vehicle accidents.	Interventional pain program. MCMI testing for psych. Current drug abuse = 46/500 (9.2%). Illicit drug use = 80/500 (16%), but did not appear to include other aberrant UDS.
Manchikanti 2007 USA	II	Consecutive Case series	As above.	As above.	Greater portion of females involved pain in more than one body	"[T]he presence of psychological features of depression and	As above.

2nd report No funding mentioned and no COI disclosed.					region (72% vs. 54%). Females diagnosed with more anxiety (69% vs. 58%). Illicit drug use higher in females 19% vs. 12%. Drug abuse higher with depression (12% vs. 5%). Illicit drug use more prevalent in depressed women than men (22% vs. 12%). Illicit drug use highest in males with somatization (22%).	somatization disorder may be markers of substance abuse diatheseis in chronic pain patients"	
Grattan 2012 N. California and Washington State, USA Funded by NIDA. No other support or COIs disclosed.	III	Telephone survey based on stratified screening criteria of opioid dosing in a large database.	June 2008 to November 2008, January 2009 to October 2009.	N = 1334 age 21-80 who filled at least 10 opioid prescriptions or received 120-day supply in the previous year. All had no history of opioid abuse.	Average pain intensity for 46% was 3-5, 31% 6-7, and 19% 8+. For depression scores 18% had severe, 19% moderate, and 31% mild; 22% had college degree; 32% high school graduates; 60% age 45 to 64; 83% Caucasian.	"[C]linicians should be alert to the risk of patients with depressive symptoms using their opioids to relieve those symptoms…Our study shows that unrelieved depressive symptoms increase risk for opioid misuse."	Phone survey. Data suggest depression associated with opioid misuse.
Boscarino 2010 Pennsylvania, USA Funding provided by a grant from the Administration Committee for Research, Geisinger Clinic. No other COIs disclosed.	II	Telephone interview/ survey. Random selection from EMR Study.	August 2007-November 2008. Geisinger Clinic System database study.	N = 705 prescription opioid patient respondents. N = 1434 non-respondents.	25.8% met criteria for current opioid dependence. Lifetime opioid dependence associated with life-time alcohol dependence ($p < 0.01$), tobacco dependence ($p < 0.01$), major depression ($p < 0.01$), generalized anxiety disorder, and life-time PTSD. Lifetime opioid dependence was associated with age <65 ($p < 0.001$), current pain, history of opioid abuse, high dependence severity ($p = 0.003$), higher number of drug orders ($p = 0.009$), or major depression ($p =$	"This data may be useful to better determine susceptibility for opioid use disorders in clinical practice for improving patient management…our study suggests that opioid dependence may be higher than expected among chronic pain patients."	33% completed and 51% cooperated. Data suggest opioid, psychiatric and substance use issues correlated.

					0.022), also current opioid dependence associated with age <65 (p = 0.001), history of abuse (p <0.001, higher lifetime dependence severity, history of depression (p = 0.022), and psychotropic medication (p = 0.006).		
Edlund 2007 AL, AR, FL, LA, MO, MS, OK, TE, TX, USA No mention of sponsored organization. One author supported by VA.	II	Secondary data analysis. South Central VA databases.	January 1, 2002 to December 30, 2002, use of opioids on chronic basis. Demographic diagnostic and pharmacy records from 2000-2005.	N = 15,160 chronic users of opioids. Database study.	Slightly less than half of sample of chronic opioid users had mental health diagnosis (45.3%). 68% had diagnosis of arthritis, 53.6% had back pain diagnosis, 8.4% had headaches and tension. Non-opioid substance abuse strong predictor of opioid abuse/dependence (OR = 2.34, 95% p <0.001). Mental disorders associated with opioid abuse (p = 0.005). Other risk factors: age, race, sex, and marital status for opioid abuse.	"[W]e found that non-opioid substance abuse is by far the strongest risk factor for opioid abuse, but is relatively uncommon. On the other hand, mental disorders are significant risk factors with a smaller magnitude than non-opioid substance misuse but are much more common among patients utilizing chronic opioids."	Large sample size of U.S. veterans. Data suggest strong predilection towards opioid abuse/ dependence if male, younger, mental health diagnosis and larger opioid supply.
Dillie 2008 Southern Wisconsin, US Funded by NIH/ NIDA. No COIs disclosed.	III	Sample of 235 primary care practices.	2002-2004, patient prescribed daily opioids	N = 801 prescribed daily opioids (divided into quartiles by dosages). N = 115 intermittent opioid users. N = 93 did not take opioids for prior 6 months. Age 18 to 81. 1/3 men, mostly white.	High-dose group reported differences in median pain duration (p <0.015), and pain interference (p <0.011). Higher opioid doses associated with lower quality of life across physical health subscales (non-opioid 43.0 vs. high-dose 32.3) vs. general U.S. population (82) in 0-100 scale (p value not given). No differences	"[L]ow-dose opioid therapy (20 to 40 mg) can improve physical function, decrease pain, and improve overall health compared with no opioid therapy. The study also found that although high-dose therapy does not improve physical well being, patients do report feeling better	Sampling bias probable based on recall of patients seen. Non-opioid user group (N = 93) too small for control for 801 chronic pain patients on opioids. Study also not appropriate to address main aim of optimum dose identification. Conclusions of improvement in pain or function not appropriate

					between control and opioids groups in overall mental health and emotional role functioning scores (p-value not given).	and have greater levels of satisfaction."	for a retrospective study.
Kidner 2009 USA Funded by NIH. No other COIs disclosed.	II	Longitudinal consecutive case series	Patients with chronic disabling occupational musculoskeletal disorder	N = 1,226 with chronic disabling occupational MSD. "No" group (n = 630): Not on Opioids. "Yes" group (n= 596): Taking Opioids at program admission. "Yes" group subdivided into 4 groups: Group 1: Low (≤30mg; n = 267), Group 2: Medium (31-60mg; n = 112), Group 3: High (61-120mg; n = 78), Group 4: Very High subgroup (>120mg; n = 59).	"Yes" group had higher pre-rehabilitation ratings of pain, disability, and depression. Patients return to work ranged 93.7% in Group 1 to 75% in Group 4 (p = 0.05). Work retention ranged 85.2% in No subgroup to 55.2% in Group 4 (p <0.001). Proportion seeking treatment from new provider 14.0% in No subgroup and ranged from 28.2%-29.6% Groups 1, 3, and 4 (p <0.001). Patients reporting receiving Social Security Disability Income/Supplemental Security Income benefits ranged from 1.9% in No subgroup to 18.5% in Group 4 (p <0.03; OR 11.62; 95% CI 3.51 to 38.46).	"[T]he findings of the present study further support the effectiveness of functional restoration in the treatment of a chronic disabling occupational musculo-skeletal disorder."	Opioids associated with RTW status. RTW was in turn dose-response related. Work retention, seeking a new provider, and Social Security Disability Income also had similar findings.
Kidner 2010 USA No mention of funding or COIs.	II	Longitudinal consecutive case series	Patients began study during the time period of Oct 1998 and Sep 2002	N = 786 with chronic disabling occupational spinal disorders (CDOSD) divided into 2 groups "No" group (n = 398), "Yes" (n = 370). In Yes group, daily dosage identified in 287. These 287 divided into 5 subgroups: Group 1: No	Significant differences found between "No" and "Yes" groups when determining level of pre-rehabilitation opioid use on Minnesota Multiphasic Personality Inventory clinical scales (MMPI) (p <0.01). Yes group more than 1.5 times as likely as	"[T]his investigation clearly demonstrated that increasing levels of pretreatment opioid use was associated with less desirable MMPI profiles (especially the DP) and, thus, greater levels of emotional distress/ psycho-pathology."	Data suggest strong correlation between psychological profiles and opioid dosing.

				subgroup (0mg, n= 397); Group 2: Low (<30mg, n = 148); Group 3: Medium (31-60mg, n = 57); Group 4: High (61-120mg, n = 47); Group 5: Very High (>120mg, n = 35).	No group to produce disability profile (DP) (p = 0.006; OR = 1.66 CI = 1.16, 2.37). Significant differences among 5 opioid subgroups when determining level of pre-rehabilitation opioid use on MMPI clinical scales (p = 0.001).		
Sullivan 2010 N. California and Washington State, USA Supported by NIDA grant. Two authors have support from Johnson & Johnson or consulted for Eli Lilly.	II	Observational cross sectional survey	Database study of opioid use. Patient interviews occurred between June 2008 and November 2008.	N = 1,144 with opioid use in prior 2 weeks. Age range: 21-80, long-term users of prescribed opioids for CNCP. Mostly females (59%) and age 65+ (66%).	Prescribed Opioids Difficulty Scale (PODS) not correlated with average pain intensity (p = 086). PODS weakly correlated to pain interference in daily activities (p = 0.002) and more correlated with depression symptoms (p <0.0001). Clinical depression and significant pain increased in high and medium groups.	"[T]he range of possible harms from COT [chronic opioid therapy] may be broader and of a different nature than has been described in treatment guidelines."	Data suggest dose problems not correlated with higher function. Higher dose problems were associated with elevated depression and other problems.
Reid 2002 Connecticut, USA No mention of funding. Two authors have support from the VA, Robert Wood Johnson Foundation and Paul Beeson Physician Faculty Scholar Award. No other COIs disclosed.	II	Retrospective cohort study	6 or more months of opioid prescriptions during April 1997 to March 1998.	N = 98 with non-cancer pain receiving 6+ months of opioids and not on methadone maintenance. Patients recruited from VA (n = 50) and primary care (n = 48) centers in Connecticut.	Non-cancer pain in VA 44% LBP, 10% injury, 16% non-LBP, 10% spinal stenosis. For PCC patients 25% LBP, 13% injury, 13% headache, 13% non-LBP, and 22% other disorders. VA patients 92% male, 44% depression and 46% alcohol abuse.	"[O]ur study has shown that a broad spectrum of chronic noncancer pain disorders are treated with opioid medications in primary care settings. The lifetime prevalence of psychiatric comorbidity was substantial in our study populations."	High prevalence of anxiety (20/21%), depression (44/54%), alcohol (46/31%), narcotic abuse (18/38%) in VA/PCC populations.
Post-traumatic Stress Disorder							
Mills 2005 Australia	II	Cohort from clinics treating	Heroin dependence in the greater	N = 202 with Posttraumatic Stress Disorder	Patients with and without PTSD had improvements in	"Although the same amount was invested in opiate treatment for	PTSD associated with worse outcomes. However, as target

No mention of supported organization or COIs.		heroin dependence.	Sydney region from February 2001 to August 2002	(PTSD); N = 279 without PTSD. Age range 18-56. Compares use of opiates among heroin dependent patients, with PTSD vs. without PTSD	physical and mental health, but poorer for those with PTSD (p-value not provided). Patients with PTSD less likely to have attempted suicide, but more likely to be diagnosed with major depression from baseline to end of 12 months follow-up.	persons with and without PTSD, those with PTSD continued to perform poorly in many domains at follow-up."	population was heroin users, generalizability of study results likely limited.
Seal 2012 USA Supported by VA, Health Services Research and Development Research Enhancement Award Program and San Francisco VA Medical Center. No COIs disclosed.	III	Retrospective cohort	1 non cancer related pain diagnosis within 1 year of entering the Department of Veterans Affairs health care system from October 1, 2005, through December 31, 2008.	N = 141,029 veterans with non-cancer-pain diagnosis within 1 year of VA enrollment. Age range: <30 (57.7%) ≥30 (42.3%). Study goal to analyze subgroups of OEF/OIF veterans with PTSD vs. non mental health diagnosed, who were prescribed opioids.	Veterans with PTSD and other mental health diagnoses more likely to receive opioids than those without those mental health diagnoses (17.8% vs. 11.7%). Outcomes that occurred in emergency context and inpatient admissions more prevalent across all mental health categories among veterans prescribed opioids.	"Among US veterans of Iraq and Afghanistan, mental health diagnoses, especially PTSD, were associated with an increased risk of receiving opioids for pain, high-risk opioid use, and adverse clinical outcomes."	Opioids use greater if PTSD or mental health disorders (depression, anxiety, alcohol use, other drug use, TBI).
Respiratory Depression							
Jungquist 2011 Non-RCT No mention of funding or COIs.	III	Case series	Opioid use No pain, n = 171; Pain/No Opioids, n = 187; Pain/ Opioid, n = 61	N = 419, ages >21 referred for assessment of sleep disorders for treatment of chronic pain for ≥ 6 months. Drop-out rates unspecified. Aim to define frequency of obstructive (OSA) and central (CSA) sleep apnea in those taking opioids.	59% reported chronic pain. No difference in central apnea index or CAI between those with and without pain. Mean CAI higher if chronic pain plus opioid treatment vs. chronic pain alone, p ≤ 0.001 (5.0 ±13 vs. 1.1±4.0). For every 1-point increase in pain intensity, central apnea events increase by 0.288/hour and obstructive apneic events decrease by 0.599 per hour.	"[O]pioid medications when used long term for chronic pain management are not associated with increased severity in OSA, but they are associated with CSA."	Data suggest opioids strongly associated with central sleep apnea.

Talbert 1988 Study supported by a grant from Bristol Laboratories.	II	Experimental	3mg/70kg butorphanol given over 2 minutes.	N = 8 males (22-31 years) with normal PFTs and within 10% of ideal body weight.	No significant findings. Mean±SEM depression of slope occurred with second butorphanol dose (0.907±0.154); p = 0.41).	"[U]nlikely that profound respiratory depression is associated with higher doses of butorphanol in most individuals who would receive these doses."	Largely negative experimental study.
Caspi 1988 No funding was mentioned or COIs.	III	Case series	100µg/kg Fentanyl anesthesia infused IV 1 year period of 1985.	N = 29 surgery patients, mean age 58±8.6 years. Delayed complications defined as: normal and stable postop. course for 2+ hours post-surgery; acute increases in peak inspiratory pressure (PIP>10cm H_2O from previously monitored value; $PaCO_2$ >46torr; covert muscular rigidity; properly positioned ET-tube and unchanged CXR; prompt response to fentanyl antagonist or muscle relaxant.	Truncal rigidity and respiratory distress developed average of 4 hours 15 minutes post-operatively (range 2-6 hours).	"An apparent normal recovery in the immediate postoperative period may not be sustained and patients may remain at risk of respiratory distress for up to 6 h after anesthesia. In ventilated patients, a sudden increase in inspiratory pressure is the first alarming sign."	Data suggested delayed post-op respiratory response.
Dahan 2006 No funding was mentioned or COIs.	II	Experimental	0.2mg per 70kg, i.v. buprenorphine (n = 10) and 0. mg per 70kg i.v. buprenorphine (n = 10)	N = 20 healthy volunteers age 22–35, weight 62-92kg. No history illicit substance abuse or smoking.	Nausea and vomiting in 40%. Peak depression between 150-180minutes after infusion. At peak respiratory depression: minute ventilation 13.1 (1.8) liter min^{-1} (0.2mg) vs. 12.0 (1.3) liter min^{-1} (0.4mg) (N.S.).	"While buprenorphine's analgesic effect increased significantly, respiratory depression was similar in magnitude and timing for the two doses tested. We conclude that over the dose range tested buprenorphine displays ceiling in respiratory effect but none in analgesic effect."	Data suggest respiratory depression peak at 2.5-3 hours after IV buprenorphine.

Goldberg 1992 Funded by a grant from Janssen Pharmaceutica, Pascataway, New Jersey. No other COIs mentioned.	III	Case series	Mean alfentanil dose 18.9±1.6mg.	N = 21 ASA physical status I or II scheduled for lumbar discectomy. Exclusions: pulmonary disease, CO_2 retention, obesity (weight >110 kg), athletes in training, pregnancy, opioids allergy, substance abuse, or renal failure. Average age 36±1.6 years.	No correlation between plasma alfentanil levels and change in CO2 response curve. From baseline to each of 3 post-op times. Mean CO_2 response slopes were depressed 40%, 28%, 19%, and 17% from baseline at 30, 60, 90 minutes, and last measure, respectively ($p < 0.001$)	"[Pr]olonged alfentanil administration may result in severe arterial O_2 desaturation with significant depression of the hypercapnic respiratory drive during the first hour in the postanesthesia care unit, even though the majority of our patients were easily aroused in response to verbal stimuli."	Data suggest respiratory depression responses.
Clemens 2008 Sponsored by the German Cancer Aid and no COIs noted.	III	Case series	Opioids	N = 27 with moderate to severe dyspnea, ≥18 years, with advanced, terminal cancer or other terminal incurable disease, yet likely to improve from symptomatic treatment of dyspnea with opioids.	Decrease in respiratory rate. Opioid-naïve group: from 40.0±5.6 per minute (range 30.0-50.0 per minute) to 28.0±3.0 (range 22.0-35.0 per minute; $p = 0.001$) after 120 minutes. Patients pretreated with opioids: from 38.9±4.5 per minute (range, 30.0-45.0) to 28.3±3.1 per minute (range, 22.0-33.0 per minute; $p = 0.002$) after 120 minutes.	"No higher risk of respiratory depression and increase in tcpaCO2 in opioid-naïve palliative care patients, compared to patients pretreated with strong opioids, during symptomatic therapy of dyspnea with strong opioids could be found."	No evidence of higher risk of respiratory depression in opioid naïve patients.
Renaud 1988 No mention of sponsored organization or COIs.	III	Case series	Fentanyl	N = 8 undergoing orthopedic knee surgery. Mean age 32 years. No clinical evidence of heart or pulmonary disease.	Respiratory frequency and tidal volume remained unchanged throughout. No respiratory depression observed.	"[W]ith the doses used in this study, the ventilatory depression remained moderate and of no demonstrable clinical consequence."	Small sample size. No significant respiratory depression.
Sam 2011 Sponsored by the Department of Anesthesia, Stanford University. No COIs noted.	III	Prospective, non-randomized study	Morphine via PCA	N = 10 ASA physical status I, II, and III postoperative surgical patients. Exclusions: contraindication to planned anesthetic,	Greatest risk of morphine-induced respiratory depression during morphine PCA between 8-24 hours post-infusion, the time during which peak effect-site	"[S]hould be monitored closely from 8 to 24 hours postoperatively. Morphine PCA given with background infusion rates up to 1.0 mg/hr does not offer distinct	Data suggest respiratory depression occurs.

				morphine, allergy or intolerance, kidney or liver disease, or lack of informed consent.	concentration occurred.	pharmacokinetic advantages over morphine PCA alone. Morphine PCA with background infusion rate of 2.0 mg/hr is associated with the greatest risk of respiratory depression."	
Niesters 2013 Netherlands Sponsored by an educational grant from Anaxsys Technology. No other COIs noted.	II	Experimental	50µg remifentanil IV over 90s after breathing either normoxic (N) gas mixture (inspired fraction 0.21) or hyperoxic (H) gas mixture (inspired fraction 0.5)	20 healthy volunteers (10 male, 10 female).	Ventilation (L/min) – mean±SD (baseline/peak effect): normoxia (7.4±1.3/2.2±1.2) vs. hyperoxia (7.9±1.0/1.2±1.2), peak effect H vs. N – p <0.01. Respiratory rate (bpm) – mean±SD (baseline/peak effect): normoxia (13.1±2.9/6.12.8) vs. hyperoxia (13.2±3.0/ 3.6±4.0), p <0.01. Sp_{O2} (%): normoxia (98.4±1.5/88.6±6.7) vs. hyperoxia (99.7±0.7/ 98.7±1.0), p <0.001. End-tidal P_{CO2} (kPa): normoxia (5.1±0.5/ 5.7±0.3) vs. hyperoxia (5.2±0.4/6.1±0.6), p <0.01.	"[O]pioid-induced respiratory depression is greater during breathing of a hyperoxic gas mixture compared with a normoxic gas mixture (i.e. room air)."	Experimental study. Data suggest respiratory depression worse with hyperoxic gas mixture.
Shapiro 2005 Israel No mention of sponsored organization or COIs.	III	Patient chart review	IV or neuraxial morphine. Data from all patients under APS care between January 1999 and December 2005 recorded.	From 4,5000 patients under anesthesiologist-supervised acute pain service between 1/1999-12/2002; 1,524 received IV or neuraxial morphine	Eighteen (1.2%) cases of an RR less than 10 breaths per minute recorded. Logistic regression: direct correlation between intraoperative fentanyl administration and post-operative respiratory depression in IV (p = 0.03) and epidural (p = 0.05) groups.	"[I]V-PCA or neuraxial morphine-induced respiratory depression may occur at any time during the APS admission."	Data suggest respiratory depression occurs, with relatively low % under RR = 10.

Taylor 2005 USA No mention of sponsored organization or COIs.	III	Retrospective case-control analysis	2003-2004, Hydromorphone, morphine, fentanyl; nurse-controlled analgesia, patient controlled analgesia (PCA), and epidural	Cases (n= 62): non-trauma patients 18+ years with surgery requiring 24+ hours post-op stay. Subset given post-op naloxone. To be included, had to have had post-op respiratory event (respiratory depression – <10/minutes) and/or decrease O_2 sat. (<90%) during post-op narcotic administration reversed by naloxone). Controls (n = 62): with no respiratory depression events.	Cases: 77.4% had respiratory event within 24 hours of surgery. Risks for respiratory event: age 65+yrs, COPD, 1+ comorbidities, and Hydromorphone. Morphine found to be protective. Given fentanyl reduced risk of respiratory event at less than 24 hours (OR 0.109, 95% CI 0.017-0.678).	"The first 24 hours after surgery represents a high-risk period for a respiratory event as a result of narcotic use."	Respiratory depression greatest in 24 hours postop. Morphine, fentanyl appeared less risky than Hydromorphone.
van Dorp 2006 Netherlands No mention of sponsored organization or COIs.	II	Non-randomized placebo-controlled double blind studies (3 studies)	Buprenorphine, naloxone, placebo – doses were per 70 kg	67 healthy males and females with no history of illicit drug use or mental disease; all women taking oral contraceptives	**Study 1.** NS between naloxone and placebo. **Study 2.** NS between naloxone and placebo. **Study 3.1** Naloxone fully reversed respiratory depression. **Study 3.2** Naloxone fully reversed respiratory depression.	"[E]ven after administration of large boluses of naloxone or boluses plus brief infusions, respiratory depression induced by buprenorphine recurred and persisted for the duration of the study (7 h in study 3)."	One report of multiple experimental studies. Respiratory depression with buprenorphine demonstrable.
Oertel 2010 Germany No conflict of interest and no mention of sponsored organization. Authors include at least 3 industry employees.	II	Double-blind, placebo-controlled, crossover study	Ampakine CX717 v. placebo. Alfentanil Naloxone	16 male subjects	Alfentanil: decreased ventilatory frequency during placebo by 25.6±27.9% from baseline ($p < 0.01$); CX717, alfentanil decreased ventilatory frequency by 2.9+33.4%; naloxone returned respiratory frequency to baseline. O_2 sat: CX717 coadmin. – alfentanil decreased by 1.5±1.4% at phase II vs. baseline; placebo	"[T]his study successfully demonstrates that translation of the principle of ampakine-mediated potentiation of AMPA-type glutamate receptors for prevention of opioid-induced respiratory depressive effects from animal research into humans."	Experimental study in healthy subjects. Data suggest respiratory depression.

					coadmin. – alfentanil decreased by 2.8±1.6%; under both conditions, naloxone reversed O_2 sat. to baseline. CX717 did not affect opioid-induced analgesia.		

Post-operative Sleep Disturbances							
Krenk 2012 Non-RCT Funded by the Lundbeck Foundation. No COIs disclosed.	III	Pronounces sleep disturbance and pre-operative sleep architecture	April 20, 2010 to September 15, 2010. Multimodal opioid-sparing postoperative analgesia. TKA 7.5mg hyperbaric bupivacaine (0.5%) and THA 12.5mg isobaric bupivacaine (0.5%). Subjects studied in their homes, 3+days before op and on 4th postop night.	N = 10 ages 62-79, either total hip (THA, n = 6) or total knee arthroplasty (TKA, n= 4). Aim to evaluate REM sleep duration and sleep architecture before and after fast track hip and knee replacement with length of stay (LOS) < 3 days.	No association between sleep disturbance and level of pain (p = - 0.19), amount of opioids use (p = - 0.031) or inflammatory response (p = - 0.57), all p >0.1.	"Despite ultra-short LOS and provision of spinal anesthesia with multimodal opioid-sparing analgesia, REM sleep was almost eliminated on the first postoperative night after fast-track orthopaedic surgery but returned to pre-admission levels when at home on the fourth postoperative night."	Small sample sizes. Observational. No control group. No association between sleep disturbance and pain level.
Webster 2008 Non-RCT Funded by Liberty Mutual Insurance Company. No other COIs.	III	Observational study	Opioids: methadone alone, non-methadone opioids: oxycodone (69%), hydro-codone (32%), fentanyl (26%), morphine (21%), hydro-morphone (4%), and tramadol (3%). All underwent polysomnography Feb. 2004-July 2005.	N = 140 ages 22-84, on around-the-clock opioids for 6+ months, with stable dose for 4+ weeks for chronic lumbar pain. Aim to assess relation between medications prescribed for chronic pain and sleep apnea.	Median daily opioid dose 266 mg MEQ and mean of other sustained –release opioids 187.5mg/day; 75% had sleep apnea. Only methadone (p = 0.004) and benzodiazepine (p = 0.042) use significant for central apnea index.	"Opioids, in particular methadone, may be related to sleep apnea in chronic pain patients."	Data suggest possible association between sleep apnea and methadone and benzodiazepines.
Prescription Opioid Deaths							
Wunsch 2009 Virginia, United States	II	Retrospective, population-based review of medical examiner case	Prescription overdose fatalities between the years 1997 and 2003 in rural western	Population: 889 death cases with youngest case 14 years, mostly from rural setting, majority non-Hispanic white.	Between 1997 and 2003, rural western Virginia medical examiner's office saw 300% increase in drug related deaths, including prescription	"In 889 drug overdose deaths from 1997-2003 among rural western Virginians, a predominance of prescription opioids, in combination with	Population-based. Data suggest higher risks with combinations of drugs. Polydrug deaths were 57.9%.

Funded by a NIDA grant. No COIs mentioned.			Virginia, including prescription opioids	Case definition: death from drug poisoning in which drug or drugs directly or contributed to cause of death.	medications that were related or contributed to the cause of death. Deaths with opioids increased 6-fold from 33 in 1997 to 184 in 2003, p <0.001. Prescription opioids found in 658 (74.0%) with methadone most common (28.0%), hydrocodone (20.4%), and oxycodone (19.6%). Of 658 cases, one opioid present in 62.9%, 2 in 26.6%, and 3+ in 10.6% of cases. Methadone significantly more likely to be only opioid present, p <0.05. Hydrocodone most frequently with one other opioid. Oxycodone was alone or with one other opioid equally.	antidepressants and benzodiazepines on toxicology, is reported as a contributing cause of death rather than illicit drugs."	
Dunn 2010 N. California and Washington State, United States See also von Korff 2008 Supported by NIDA and Group Health Research Institute. 1 author with multiple industry COIs	II	Retrospective cohort	New episode of opioid use with 3+ prescriptions in first 90 days for chronic non-cancer pain from 1997-2005.	Group Health Cooperative (N = 500k insured). Computerized pharmacy records. Mean age 54 years, 29% tobacco use, 27% depression diagnoses, 38% back/30% extremity/13% OA, 12% injury/ contusion/fracture.	N = 51 opioid related overdoses, with 6 deaths. HRs for overdoses increased from 1 to 1.4 to 3.7 to 8.9-fold for 1-20/20-50/50-99/>100MED/day.	"Patients receiving higher doses of prescribed opioids are at increased risk for overdose, which underscores the need for close supervision of these patients."	Data suggest strong dose-response relationship between opioid dose and death. (See Figure 2).
Gomes 2011 Canada Supported by grant from Ontario	III	Cross-sectional study	January 2003 to 2008	N = 154,441 ages 15 to 64 years, receiving at least one opioid prescription in the last year. Exclusion	During study period, prescribing rate of opioid rose by 16.2%, from 1,848 per 1000 eligible residents to 2,148 per 1000.	"By 2008, roughly 1 or every 3 patients with a prescription for long-acting oxycodone received a mean daily dose exceeding current	Study of Ontario's public drug plan. Data suggest population-based relationship

Ministry of Health and Long-Term Care (MOHLTC) Drug Innovation Fund and Institute for the Clinical Evaluative Sciences (ICES), a nonprofit research institute sponsored by the Ontario MOHLTC. No other COIs disclosed.				included prior diagnosis of cancer and those receiving opioid within 180 days of enrollment.	Among those receiving opioids, annual prevalence of long-acting opioids increased from 12.4% to 18.9%. Use of long-acting oxycodone doubled from 331 per 1000 population in 2003 to 675 per 1000 in 2008. Long-acting oxycodone accounted for one-fifth of opioid prescriptions (18.8%).	clinical guidelines…[T]he all-cause mortality rate was more than 10 times higher among patients who received very high doses of opioids than among Ontarians without prescriptions for opioids."	between opioid dose and mortality.
Franklin 2012 Washington State, United States CDC grant. No industry sponsorship and no COIs.	II	Population-based study, pre/post intervention of public policy	Implementation of guideline to require pain consultation for dosing above 120mg MED/day in 2007.	Washington workers' compensation database, including approximately 2.3M workers.	Peak % time loss claimants on opioids at approximately 33% (2008), decreased steadily to 20% (2010). Opioid definite/probable deaths peaked in 2009 at N = 23, and dropped in 2010 to N = 12.	"The introduction in WA of an opioid dosing guideline appears to be associated temporally with a decline in the mean dose for long-acting opioids…and number of opioid-related deaths among injured workers."	Data suggest dosing guideline may have impacted rates of prescriptions and deaths. Other influences, including public attention may have partially confounded these data, especially as rates have continued to track downwards in subsequent years and peaks did not precisely mirror the policy.
Webster 2009 United States Sponsored by Liberty Mutual Insurance Company. No other COIs.	II	Population-based database study	Data from January 1, 2002 and December 31, 2003. Liberty Mutual Insurance Company database. 39 states included.	N = 8,263 lost-time LBP WC claims, 2002-2003. Approximately 10% of private, US WC market. Mean 40.3 years old, 72% male.	21.3% of 8,262 had early opioid Rx, range 6% in MA to 53% in SC. 79% explained by household income inequality, #MD/capita, WC cost containment efforts.	"Geographic variation of early opioid prescribing for acute LBP is important and almost fully explained by state-level contextual factors…(suggesting) clinical and patient interaction and the subsequent decision to use opioids are substantially framed by social conditions and control systems."	Massive (8.8-fold) range in opioid prescribing by state. Emphasis on lost-time likely significantly altered the data.
Braden 2010 Arkansas, USA	II	Population-based database study	January 1, 2001 to December 31, 2004. Arkansas	Adult Medicaid enrollees (38,491 HealthCore, 10,159 Arkansas Medicaid) aged 18 and older	24.2% of HealthCore patients and 28.2% of Arkansas Medicaid patients had emergency department	"Use of Schedule II opioids, headache, back pain, and substance use disorders are associated with EDVs	Schedule II long-acting opioids associated with alcohol or drug-related encounters. Substance abuse or dependence

Supported by a NIDA grant. No other COIs disclosed.			Medicaid and HealthCore.	who used opioids for at least 90 continuous days over 6 months. Continuous use definition: opioid prescription claims without a gap of 32+ days between the end of one prescription and the fill date of the next prescription. Index date: the first day of an opioid use episode	(ED) visit in 12 months following index date of chronic opioid therapy use. Primary diagnoses first ED visit: headache (10.0%), back problems (9.9%), abdominal pain (6.8%), sprains/strains (6.65), heart diseases (6.3%) in HealthCore group. Primary diagnoses first ED visit in Arkansas Medicaid group: back problems (10.4%), heart diseases (7.7%), headache (5.3%), respiratory infections (5.3%), sprains/strains (5.2%). In HealthCore group, a mean (SD) daily opioid dose increased from 53.5±98.6mg MED with 0 to 2 ED visits for 71.6±141.5mg MED for 3 or more ED visits in following year after start of COT, p <0.001. In Arkansas Medicaid group, mean daily dose did not differ between those who had 0 to 2 ED visits compared to those who had 3 or more (52.8 v. 53.6).	[emergency department visits] and ADEs [alcohol- or drug-related encounters] among adults prescribed opioids for 90 days or more."	most strongly associated.
Sullivan 2006 Arkansas, USA Funded by a NIDA grant. No other COIs disclosed.	II	Population-based sampling for research study	1998 and 2001 Healthcare for Communities (HCC) population based survey	Information via telephone from random sampled US cities. Regular opioid prescription use for at least one month.	Common mental disorder in 1998 had higher opioid Rx rate in 2001 (OR 4.43, 95% CI 3.64-5.38, p <0.001). Drug use problem in 1998 had higher rates of opioid use (OR 3.57, 95% CI 2.32-5.50, p <0.001).	"Common mental health disorders and problem drug use are associated with initiation and use of prescribed opioids in the general population."	Data suggest associations between major depression, dysthymia, generalized anxiety disorder and panic attack and opioid use.

				Evidence of a common mental disorder (major depression, dysthymia, generalized anxiety disorder, or panic disorder).	Alcohol use problem in 1998 not more likely to use opioid (OR 0.73, 95% CI 0.43-1.24, p = 0.25). Mental disorder (OR 3.26) or problem related to drug use (OR 4.03) associated with increased risk of initiation of regular opioid use, p <0.001. Alcohol use problems not associated with initiation of regular opioid use (OR 0.68). Mental disorders in 1998 were associated with increased risk of continuation of opioid from 1998 to 2001(OR 2.30, p = 0.04). Neither problems with drug use or alcohol associated with opioid continuation.		
Sullivan 2010 N. California and Washington State, USA Supported by a NIDA grant.	II	Observational cross sectional survey	Database study of opioid use.	N = 1144 with opioid use in prior 2 weeks. Age range: 21-80, long-term users of prescribed opioids for CNCP. Mostly females (59%) and 65+ years old (66%).	Prescribed Opioids Difficulty Scale (PODS) not correlated with average pain intensity (p = 086). PODS weakly correlated to pain interference in daily activities (p = 0.002) and more correlated with depression symptoms (p <0.0001). Clinical depression and significant pain increased in high and medium groups.	"[T]he range of possible harms from COT [chronic opioid therapy] may be broader and of a different nature than has been described in treatment guidelines."	Data suggest dose problems not correlated with higher function. Higher dose problems were associated with elevated depression and other problems.
Cifuentes 2010 USA No mention of funding, however, 2 of 4 authors	II	Cohort study from Liberty Mutual databases	January 1, 2002 to December 31, 2003 of acute LBP claims extracted in February 2006	8443 cases work related disabling LBP (those with paid lost time from work) with lost time beginning within 10 days of pain onset,	Roughly 70% had first opioid during 1st month. Of non-surgical group, 74.7% began opioids in first 4 weeks vs. 54.2% of surgical group. By 3 months,	"Opioid prescribing for work-related, disabling LBP tended to begin soon after claim onset and, in most cases, persisted far beyond the recommendations for	34% received 1+ opioids. Duration of opioids much longer if surgical. Greater dose escalation if higher initial dose. Dose

employees of Liberty Mutual Research Institute for Safety.				no LBP claims in prior years, no treatment for other concurrent conditions within 15 days post-onset, and receiving opioids. Cases (N = 2868) classified as more severe if: received medical care within 15 days post onset of LBP with an ICD-9 compatible with radiculopathy, spinal stenosis, instability, or sequelae of prior back surgery. Less severe cases: classified depending on presence of services with CPT codes for lumbar surgery and also considered as additional indicator of case severity.	86.7% of non-surgical and 71.8% of surgical cases received opioids. In first 3 months, 55.7% of nonsurgical and 10.6% of surgical cases stopped using opioids. At 2 years, 7.1% of nonsurgical and 30.6% of surgical cases still receiving opioids. Median opioid treatment 27 days for nonsurgical and 364 days for surgical cases. 95.3% of all cases received at least one weak opioid Rx, 22.7% received strong opioids, and 17.7% received both weak and strong opioids. 270 prescribed long-acting opioids at least once. 25.7% of cases received 1+ pure opioid Rx, and pure opioid Rx increased with opioid treatment duration. Higher initial opioid dose associated with higher rate of dose escalation.	acute LBP treatment, demonstrating that de facto approach of dealing with LBP as a chronic health problem."	escalation of 0.7%/week.
Seal 2012 USA Supported by the Department of Veterans Affairs, Health Services Research and Development Research Enhancement Award Program and the San	II	Retrospective cohort	1 non cancer related pain diagnosis within 1 year of entering the Department of Veterans Affairs health care system from October 1, 2005 through December 31, 2008	Iraq and Afghanistan veterans who received a new non-cancer-pain diagnosis within 1 year of VA entry (N = 141,029). Each veteran followed-up for 1 additional year from initial diagnosis to evaluate whether the person received	Of 141,029 veterans with a pain diagnosis, 11.1% received opioid prescriptions for 20+ consecutive days.Those with PTSD (17.8%, RR 2.58, 95% CI 2.49-2.67) or other mental health diagnoses (11.7%, RR 1.74, 95% CI 1.67-1.82) more likely to receive opioids than those without a mental	"Among US veterans of Iraq and Afghanistan, mental health diagnoses, especially PTSD, were associated with an increased risk of receiving opioids for pain, high-risk opioid use, and adverse clinical outcomes."	Large sample size. Data suggest strong associations between psychiatric disorders and opioid use.

Francisco VA Medical Center.				an opioid prescription and had adverse outcomes during the 1 year follow-up.	health diagnosis. In total population of veterans with and without pain diagnoses (N = 291,205), 12.3% with PTSD (RR 4.32, 95% CI 4.17-4.49) and 7.3% with other mental health diagnoses (RR 2.65, 95% CI 2.54-2.77) more likely to receive opioids than those without mental health diagnoses receiving opioids for pain. Veterans with a mental health disorder more likely to be prescribed opioids compared to those without a mental health disorder. Those with drug use disorders and PTSD were more likely to be prescribed opioids than those without mental health disorders (33.5% v. 6.5%, RR 4.19, 95% CI 3.84-4.57). Veterans with PTSD were more likely to be in highest quintile for dose of prescription opioids (22.7% v. 15.9%, RR 1.42, 95% CI 1.31-1.54), receive more than 1 type of opioid at same time (19.8% v. 10.7%, RR 1.87, 95% CI 1.70-2.06), receive concurrent sedative hypnotics (40.7% v. 7.6%, RR 5.46, 95% CI 4.91-6.07), and receive early refills on opioids (33.8% v.		

					20.4%, RR 1.64, 95% CI 1.53-1.75) compared to those without a mental disorder.		
Mailis-Gagnon 2011 Toronto, Ontario, Canada No sponsored organizations. No COIs disclosed.	III	Clinical case series	Data from each patient at time of first visit to comprehensive Pain Program (CPP) between June 2008 and April 2009	455 subjects with a mean age of 48.2, 61% identified Canada and country of birth, LBP was the most common complaints	63% of total sample was taking prescribed opioids with 19% exceeding an MED of 200mg/day. Lowest daily consumption of opioids found in biomedical group; highest in group with no detectable peripheral pathology. Diagnostic and Statistical Manual of Mental Disorders group 1 patients had 59% taking opioids and 10% of those exceeding a 200mg/day MED. 89% of group 1 patients used relatively low daily doses with a mean MED of 39.6mg/day; 66% of patients in other 2 groups taking opioids, 21% and 26% exceeding a 200mg/day MED in groups 2 and 3 respectively.	"[M]ale, Canadian-born CNCP patients presenting psychological morbidity or comorbidity and reporting higher pain severity rating were more likely to receive opioids."	Data suggest opioids more likely in association with psychological morbidity and higher pain ratings. As data from pain program, generalizability may be limited.
Dhalla 2011 Ontario, Canada No mention of sponsored organization. No COIs disclosed.	III	Population based cross-sectional analysis	January 1, 2006	Ontarians age 15 to 64 eligible for prescription drug coverage with the Ontario Public Drug Program. In this population, opioid prescribing is high and high dose prescribing (200mg/d MED) is common.	Family physicians in uppermost quintile had average opioid prescribing rate of 931.5 per 1000 patients. Physicians in lowermost quintile had rate of 16.7 per 1000 eligible patients. Physician characteristics associated with more	"Opioid prescribing varies remarkably among family physicians, and opioid-related deaths are concentrated among patients treated by physicians who prescribe opioids frequently."	Data suggest opioid clustering likely in association with practice patterns with differences in prescribing rates approximately 56-fold comparing higher vs. low quintiles. Deaths increased with dose.

					opioid prescribing were male (p = 0.003), older age (p <0.001), and more years in practice (p<0.001). 408 patients had opioid related deaths in 2006. Of those, 40.7% received 1+ publicly funded opioid Rx in year before death. Of those, 61.4% received last opioid Rx from family physician before death. Opioid related deaths increased across quintiles, p <0.001.		
Tao 2012 Louisiana USA Partially funded by Louisiana Workers' Compensation Corporation. No COIs disclosed.	II	Population-based cohort study	1992 to 2002 and followed for 7 years post-injury	Cohort of the Louisiana Workers' Compensation Corporation (LWCC) with lost time injury claims (indemnity claims), N=11,394 categorized into 3 groups, Group 1 (claims involving individuals who never were prescribed opioid medications), Group 2 (claims involving individuals who ever used only short-acting (SA) opioids during the entire study period), and Group 3 (claims involving individual who ever used long acting (LA) opioids with or without SA opioids during the study period).	Percentage of claims ever prescribed opioids increased from 43.3% to 80.8% among open claims. Those ever received only SA opioids increased from 38.1% to 51.2% and LA opioids from 5.2% to 29.6%. Mean MED increased with claim duration. Those received an LA opioid with or without SA opioid saw increase in MED from 10.0 to 143.2mg/day over 7 years. Claims ever prescribed only SA opioid had mean SA opioid MED increase from 1.3 to 18.9mg/day. Claims involving opioids stay open longer than without opioids (12.5 %), and those with LA opioids (86.3%) stay open longer than SA opioids (39.2%), p	"Opioid dosage escalates as claims mature."	7-year follow-up data. Data suggest opioids associated with catastrophic claim. Greater associated risk with long-acting opioids.

					<0.001. Average duration of claims for no opioids 414.6 days, SA opioids 929.8 days, and LA opioids 2,025 days, p <0.001.		
White 2012 Michigan, USA Partially funded by Accident Fund Holdings, Inc. 3 of 5 authors employees of same.	II	Population-based review of claims and billing data	January 1, 2006 to February 28, 2010	Workers compensation claims (n=12,226) in Michigan's Accident Fund database. 66% were male, mean age of 44.3 years for males, 45.8 years for females, p<0.0001.	Mean claim duration 304.5 days for population with mean number of lost time days greater in males (118.3 days) vs. females (101.8 days), p<0.0001. Mean total claim payments $19,127 for females vs. $29,023 for males, p <0.0001. Mean medical paid: females ($9,164) v. males ($11,790), p <0.0001. Mean indemnity: female ($9,893) v. male (17,126), p <0.0001. Average total claim cost by opioid script: no prescription ($13,295), other non-opioid prescriptions ($16, 918), short acting only ($47,742), ever long acting ($156,748).	"The use of opioids for the treatment of nonmalignant chronic pain in workers' compensation is a significant driver of medical and indemnity expenses."	Data suggest higher costs associated with opioid use.
Franklin 2008 Washington State, USA Funded by CDC/NIOSH grant. No COIs disclosed.	II	Prospective, population-based cohort	July 2002 to April 2004 - State of Washington	1843 workers with acute back injury with accepted back injury claim with Washington State workers' compensation program with 4+ days of lost time from work due to injury, received 1+ day of wage replacement compensation in first year of claim, not hospitalized in	34.1% of cohort received 1+ opioid Rx during 1st 6 weeks after injury; 50.6% at 1st medical visit. During 6 week period, mean days opioids prescribed 12.1± 9.9, mean prescriptions 2.2±1.7, mean MED/day 47.9±46.4mg, and mean total MED 547.6±759.5 mg. 53% who received opioids had them for 7+ days	"Prescription of opioids for more than 7 days for workers with acute back injuries is a risk factor for long-term disability."	Opioids associated with disability at one year with evidence of dose-response effect.

				acute period after injury, and 18+ years of age.	and 10% for 28+ days during 6 weeks. Being disabled at 1 year associated with number of opioids Rx during 1st 6 weeks, number of prescribed opioids, and total MED. Those with opioids for >7 days associated with disability at 1 year (OR 2.2, 95% CI 1.5-3.1). Compared to no opioid prescription, those who received 2 prescriptions nearly doubled their odds of disability at 1 year (OR 1.8, 95% CI 1.1-30.), those using 3 (OR 2.5, 95% CI 1.4-4.3), and those using >3 (OR 2.2, 95% CI 1.3-3.6). Compared to no prescription, those with an MED up to 150mg (OR 1.9, 95% CI 1.2-3.1), 151-300mg (OR 2.0, 95% CI 1.2-3.3), 301-650mg (OR 1.6, 95% CI 0.9-2.6), and >650mg (OR 1.9, 95% CI 1.2-2.9) associated with disability at 1 year. Compared to no prescription, those with a II or III drug schedule for 1-7 days had 1.5 times the odds of 1 year disability (OR1.5, 95% CI 1.0-2.3), those with a drug schedule III opioid for >7 days had 2.7 times the odds (OR 2.7, 95% CI1.8-4.1), and schedule II for >7 days had 1.3 times		

					odds (OR 1.3, 95% CI 0.8-2.3).		
Deyo 2011 Oregon, USA Funded by the Oregon Clinical and Translational Research Institute, National Center for Research Resources, NIH, and the NIH Roadmap for Medical Research. No COIs disclosed.	III	Cross sectional analysis of database – Kaiser Permanente.	Opioid use for treatment of index visit for LBP. Acute pain defined as less than 90 days.	N = 26,014 with LBP with 15,830 taking opioids to examine prevalence of unhealthy lifestyles, psychological distress, health care utilization increased with increasing duration of prescription opioid use.	Comorbidity score increase with increasing duration of opioid use, $p < 0.001$. More than 30% of those with any opioid use had ER visit. Adjusting for age, sex, co-morbidity; those receiving long-term opioids had 41% higher rate of clinical visits than those with no opioid use. Increasing duration of opioid use strongly associated with incremental increasing prevalence of mental health conditions (50% had at least one of: depression, anxiety and post-traumatic stress disorder being most frequent.	"Prescription of opioids was common among patients with back pain."	Data suggest associations between duration of opioids and depression, anxiety, PTSD, and substance abuse. Obesity and smoking also strongly associated with long-term opioid use. Association of progressive mental health problems with long term pain and opioid use, was incremental, thought that more depression leads to more opioid use.
Volinn 2009 Utah, USA Funded by the Workers' Compensation Fund of Utah and the Utah State Labor Commission. No COIs disclosed.	II	Prospective cohort	Dataset created on Dec.1, 2005. Included claims from Jan. 1, 2002 to June 30, 2005	N = 2,005 workers with claims for non-specific low back sprain/strain who received compensation for lost work time. *Reference Group* (n= 959): No opioids. *Subgroup 1* (n = 308): Any schedule II opioids. This group divided into *Subgroup 3* (n = 176): Any schedule II opioids and opioids of any type ≥90 days. *Subgroup 2* (n = 738): Any schedule III-IV opioids. This	More than half (52%) of claimants filled an opioid prescription. Odds of work loss were almost twice as high for those in Subgroup 2 and more than 6 times higher for those in subgroup 1 when compared to reference group. Odds were 11 times higher for those in subgroup 4 and more than 14 times higher for those in subgroup 3 when compared to reference group. Costs averaged from $3,138 higher for claimants in subgroup 2 and $25,678 higher	"These associations suggest that for most claimants who filled opioid prescriptions for nonspecific low back pain, opioid therapy in itself did not arrest the cycle of pain and work loss."	Data suggest opioids associated with worse outcomes. Less chronic work loss if no opioids or weak opioids prescribed. Use of opioids beyond 90 days also associated with chronic work loss.

				group divided again into Subgroup 4 (n = 184): Any schedule III-IV opioids and opioids of any type ≥90 days.	for claimants in subgroup 3 when compared to reference group.		
Khademi 2012 North Eastern Iran Funded by Tehran University of Medical Sciences, Cancer Research UK, Intramural Research Program of the NCI, and NIH, IARC and Social Security Organization of Iran Golestan Branch.	II	Prospective cohort	Enrolled January 2004-January 2008 and followed to May 2011	N = 50,045 with a total of 234,928 person years of follow-up. Mean age at baseline 52.1 years. 58% of population was women, 74% were Turkmen, 80% lived in rural areas, 88% were married, 83% were non-smokers, and 70% had no formal education. Follow-up success rate of over 99%.	Opium use associated with an increased risk of mortality among all strata. Opium use associated with an increased risk of death in all major categories, except category which included unintentional injuries and trauma. Strongest associations found for infections (HR = 5.47), respiratory diseases (HR = 3.78), and digestive diseases (HR = 3.12). Opium use associated with an increased risk of esophageal, gastric, and lung cancers. Examination of opium use and deaths from respiratory conditions showed adjusted hazard ratios were 11.0 (95% confidence interval 3.97 to 30.6) for asthma, 6.22 (2.36 to 16.4) for TB, and 5.44 (2.03 to 14.5) for chronic obstructive pulmonary disease.	"[W]e found strong increased risks of death from multiple causes in opium users compared with non-users, even among those who used low doses of opium."	Data suggest elevated mortality associated with opioids.
Sjøgren 2010 Denmark No mention of sponsored organization. No COIs mentioned.	II	Population-based registry study Danish Health Interview Survey	Baseline questionnaire sent out in 2000. Participants were followed up until death, immigration, or	N=2,242 participants who responded yes to a chronic pain question	Association between opioid treated chronic pain and mortality (p = 0.0427). Those not using opioids almost 4 times more likely to recover from chronic pain at follow-up vs. those using opioids at	[T]he odds of recovery from chronic pain were almost 4 times higher among individuals not using opioids compared with individuals using opioids."	Strong opioids associated with mortality and less recovery. Opioids associated with worse perceptions of health.

			November 26, 2008		baseline. Opioids users at baseline reported a fair/poor self reported health measure vs. those not using opioids (OR: 3.89; 95% CI: 1.45-10.46).		
Kidner 2009 USA Funded by a NIH grant. No COIs disclosed.	II	Longitudinal consecutive case series	Patients with chronic disabling occupational musculoskeletal disorder	N = 1,226 with chronic disabling occupational MSD. "No" group (n = 630): Not on Opioids. "Yes" group (n = 596): Taking Opioids at program admission. "Yes" group subdivided into 4 groups: Group 1: Low (≤30mg; n = 267), Group 2: Medium (31-60mg; n = 112), Group 3: High (61-120mg; n = 78), Group 4: Very High subgroup (>120mg; n = 59)	Patients return to work ranged 93.7% in Group 1 to 75% in Group 4 (p = 0.05). Work retention: 85.2% in No subgroup to 55.2% in Group 4 (p < 0.001). Proportion seeking treatment from new provider 14.0% in No subgroup and ranged from 28.2%-29.6% Groups 1, 3, and 4 (p < 0.001). Patients reporting receiving Social Security Disability Income/ Supplemental Security Income benefits ranged from 1.9% in No subgroup to 18.5% in Group 4 (p <0.03; OR 11.62; 95% CI 3.51 to 38.46).	"[T]he findings of the present study further support the effectiveness of functional restoration in the treatment of a chronic disabling occupational musculo-skeletal disorder."	Opioids associated with RTW status. That RTW was in turn dose-response related. Work retention, seeking a new provider, and SSD also had similar findings.
Kidner 2010 USA No mention of supported organizations. No COIs mentioned.	II	Longitudinal consecutive case series	Patients began study during time period of Oct 1998 and Sept 2002	N = 786 who had chronic disabling occupational spinal disorders. Initial 786 participants divided into 2 groups: "No" group (n = 398), "Yes" group (n = 370). Of 370 in Yes group, daily dosage identified in 287. These 287 were divided into 4 subgroups: Low (<30 mg, n = 148);	Significant differences found between No and Yes Groups when determining level of pre-rehabilitation opioid use on Minnesota Multiphasic Personality Inventory clinical scales (MMPI) (p <0.01). Yes group more than 1.5 times as likely as No group to produce disability profile (DP) (p = 0.006; OR = 1.66	"[T]his investigation clearly demonstrated that increasing levels of pretreatment opioid use was associated with less desirable MMPI profiles (especially the DP) and, thus, greater levels of emotional distress/psycho-pathology."	Data suggest strong correlation between psychological profiles and opioid dosing.

				Medium (31-60 mg, n = 57); High (61-120 mg, n = 47); and Very High (>120 mg, n = 35).	CI = 1.16, 2.37). Significant differences found among 5 opioid subgroups when determining level of pre-rehabilitation opioid use on MMPI clinical scales (p = 0.001).		
Inciardi 2009 Wilmington, Delaware, USA No mention of supported organizations. No COIs mentioned.	IV	Descriptive - Focus groups	N/A	N = 32 recruited from 2 residential substance abuse treatment programs in Wilmington. Patients interviewed over a 3 day period. 50% women, 50% men, mean age of 25.9 years, 78.1% white, 9.4% African American and 12.5% Hispanic, 69.2% had a high school education. All had histories of prescription opioid abuse, 87.5% had used prescription opioids in the last year to get high.	Major drug for diversion and abuse was hydrocodone and biggest diverters were doctor shoppers followed by students. Focus group said that elderly and pain patients as major sources of drugs. All focus groups agreed prescription drugs are popular as considered more acceptable, less dangerous, and carry fewer legal consequences. Most popular drug of choice in focus group was fentanyl patch. Extended release oxycodone was most sought after. All focus groups reported abusing alcohol and marijuana before using prescription drugs. Most reported that prescription opioids were gateway to heroin.	"The diversion of prescription opioids might be reduced through physician education focusing on 1) recognizing that a patient is misusing and/or diverting prescribed medications; 2) considering a patient's risk for opioid misuse before initiating opioid therapy; and 3) understanding the variation in the abuse potential of different opioid medications currently on the market. Patient education also appears appropriate in the areas of safeguarding medications, disposal of unused medications, and understanding the consequences of manipulating physicians and selling their medications."	Pilot study. Anecdotal data on opioid diversion.

Dersh 2008 Dallas, Texas, USA Funded by NIH grants. No COIs disclosed.	III	Longitudinal consecutive case series	1994-1999	N = 1,323 with chronic disabling occupational spinal disorders who entered treatment in an interdisciplinary functional restoration program. Relationship of opioid dependence with completion of program, and 1 year post treatment SES outcomes used to determine whether opioid-dependence disorder (ODD) is risk factor. Significant difference in ODD and non-ODD Groups for race, length of disability, prerehabilitation pain intensity, any previous surgeries to compensable body part, and legal representation status	Diagnosis for ODD associated with greater number of DSM-IV axis I ($p < 0.001$) and II ($p < 0.001$) disorders. ODD had greater prevalence of combine axis I and axis II co morbidity when compared to non-ODD patients ($p < 0.001$). ODD program completers (n = 1200) had less successful work and health related outcomes in RTW ($p < 0.043$), work retention ($p < 0.002$), seeking health care from new provider ($p < 0.004$), mean number of visits to new provider ($p < 0.010$) and not significant in new surgeries, new injury, and claim settled.	"Iatrogenic prescription opioid dependence may be a risk factor for less successful long-term work and health outcomes, even after detoxification from opioids as part of an interdisciplinary functional rehabilitation program. Chronic prescription opioid dependence in this patient population is also associated with a significantly higher prevalence of comorbid psychiatric conditions."	Opioid dependence disorder associated with longer disability length, surgical status, and higher legal representation. Opioids dependence associated with lower RTW.
Webster 2007 United States Lead author employed by Liberty Mutual Research Institute for Safety. No other COIs mentioned.	II	Population-based retrospective cohort Liberty Mutual Insurance Company database	Onset of LBP occurred between January 1, 2002 and December 31, 2003	N = 8443 claimants from workers' comp database (WC) with new onset of low back pain that occurred during the dates in the exposure column. Age and proportion of claimants with more severe injuries not significant.	1792 (21.2%) received 1+ early opioid and 879 (10.4%) receive 5+ late opioid prescription. Late opioid prescription defined as 30 to 730 days post onset. Average disability duration increased with increasing MEA. MEA of 1-140mg ($p = 0.609$), 141-225mg ($p = 0.022$), 226-450mg	"Early use of higher morphine equivalent amounts of opiates in acute LBP was significantly associated with worse long-term outcomes, including prolonged disability, increased medical utilization including surgery, and continued opioid use."	Higher opioid doses associated with greater disability among new LBP claims.

				The 8443 were classified into amount of Morphine Equivalent Amounts (MEA) as followed: 0mg (n = 6651), 1-140mg (n = 437), 141-225mg (n = 494), 226-450mg (n = 423), 450mg+ (n = 438).	(p <0.001), 450mg+ (p <0.001). Those receiving 450mg+ MEA on average disabled 69 days longer vs. no early opioids (p <0.001). Mean medical cost increased with increasing MEA. MEA of 1-140mg (p = 0.072), 141-225mg (p = 0.006), 226-450mg (p <0.001), 450mg+ (p <0.001). Receipt of early opioid associated with risk of surgery. MEA and risk of surgery are 1-140mg (p = 0.024), 141-225mg (p = 0.018), 226-450mg (p <0.001), 450 mg+ (p <0.001).		
Causes of Death in Those Taking Opioids							
Soyka 2006 Germany Supported by German Federal funds and an educational grant from Essex Pharma GmbH, Germany.	II	Cohort COBRA Study.	12 months	N = 2694 opioid-dependent men (68.4%)/women (31.6%); mean age: 34.8 +/-8.1 years (range 17-62). 74.7% methadone, 24.6% buprenorphine, 0.7% codeine. After 12-months; 1,629 continued in treatment.	Over 12-months, 28 deaths. 39.3% (n = 11) overdose and 10.7% (n = 3) for HIV/AIDS, accidents, infection, suicide, other; 3.6% (n = 1) died from carcinoma. Overall mortality rate of 1% in patients treated in buprenorphine and methadone.	"It should be noted that 4 of 11 patients who died of overdose/ poly-intoxication were not anymore in treatment at the time of their death for at least several weeks, indicating a very low mortality from overdose among patients in substitution treatment."	Data suggest lower death rate in buprenorphine than methadone. Doses not noted.
Anchersen 2009 Oslo, Norway This study was funded by the Norwegian Center for Addiction Research at the University of Oslo.	III	Prevalence of adverse effect in case series	January 1, 1997 to December 21, 2003. Observation period of October 2006 to August 2007. 6450 patient-years.	N = 200 (138 male, 62 female) from larger cohort of 2,382 86.5% prescribed methadone; 13.5% buprenorphine. Mean dosage of methadone 111+/-35mg and	90 of 2382 died during observation period. Top causes of death were somatic (cardiac, HIV, hepatitis, cancer, or other infections) (53.3%; n = 48), overdose (26.7%; n = 24) traumatic event (defined as accidents,	"[T]he results of this study do not support any severe limitations to methadone maintenance treatment...[W]e suggest that an ECG should be taken when the methadone is	Data suggest 4.6% of methadone patients had QTc >500ms.

				sublingual buprenorphine 19 +/-5mg.	suicide, or homicide) (17.8%; n = 16).	prescribed at doses of 120mg/day more."	
Bjornaas 2008 Oslo, Norway No mention of supported organizations.	III	Longitudinal case series	Recruited 1980 to 1981 and followed for 20 years.	N = 185 opioid addicts treated for self-poisoning (n = 93), voluntary detox (n = 75), or both (n = 17). Females (n = 86), males (n = 99), median age 24 (range 16-41).	Standardized mortality ratios (SMRs) calculated to compare mortality rates of opioid addicts to general population. Over 20-years, 70/185 (37.8%) died. SMR 23.6 (95% CI 18.7-29.6). Median age at death: 34 years (range 20 to 58). Main causes of death were drug dependence (n = 37), accidents (n = 8), and suicide (n = 5).	"This study's main finding was the high mortality rate of 37.8%. One-third of females and almost half of males died. This high mortality rate was observed in a young patient group, for which the median age during 1980 and 1981 was 24 years…[T]he effect of opioid addiction seemed to overrule the effects of age and gender on mortality."	Very high mortality over time associated with opioid addiction.
Clausen 2009 Norway This study was funded by the Norwegian Center for Addiction Research at the University of Oslo.	II	Population-based, prospective. "All opioid dependents in Norway."	January 1, 1997 to December 31, 2003. Total observation time was 10,934 person-years.	N = 3789 opioid-dependent people accepted into opioid maintenance therapy (OMT). Mean age 41.6 +/-7.1 years (range 23-66).	213 deaths (62 females) occurred; crude mortality rate was 1.9 per 100 person-years. Mean age of death was 44.5 +/-7.5 years (range 26-63). Main cause of death was overdose (n = 113; 54%), somatic causes (32%), and trauma (14%).	"The overall death rate among the dependent opioid users in this study was about 2% per annum. This high rate is similar to that reported by other studies in other countries."	Data suggest higher rates immediately prior to and after treatment.

Evidence for Financial Costs of Opioid Usage

Name/Year Location Potential Conflict of Interest	Score	Study Design	Exposure	Population. Age range. Dropout Rate. Case Definition	Results	Conclusion	Comments
Choiniere 1998 2nd report, Rittenhouse 1999 Montreal, Quebec, Canada David Bull Laboratories provided PCA pumps and prefilled cartridges for study.	I (5.5)	RCT	PCA (1mg, lockout 6min) vs. intra-muscular opioids (MS 3mg IV up to 15 minutes).	N = 126 who underwent abdominal hysterectomy randomly assigned to patient controlled analgesia (PCA) or regularly timed intramuscular injections of morphine during a period of 48 hours. Cost calculated based on personal time and drug and material requirements.	No significant difference in incidence of adverse effects or patient satisfaction. PCA was more costly vs. regular group in the analysis.	"Compared with regular scheduled intramuscular dosing, PCA is more costly and does not have clinical advantages for pain management after hysterectomy."	High dropouts both groups from adverse drug reactions. Data suggest equal pain efficacy, but higher costs for PCA.
Davies 2009 Liverpool, United Kingdom Study funded by Royal Liverpool and Broadgreen University Hospitals Trust Research and Development Fund and Liverpool John Moores University.	II	Hospitalized case series	June – December 2005	N = 3,695 patient episodes with 545 who had experienced one or more adverse drug reactions (ADRs).	ADRs directly increased length of stay in 147 or 26.8% patients and increased length of stay by 0.25 days. Cost of treatment was 32% greater in the narcotic group and average postoperative treatment cost.	"[A]pproximately one in seven hospital in-patients experience an ADR, which is significant cause of morbidity, increasing length of stay of patients by an average of 0.25 days/patient admission episode."	Data suggest opioids 2nd most common in-hospital ADR.
Gora-Harper 2001 USA No mention of supported organizations.	III	Retrospective	2-year period	N = 559 underwent spine or joint procedure and received either morphine or meperidine (n = 284) vs. ketorolac (n = 275).	Incidence of serious adverse events similar between groups, $p < 0.05$. Ketorolac group had significantly shorter length of stay, $p < 0.05$. Cost in narcotic analgesic group per-patient 32% higher vs. ketorolac group and 35% more for hospitalization costs.	"[Healthcare] resource utilization and total per-patient cost of treatment were lower for patients in the ketorolac group compared with patients in the narcotic analgesic study group."	Higher costs in narcotic group. Lower costs if ketorolac used.

Kwong 2010 USA The study was funded by the America Society of Health-System Pharmacists Mid-Year Clinical Meeting.	III	Retrospective analysis of massive prescription database (80 health plans, 60M population)	January 1, 2002 – December 31, 2005	N = 8,730 with gastrointestinal (GI) adverse effects associated with oral opioid treatment.	Among different GI adverse event patients with largest increase in other type of health-care costs had largest increase in other health care costs. Patients with prescription claims for antiemetics or laxatives had higher overall costs vs. without GI, $p < 0.001$.	"The economic burden of GI events coincident with opioid treatment is significant for patients with a GI event recorded in claims."	High economic burden associated with opioid-related GI effects.
Masson 2002 San Francisco, California, USA This study was funded by NIH.	II	Consecutive case series abstracted from database	January 1, 1997 – December 31, 1998	N = 3147 individuals with diagnoses related to opioid use or dependence.	Patients with diagnoses related to opioid use or dependence comprised 2% (N = 147,785), of total patient and 5% of the total charges ($829 million).	"The findings suggest that health care providers and policy makers consider policies that promote ambulatory care use among opioid users seeking medical care through the public health care system."	Opioid use/dependence associated with 2.5-fold cost burden.
Obradovic 2012 Spain Study supported by Grünenthal GmbH, Aachen, Germany.	II	State-transition model, cost-effectiveness.	2009	N = 1981 with severe, chronic, nonmalignant pain, initiating 1st line treatment with tapentadol.	Cost: Tapentadol, Oxycodone, Morphine, and TDF, €1884.46, €1928.65, 1837.58, €1845.48, of 1 year in patients with chronic pain. Outcome was sensitive to change in cost of regular treatment and cost of treating adverse events.	"[Tapentadol] is likely to be cost-effective first-line treatment in patients with severe, chronic, nonmalignant pain in Spain according to the commonly accepted willingness-to-pay thresholds."	Data suggest tapentadol may be cost effective compared with opioids.
Oderda 2007 Salt Lake City, Utah, USA Study was funded by Pfizer Inc.	III	Retrospective	1998-2003	N = 10,857 surgical patients received opioids. N = 789 experienced opioid related adverse drug events (ADEs).	Statistically significant increase in cost for patient with ADE. Mean average days of stay 7.3 for ADE patients vs. 7.1 in non-ADE patients.	"Opioid-treated ADEs following surgery were associated with significantly increased LOS and hospitalization costs."	Large sample size. Database study. Opioids ADEs costly and contributed to hospital length of stay.
Vogt 2005 USA	III	Cross-sectional database study of University of Pittsburgh	Patients enrolled in University of	N = 7631 with LBP with and without pharmacy analgesic pharmacy claims.	71.4% who had pharmacy claims for opioids used these drugs <1 month and	"With this health plan, a higher proportion of patients with LBP had	Database study with uncertainty regarding validity of some data. Opioid

No mention of supported organizations.		Health System Health Plan insurance claims.	Pittsburgh Health System in 2001		15.4% had opioid prescription claims for >90 days, plus 9.2% for >180 days.	claims for opioids during 2001."	use for LBP associated with higher costs.

Evidence for Comorbidities

Name/Year Location Potential Conflict of Interest	Score	Study Design	Exposure	Population. Age range. Dropout Rate. Case Definition	Results	Conclusion	Comments
Deyo 2011 Oregon, USA Funded by the Oregon Clinicaland Translational Research Institute, National Center for Research Resources, NIH, and NIH Roadmap for Medical Research.	III	Cross sectional analysis of database – Kaiser Permanente.	Opioid use for treatment of index visit for LBP. Acute pain defined as less than 90 days.	N = 26,014 with LBP; 15,830 taking opioids to examine prevalence of unhealthy lifestyles, psychological distress, health care utilization increased with increasing duration of prescription opioid use.	Comorbidity score increase with increasing duration of opioid use, p <0.001. More than 30% of those with any opioid use had ER visit. Adjusting for age, sex, and comorbidity, those receiving long-term opioids had 41% higher rate of clinical visits than patients with no opioid use. Increasing duration of opioid use strongly associated with incremental increasing prevalence of mental health conditions (50% had at least one of: depression, anxiety and post-traumatic stress disorder being most frequent.)	"Prescription of opioids was common among patients with back pain."	Data suggest associations between duration of opioids and depression, anxiety, PTSD, and substance abuse. Obesity and smoking also strongly associated with long-term opioid use. Association of progressive mental health problems with long-term pain and opioid use, was incremental, thought that more depression leads to more opioid use.
Dominick 2012 New Zealand Funded by the Ministry of Health.	III	Population-based, representative cross-sectional. New Zealand Health Study	2006 - 2007	N = 12,488 adults age 15+ years. Random selection allocated to 1 of 4 seasons of year, using face-to-face interview. Questions on comorbid chronic physical conditions and number of conditions, chronic pain and socio-demographics.	56.6% reporting chronic pain also reported 2 or more comorbid chronic conditions, p <0.0001. Conditions comprising accumulated comorbidity do not need to have independent association with chronic pain to increase risk of chronic pain. Two specific conditions, arthritis and neck/back pain, interact with anxiety/depression to increase risk synergistically.	"[B]oth accumulated comorbid load and several discrete chronic physical conditions are independently associated with chronic pain."	Data suggest associations with psychological morbidity. Chronic medical problems result in comorbidity, were independently associated with chronic neck or back pain and arthritis increase the risk of anxiety/depression synergistically.
Gerhardt 2011 Rhein-Neckar, Germany Funded by a research grant from the Federal Ministry of Education and Research.	II	Random sample, population-based, postal survey.	Those with chronic back pain reported on questionnaire in southwestern Germany. 61.8% response rate.	N = 1,091 completed questionnaire including pain assessment. Of those with chronic back pain, 131/188 who were invited, participated in a clinical examination.	17% had chronic back pain. Overall, prevalence of mental comorbidity of Axis-I and II disorders 35.5% and 15.5%, respectively. Anxiety disorder most common followed by affective, substance abuse, and eating disorders. Personality disorder affected was anxious/inhibited type, e.g., obsessive compulsive. When compared to general population,	"The consistent diagnoses of anxiety, fear, and avoidance in these subjects indicate that also primary care health professional should consider anxiety disorders in patients with chronic pain, in	Proportion with chronic back pain appears quite low, further raising selection bias issues. Data suggest associations with affective disorders including anxiety and depression, as well as substance abuse, emphasizing need for standard screening of mental disorders during

					rate of Axis I co-morbidity higher, while rate of Axis II personality disorders slightly higher.	addition to the affective disorders that are more frequently self-reported in pain patients."	initial pain assessment and treatment.
Gerrits 2012 Netherlands Funded by Geestkracht program of the Netherlands Organization for Health Research and Development and supported by participation universities and mental health care organizations.	II	Longitudinal Netherlands Study of Depression and Anxiety (NESDA)	2004-2009: Study investigated relationship between chronic pain and two-year course of depressive and anxiety disorders in a cohort	N = 1209 with depression/anxiety disorder, followed up for 2 years.	Highest number of pain locations, OR = 1.10, p = 0.008, joint pain, OR = 1.64, p < 0.001, ≥90 days pain, OR = 1.40, p = 0.009, daily use of pain medication, OR = 1.57, p = 0.047, and higher chronic pain score, OR = 1.27, p <0.001. Longer duration and higher pain severity associated with chronic course of depression and or anxiety disorders. Relationships largely mediated by greater severity of baseline depressive and/or anxiety disorders among those with pain.	"In conclusion, this large longitudinal study shows that the course of depressive and anxiety disorders is poorer when pain is present."	Data suggest chronic pain course worse with depression and anxiety. About 10% of participants stated they had "chronic pain" used pain medication daily, yet 27% characterized they had high disability from chronic pain (Grade 3-4) suggesting they had severe pain. This may limit how comparable this population is to others.
Ho 2011 Hong Kong No mention of supported organizations or COIs.	III	Consecutive case series	2001: chronic pain clinic	N = 89 with at least 6 months chronic pain, to estimate prevalence of morbidity in chronic pain patients (CCPs) in Hong Kong.	Prevalence of psychiatric disorders in this 89-patient sample was 62.9%. Majority of patients experienced at least one social problem – social and leisure activities (70.8%), household duties (65.2%), and family relationship (47.2%).	"Prevalence of psychiatric disorders in this Chinese chronic pain clinic sample with reference to the DSM-IV was similar to that reported in previous studies."	Data suggest psychological comorbidity in chronic pain patients, especially depressive disorder, followed by anxiety disorders. Psychiatric morbidity prevalence with chronic pain higher than general population, with specific pain parameters, pain cognition, and social factors increasing risk. Notes high variability of reports of psychiatric disorders in chronic pain patients and reasons.
Knaster 2012 Helsinki, Finland Supported by grants from Signe and Ane Gyllenberg Foundation, Foundation for	III	Consecutive case series from a pain clinic	February 2004 – July 2006	N = 100 who underwent psychiatric assessment using structural clinical interview manual or mental disorders Axis I. 49% neuropathic, 21% nociceptive, 5% visual pain, and 25% idiopathic pain.	Prevalence of at least one diagnosis was 59%, with most prevalent being major depressive disorder (37%). Anxiety disorders appeared to precede onset of chronic pain whereas depressive disorder followed onset of chronic pain.	"Chronic pain patients have a remarkable psychiatric morbidity."	Depression, anxiety, and substance abuse strongly associated with chronic pain. If others substantiate anxiety precedes onset of pain, more attention may be needed for assessing that issue in chronic pain patients.

Psychiatric Research, Wilhelm and Else Stockman Foundation, Finnish Association for the Study of Pain, and the Helsinki University Central Hospital Research Funds.							
Ohayon 2012 Germany Funded by an unrestricted grant from Pfizer Inc.	II	Prevalence study, population-based, with telephone interviews.	2,007 with neuropathic pain defined as pain caused by lesion or disease of somato-sensory nervous system.	N = 3,011 with prevalence of chronic and neuropathic pain features or pain caused by a lesion or disease (NeP). These individuals not examined.	26.8% of sample reported having pain – 1.9% had acute pain, 24.9% had chronic pain. Neuropathic pain associated with higher morbidity. Risk factors for neuropathic pain include increased age, obesity, diabetes, hypertension, heart disease, musculoskeletal diseases, vascular disease, nervous system disease, and psychiatric disorders. Active lifestyle interventions recommended as well as control of chronic disease, such as diabetes.	"Participants' features show how important it is to regard these different modalities of pain separately."	Data suggest neuropathic pain associated with higher morbidity. Strong association between major depressive disorder and chronic pain, with individuals with a major depressive episode having nearly 6 times higher risk of neuropathic and 3 times higher of non-neuropathic pain.
Reme 2011 Norway Funded by the Research Council of Norway.	II	Prevalence study	Sick-listed patients 2-10 months	N = 565 patients sick listed between 2 and 10 months for nonspecific low back pain (LBP) were included in the study. Analyzed point-prevalence.	99% had other health complications; 21%, 6% and 6% had 1, 2, 3 diagnoses. 74.2% with NeP features consulted for their pain in previous year vs. 60.5% in non-NeP group; 38% had 1+ current or lifetime psychiatric disorder; 31% had 1+ current psychiatric disorder. Most prevalent diagnosis was somatoform disorder (18%); anxiety disorder (12%), major depression was 4% of time.	"In a large population of CLBP patients, 31% fulfilled the criteria for at least one current psychiatric disorder when measured with diagnostic interview."	Sick-listed study, may limit results to countries with comparable sick-lists; 31% with CLBP had psychiatric disorder(s). Screening chronic low back pain patients for the presence of a psycho pathology may be indicated because of a high prevalence of psychiatric comorbidity.
Tang 2012 Straffordshire, United Kingdom Research funded by a personal NIHR, UK, award	II	Longitudinal consecutive case series	Chronic pain patients plus insomnia	N = 133 with chronic pain and concomitant insomnia patients recruited from the pain clinic. Monitoring procedure included, wearing the actigraph and on completing	Sleep quality/efficiency (SQ/SE) significantly related to pain upon awakening, p >0.001. These had multi-factorial etiology of chronic pain, LBP most common. Sleep quality and efficiency fairly consistent predictors of pain for next day. Intensity of pre-sleep	"These findings challenge the often-assumed reciprocal relationship between pain and sleep and call for diversification in	Data suggest diversity of relationships between pain and insomnia. Relationship of pre-sleep pain is not reliable predictor of sleep quality and sleep efficacy, rather associated with pre-sleep cogitative arousal.

to Nicole Tang. Not an industry supported study. Authors note no COIs.				the electronic diary. Monitoring: sleep and pain for 1 week.	pain not particularly reliable predictor of subsequent sleep, but instead best predictor was pre-sleep cognitive and somatic arousal (worse mood and arousal) predicted poorer SQ. Improved sleep quality associated with less pain earlier part but not later part of following day. No clear link between sleep efficiency estimates and subsequent pain reports. Depression interacts with pre-cognitive arousal and only individual difference factor associated with prediction of sleep.	thinking of the daily interaction of these 2 processes."	Depression associated with pre-sleep rumination in pain related insomnia and maybe expressed in form of excessive negative worry. This leads to pre-sleep arousal and that is predictive of poor sleep quality and efficiency; suggesting pain is not directly problem, but rather depression related pre-sleep arousal that leads to poor sleep quality/efficiency.
Wong 2012 Hong Kong Supported by grant from Hong Kong Government Health Service Research Committee (HSRC #04060591). No COIs declared.	III	Population and cross-sectional telephone survey	March – May 2007	N = 5,001 general population completed Chronic Pain Grade Questionnaire, plus, Pittsburgh Sleep Quality Index (PSQI), the Chronic Fatigue Scale (CFS), Hospital Anxiety and Depression Scale (HADS), and socio demographic questions.	Overall prevalence of chronic condition was 5.6%, those with multiple syndromes reported poorer health. Only employee status significantly associated with comorbid pain and fatigue, 1.3% OR = 2.81 vs. unemployment 2.8%, OR = 1.97.	"[T]he co-occurrence of chronic pain, fatigue, and sleep disturbances were common in the general adult population."	Large sample size. Chronic pain, fatigue and sleep disturbances coexisted. Data suggest psychological co-morbidities.

Evidence for Diagnostics and Monitoring

Name/Year Location Potential Conflict of Interest	Score	Study Design	Exposure	Population Age range Dropout Rate Case Definition	Results	Conclusion	Comments
Michna 2007 Boston, MA, USA No mention of industry sponsorship or COIs.	II	Case series	Pain management center patients with urine drug screens	N = 470 prescribed opioids for chronic pain. Patients had urine screening. Age 21-85; 54% male.	Oxycodone (59.5%) most prescribed opioid followed by methadone (21.9%); 11.1 % prescribed hydromorphone, but hydromorphone detected in 25.3%. Less oxycodone detected (46.2%) than prescribed (59.5%) in total sample. Younger patients had more abnormal urine results than older ones (p <0.001). Mean age 44-48.	"[R]andom urine toxicology screens among patients prescribed opioids for pain reveal a high incidence of abnormal findings. Common patient descriptors, and number, type, and dose of prescribed opioids were found to be poor predictors of abnormal results."	Overall 45% of urine drug screens aberrant.
Katz 2002 Boston, MA, USA Publication supported by unrestricted educational grant from Purdue Pharma LP	II	Retrospective review of consecutive case series.	Review of 3 years of clinic records and results from 2 university pain management centers	N = 122 on chronic opioid therapy. Population not otherwise well described other than chronic pain and opioids.	Behavioral issues in 10 (8%) who tested positive with urine drug screening (UDS) vs. 17 (14%) who tested negative. No behavioral issues and negative UDS were 69 (57%) while 26 (21%) had no issues and positive UDS.	"[A]lthough further research is urgently needed, at this time it is appropriate to conduct routine urine toxicology testing in patients with chronic pain treated with opioids."	Overall 43% aberrant results or behavioral issue(s).
Hariharan 2007 Milwaukee, WI, USA No disclosed conflicts of interest or COIs.	III	Retrospective cohort study	January 1, 1998 to December 31, 2003 – 5-year experience using opioid contracts for chronic pain management in large academic	N = 332, median age 49 years, 52% male. Patients with chronic non-cancer pain, who signed medication contract agreement for long-term opioids. Results for urine toxicology screening (UTS) categorized as negative, positive for marijuana, cocaine or positive for both.	140 (42%) had UTS performed during course of the study. Among those tested, 38% had an illicit substance detected (n = 53); 18% positive for cocaine, marijuana, and 6% positive for both.	"Over 60% of patients adhered to the contract agreement for opioids with a median follow-up of 22.5 months. Our experience provides insight into establishing a systematic approach to opioid administration and	Not all patients placed on agreements. No systematic testing protocol. Of those placed on agreements/contracts, 38% tested positive for illicit substance(s).

			primary care practice			monitoring in primary care practices. A more structured drug testing strategy is needed to identify nonadherent patients."	
Compton 2008 Los Angeles, CA, USA Work supported by VA Health Services Research and Development. No COIs disclosed.	II	Longitudinal consecutive case series	Opioid use	N = 135, mean age 53, age range 25-65. Veterans recruited from chronic pain clinic at Greater Los Angeles VA Healthcare System. Patients with substance-use disorder excluded. Baseline and monthly assessments – pain, medication, and Prescription Drug Use Questionnaire-Patient version (PDUQ and PDUQp). Prospectively followed over 1 year of opioid therapy.	Scores from PDUQ consistently lower than PDUQp. PDUQ showed good stability over time with significant correlation between scores at 4 and 8 months and from 2 to 12 months.	"This study supports the PDUQp as a useful tool for assessing and predicting problematic opioid medication use in a chronic pain patient sample."	PDUQ scores correlated with opioid misuse.
Ives 2006 North Carolina, USA No industry sponsorship or COIs disclosed.	II	Prospective cohort study	Opioid misuse	N = 196 opioid-treated with chronic, non-cancer pain ≥3 months. Opioid misuse defined as negative urine toxicological screen (UTS) for prescribed opioids, UTS positive for opioids or controlled substance not prescribed, evidence from multiple providers, diversion of opioids, prescription forgery, stimulants on UTS. Mean age 52; 12 month follow-up.	Opioid misuse occurred in 62 (32%) patients. Misusers more likely to have past cocaine abuse (68% vs. 21%), prior drug or DUI conviction (40% vs. 11%), past alcohol use (44% vs. 23%), or male (59.7% vs. 38%).	"Opioid misuse occurred frequently in chronic pain patients in a pain management program within an academic primary care practice."	32% misused opioids.
Wiedemer 2007 Philadelphia, USA	II	Naturalistic prospective outcome study	Opioid therapy	N = 335 referred out of patient base of 50,000 to Opioid Renewal Clinic, structured	51% with documented aberrant behaviors and 45% adhered to opioid treatment agreement.	"An NP/clinical pharmacist-run clinic, supported by a multi-specialty	Drew from large patient base. 51% aberrant results. Methods used to select

No mention of industry sponsorship or COIs.				program were diagnosed to support primary care providers (PCPs). Outcomes evaluated 22 months after start of phase 1.		team, can successfully support a primary care practice in managing opioids in complex chronic pain patients."	may have increased proportion by selecting those more likely to misuse.
Vaglienti 2003 West Virginia, USA No mention of industry sponsorship or conflict of interest. The authors thanked 4 PharmD candidates from WVU School of Pharmacy for their contributions.	III	Retrospective case series	Misuse or abuse of medications	Narcotic protocol is employed at pain center which consists of narcotic contract, consent, psychological evaluation, and random urinalysis to ensure the safe and proper use of controlled substances. N = 186 patients at center from Jan. 1, 2001 to Dec. 31, 2001.	Of 398 infractions, 355 involved legal drugs, 195 due to inappropriate positive urinalyses and 160 to negative drug screens. Hydrocodone products had higher incidence of infractions due to inappropriately positive tests compared to negative tests (55.6% v. 44.4%). Oxycodone infractions from inappropriately negative tests were 75.7% compared to positive tests (24.3%). Benzodiazepines had greater incidence of inappropriate negative tests (69.5%) compared to positive tests (30.5%). Products containing hydrocodone most frequently misused (20.3%), followed by oxycodone products (19.7%). During study, 21% of patients discharged after 1 inappropriate urine test.	"Patients prescribed controlled substances should be repeatedly evaluated for medication misuse and the presence of addictive behaviors."	Hydrocodone and oxycodone most likely to be misused.
Chelminski 2005 North Carolina, USA No mention of industry	II	Longitudinal case series	Multi-disciplinary team intervention: titration of medications – patients returned at 1	N=85 with pain >3 months either taking or considering opioids. Physicians referred patients if difficulty managing pain or suspected misuse of opioid medication.	Pain at worst in last month (pre/post/improvement %): 9.2/8.1/12, p <0.001. Pain at least during prior month: 4.6/3.9/15, p = 0.038. Pain on average during	"In a 3 month trial conducted in an academic primary care setting, a systematic, multi-disciplinary approach to chronic pain management	Methods may have increased proportion of tests positive. Overall substance misuse rate 32%. Authors suggest higher rate of diversion than measured.

sponsorship or COIs.			month intervals; psychiatric evaluation. Monitored substance misuse through history, review of medications, communication with physicians and pharmacies, and urine screenings. Assessments at baseline and 3 months.	Average age 51 years, 60% male, 78% Caucasian, 83% income less than $20,000/year, 65% disabled. Three month trial.	prior month: 6.5/5.5/15, p = 0.003. Pain now: 6.8/5.8/15, p = 0.014. Pain Disability Index: 47.0/39.3/16, p <0.001. % CESD in depression range: conventional cutoffs – 79.4/54.0/32, p = 0.003; chronic pain cutoff – 38.1/23.8/37, p = 0.049. %; depression medication: 44.4/52.4/15, p = 0.059. Stimulants on urine toxicological screening (UTS): n = 13 (15%) – cocaine n = 11 (14%), amphetamines n = 2 (2%). Inappropriate/ inconsistent UTS: n = 2 (2%).	that included the use of opioids and tools to prevent misuse was effective in improving pain, depression, and function scores."	
Manchikanti 2006a Kentucky, USA No external funding and no COIs disclosed.	II	Consecutive case series	Opioids/rapid urine drug testing	N = 500 prescribed opioids (hydrocodone, oxycodone, methadone, morphine) in pain management program encompassing interventional techniques and opioid drug administration; 41% male, 59% female, mean age 48.6, pain duration 10.7 years, past history of illicit drug use 16%.	Drug abuse methods included: doctor shopping (5%) and trafficking (4%). Prevalence of illicit drug use was 16%. There was a higher illicit drug use rise in those less than 45 year of age and female patients. 51% of patients with a history of illicit drug use were current users.	"Opioid abuse and illicit drug use were seen in 9% and 16% of patients, though, less commonly than previously reported."	Illicit drug use in 12% gradual pain onset, 29% MVC-related pain, 17% work-related injury. Overall illicit rate 16%. Opioid abuse rate estimated at 9%.
Manchikanti 2006b Kentucky, USA No external funding and no COIs disclosed.	II	Prospective evaluation with historical controls	Opioids/assessments for drug misuse	N = 500 in comprehensive, multi-disciplinary pain program receiving controlled substances; 41% male, 59% female, mean age 48.6, pain duration 10.7 years.	Drug abuse methods included: doctor shopping (5%) and trafficking (4%) for a total of 9%.	"[A]dherence monitoring was associated with a 50% decrease in opioid abuse among patients in chronic pain management settings."	Second report of apparently same population; 9% drug abuse detected.

Manchikanti 2006c Kentucky, USA No external funding and no COIs disclosed.	II			Same	Illicit drug use in 80/500 = 16%.	"The prevalence of illicit drug abuse in patients with chronic pain receiving opioids continues to be a common occurrence. This study showed significant reductions in overall illicit drug use with adherence monitoring combined with random urine drug testing."	Consecutive case series. Conclusion that drug screening reduces overall illicit drug use, while possible, is not necessarily a valid conclusion from this study design. Unclear how same case series can derive this many conclusions.
Manchikanti 2007 Kentucky, USA Study funded in part by Center for Clinical Bioethics and Division of Palliative Medicine, Georgetown University Medical Center, and Samueli Institute. JP has a COI with Samueli Institute.	II	Save as above	Same as above	Same as above	Higher drug use if depression (12 vs. 5%), Also higher if somatization disorder (22 vs. 9%).	"[T]he presence of psychological features of depression and somatization disorder may be markers of substance abuse diathesis in chronic pain patients."	Third report of same population.
Manchikanti 2001 Kentucky USA No external funding. No COIs disclosed.	III	Case series	Opioids	N = 100 patients actively treated at interventional pain medicine setting receiving controlled substances (opioids). No specific exclusion criteria	No demographic differences between non-abusers (Group I) and abusers (Group II). Depression: 45% of Group I, 75% of Group II. Non-physiological symptoms: 9% of Group I, 17% of Group II.	"[T]here was significant abuse of opioids in an interventional pain medicine setting, with an incidence [sic] of 24%."	Title suggests a randomized study. Methods support that study is a case series with random selection of patients from a database.
Fishbain 1999 Miami, FL Study was supported in part by a grant from	III	Retrospective consecutive case series	Urine toxicology testing at a pain facility	N = 274 chronic pain patients (CPP). Toxicology available group (n = 226) with mean age 45.46 ± 16.49 years, 52% male, 90% white, 56%	Drug classification: 20.4% benzodiazepines, 63.3% opioids, 9.3% tricyclic antidepressants, 7.5% propoxyphene, 6.1%	"A significant percentage of CPPs appears to provide incorrect information on current illicit drug use. Urine toxicology studies may have a	Retrospective methods. 17.5% had no urine toxicology results with most (13.9%) due to refusal. Suggests high likelihood of bias and

the National Institute of Disability and Disability Research. No COIs disclosed.				workers' compensation patients and toxicology refused/not found group (n = 48).	cannabinoid, 3.1% barbiturates, 2.7% alcohol, 2.2% cocaine. 20 chronic pain patients provided incorrect information about their drug use. Sensitivity for urine toxicology lowest for tricyclic antidepressants and alcohol; highest for cannabinoids, barbiturates, and cocaine. Psychiatric examination CPP self-reported drug use by drug class: sensitivity lowest for cannabinoids, barbiturates, and cocaine.	place in the identification of drugs for which incorrect information may be provided by CPPs."	potential to considerably underestimate aberrant drug use (e.g., 6.2% THC and 2.2% cocaine).

Evidence for Screening Tools

Name/Year Location Potential Conflict of Interest	Score	Study Design	Exposure	Population. Age range. Dropout Rate. Case Definition	Results	Conclusion	Comments
SOAPP-R							
Jamison 2010 USA Sponsored by investigator-initiated grant from Endo Pharmaceuticals, Chadds Ford, PA, and Grants from NIH's National Institute on Drugs Abuse (NIDA), Bethesda, MD, and the Arthritis Foundation (Investigator Award; Wasan, PI). No COIs disclosed.	I(5.0)	RCT	Chronic neck or LBP, medication misuse, >6 months.	N = 66; Low Risk Control (n = 20) vs. High Risk Control (n = 20) vs. High Risk Experimental (n = 21), based on SOAPP-R scores or physician referrals for 6 months with a post 6-month follow-up.	SOAPP-R score/COMM/ ABC/urine/diary/mood/ side effects/activity interference; (μ = 13.3± 6.77 vs. μ = 23.1±9.3 vs. μ = 18.6±9.3, p <0.01 with F = 6.64)/(p <0.05)/(p <0.05)/(p <0.001)/(p <0.001)/(high vs. low risk control, p <0.01)/(44.9%, 38%, 37.5%, 28.4% 24.1%, 23.9%, 18.5% mouth dry, constipation, sweating, memory lapse, weakness, itching, headache, respectively)/(p <0.05) at base line between groups. SOAPP-R scores (15.24±7.94 vs. 22.75±10.51; t = 3.10, p <0.01) & COMM (7.50±4.80 vs. 13.65±8.41; t = 3.51, p <0.001, end results vs. baseline.	"The results of this study demonstrate support for the benefits of a brief behavioral intervention in the management of opioid compliance among chronic back pain patient at high-risk for prescription opioid misuse."	No blinding. Compliance details sparse. Data suggests benefit of cognitive behavioral training program of pain diaries.
Butler 2004 Massachusetts, USA Study supported in part by a grant awarded to the Butler SF (DA015617) from National Institutes of Health, Bethesda, MD and by an unrestricted grant to Inflexxion, Inc. from Endo Pharmaceuticals,	II	Validation Study	SOAPP screening tool	N = 175 chronic non-cancer pain patients either currently prescribed long-term opioid therapy or being evaluated for long-term opioid therapy. Average age 47.7, 54.3% women, 90.9% Caucasian, 43.2% low back pain as primary pain site; 95 patients completed a questionnaire at 6 months.	27% of patients taking both long and short acting opioids for pain. SOAPP reliability: α of 0.74 achieved at the initial test and for the follow-up retest. Pearson correlation between SOAPP prediction score at baseline and at 6 month follow-up, 0.71.	"This screener provides clinicians with the ability to be more aware of those patients who may have greater difficulty modulating their own medical use of these drugs and therefore may require extra help in monitoring and management."	175 enrolled and 95 followed up on 6 months, thus significant dropout rate. SOAPP predicted subsequent aberrant behavior. Positive likelihood ratios for scores 7+ (2.94), 8+ (3.19) and 9+ (3.90).

Chadds Ford, PA; 2 authors employed by Inflexxion, Inc.							
Moore 2009 Knoxville, Tennessee, USA No mention of industry sponsorship or COIs.	II	Longitudinal case series, convenience sample from Pain Clinic	November 2006-2007.	N = 48 underwent risk assessment and completed questionnaires. Age range: 18+ (mean 43.9) SOAPP, Opioid Risk Tool (ORT), and/or Diagnosis, Intractability, Risk, and Efficacy inventory (DIRE) used to measure risks for aberrant behavior related with drug-use.	N = 37 received medium or high in Clinical Interview at baseline (p = 0.77): 35 received high risk in SOAPP [>6 in a scale from 0-56] (p = 0.73); 21 in ORT medium or high [>4in range from 0-26] (p = 0.45); 8 high risk DIRE [<14 in a scale from 7-21] (p = 0.17). From 13 patients classified as low by SOAPP, 5 classified as medium or high by DIRE or ORT, 11 classified as high by SOAPP were classified as low in ORT and DIRE.	"Among patients who were discontinued from opioids for aberrant drug-related behaviors, the clinical interview and the SOAPP were most effective at predicting risk at baseline."	Modest sample size. Data suggest after clinical interview (Se = 0.77), SOAPP screening and history had highest apparent sensitivity (0.72) to predict aberrant drug-related behavior, then ORT (0.45) and DIRE (0.17). Modest sample size and lack of analysis of "normals" limits conclusions.
Akbik 2006 Boston, Massachusetts, USA Study supported in part by NIH Grant and unrestricted grant from Endo Pharmaceuticals, Chadds Ford, PA. 4 of 6 authors employed by Inflexxion.	II	Case series	No exposure mentioned.	Center A: N = 238 chronic pain patients prescribed opioids for pain at tertiary hospital. Age: 18-88; 43.9% male. Center B: N = 319 prescribed opioids (long-and short-acting) at Veterans Administration Pain Center. Age: 27-86; 98.1% male. Patients completed 14 items in SOAPP to identify aberrant drug-related behavior.	Center B reported less lower back pain than Center A ($p < 0.05$). Center A had higher scores in SOAPP (p value not mentioned). N = 164 scored <8 showing less abuse potential compared to 192 who scored ≥8 identified as high abuse potentials (p value not mentioned). Patients with higher SOAPP score younger/more likely to have abnormal screen results (p value not mentioned).	"[S]upport was found for the use of the SOAPP for individuals with chronic pain who are being considered for opioid therapy."	Methods sparse. Apparently no systematic drug screen or other data collection other than questionnaire. Strongest predictors of opioid misuse were history of substance abuse, legal problems, craving medication, heavy smoking, and mood swings.
Butler 2008 Boston, Massachusetts, USA No mention of COIs.	II	Validation Study	SOAPP-R Screening Tool	N = 283; age: mean: 49.8 (SD = 9.8; range = 29 to 81); years taking opioids mean: 5.9 (SD = 10.5; range: 5 months to 77 years); n = 223 (79%) successfully provided enough data to	Item correlations for SOAPP-R v. ADBI ranged from .20 to .41 (mean = 0.26). SOAPP-R v. Marlowe-Crowne correlations ranged from -0.34 to -0.10 (mean = -0.26). Correlation of total SOAPP-R score with	"Similar to the original, SOAPP-R is easily understood by patients, takes little time to administer and score, and taps information believed by experienced professionals to be	SOAPP-R sensitivity 81% and specificity 68%; 34% of urine drug screens aberrant, most (62/90) positive for non-prescribed opioid.

				establish predictive criterion (ADBI score).	ADBI was .51 and -.47 with Marlowe-Crowne.	important for determining which chronic pain patients may have problems with long-term opioid medication….The SOAPP-R provides clinicians with the ability to be more aware of patients who may have greater difficulty modulating their own medical use of opioids and who may require extra monitoring and management."	
Butler 2009 Boston, MA; Toledo, OH; Allentown, PA; Indianapolis, IN; and Lebanon, NH, USA No mention of COIs.	II	Cross-validation study	Chronic non-cancer pain patients recruited from pain management centers in 5 states (Boston, Toledo, Allentown, Indianapolis, Lebanon). Each asked to complete 7 self-report: demographic questionnaire, SOAPP-R, Brief Pain Inventory (BPI), Patient Inventory Measure, Physician Completed Measure, Toxicology screen, and Aberrant Drug Behavior Index (ADBI).	N = 302; average age 51.3 (SD = 13.2; range 22-83 years). N = 82 selected to take SOAPP-R retest 1 week later and 80% (n = 66) successfully returned completed questionnaire. Average age 50.3 (SD = 12.6; range 25-77 years).	Test-retest reliability over 1-week period yielded ICC of 0.91 (95% CI: 0.86 to 0.94). Internal consistency for cross-validation also excellent with coefficient α of 0.86. These compare well with those obtained on original sample (test-retest ICC = 0.92, coefficient α = 0.88) suggesting SOAPP-R has stable reliability parameters. ROC curve analysis conducted on cross-validation sample 20, revealed AUC of 0.74 (95% CI: 0.670 to 0.810; p <0.001). Compared with ROC on initial sample (AUC = 0.81, 95% CI: 0.748 to 0.869, p <0.001) 6, there was slight decrease (to be expected when measure is tested in entirely new population).	"Results of this cross-validation study suggest that the psychometric parameters of the SOAPP-R are not based solely on the unique characteristics of the initial validation sample. The SOAPP-R is found to be a reliable and valid screening tool for risk of aberrant drug-related behavior among chronic pain patients."	Larger sample size than prior Butler 2004. 73% follow-up. Cutoff of 18 had sensitivity 80% and specificity 52%.

Edwards 2011 Boston, MA, USA Supported by NIH Grants. Authors state no conflicts of interest	III	Cross-sectional cohort study	Patients recruited from Pain Management Center at Brigham & Women's Hospital. Recruited if pain for 6+ months. Completed demographic questionnaire, SOAPP-R to classify low- or high-risk for opioid misuse, and Pain Catas-trophizing Scale.	N = 276 (161 in high-risk group, SOAPP-R score >18; 115 low-risk group. High-risk group had higher reported pain levels, lower pressure and thermal pain thresholds. Repetitive mechanical stimuli reported as more painful vs. low-risk group (n = 115; p <0.01).	ANOVAs no main effects (of opioid group or SOAPP-R score) or interaction for age or sex (all p-values > 0.30).	"[C]hronic spinal pain patients at high risk for misuse of prescription opioids are more pain-sensitive than low-risk patients, whether or not they are currently taking opioids. Indices of pain-related distress were important predictors of pain sensitivity, particularly among those patients taking opioids for pain."	Data suggest opioid use associated with reduced pain thresholds. Effect appears stronger if higher doses used. Weak trend for Pain Catastrophizing Scale.
Martel 2013 Boston, MA, USA Study funded by NIH Grants. Authors report no conflicts of interest.	III	Cross-sectional	Diagnosis of spinal pain with pain for >6 months. Completed SOAPP-R, Brief Pain Inventory (BPI), Pain Anxiety Symptoms, Beck Depression Inventory, Pain Catastrophizing Scale, and Pain sensitivity.	N = 115	No significant sex differences in age, self-reported pain severity (BPI), pain interference (BPI), pain sensitivity (TPThs), pain-related anxiety (PASS), depression (BDI), catastrophizing (PCS), or risk for prescription opioid misuse (SOAPP-R) (all p >0.05). Genders not different in use of opioids, X2(1) = .38, ns. BPI correlated with PASS (r = 0.43, p <0.01), BDI (r = 0.39, p <0.01), and PCS (r = 0.55, p <0.01).	"Discussion addresses the factors that might place patients with high levels of catastrophizing at increased risk for prescription opioid misuse. The implications of our findings for the management of patients considered for opioid therapy are also discussed."	Catastrophizing associated with opioid use.
Jones 2012 Knoxville, Tennessee, USA No mention of COIs.	III, II	Cross sectional and prospective case series	Each patient assessed by psychologist and administered 3 written risk assessment tests: SOAPP-R, PMQ and ORT.	Study 1: N = 132; mean age 42.7 (SD = 12.0 with age range 19 to 76. Study 2: N = 263; mean age 47.5 (SD = 12.7) 96% of sample Caucaison which is reflective of population of region.	Study 1: Psychologist correctly identified 43% of discharged patients at high risk for abuse. SOAPP-R identified 32 % at high risk of abuse. PMQ identified 22%, ORT identified 10% who were high risk of abuse. Study 2: Data collected during 6 month follow-up.	"The results suggest that a clinical interview by an experienced psychologist offers the highest level of risk assessment sensitivity. Among the written measures studied, the SOAPP-R has higher sensitivity than the	Report of 2 studies. Data from study #2 (prospective) initially screened for possible opioids by pain management practice, may have reduced prevalence of aberrant behaviors. Data suggest clinical

					Psychologist correctly identified 71% of those discharged at high risk for abuse, SOAPP-R-39%, PMQ- 34% and ORT-20%.	PMQ and the ORT has less sensitivity."	psychology interview most sensitive, then SOAPP-R and PMQ.
PMQ							
Adams 2004 Dallas, Texas, USA Supported in part by NIH Grants and grant from Sid Richardson of Foundation.	II	Cross-sectional	October 2001-May 2002. Consecutive cases in pain center, both medical only and interdisciplinary pain program patients.	N = 184 who answered Pain Medication Questionnaire (PMQ), and gave measures of pain and functional capacity. Age range: 17-84, 66% female, 84.2% Caucasian. Patients completed group of instruments and outcome measures to capture behaviors associated with risks of opioid misuse.	Patients on opioids found to have High-PMQ (showing more opioid-related behaviors – 70.5%), than Lower-PMQ (44.6%; ($p < 0.01$). H-PMQ reported more pain disability than L-PMQ ($p < 0.01$). Patients with history of opioid misuse had higher PMQ scores (p value no mentioned).	"[W]ithin the scope of the present investigation, psychometric outcomes of this study suggest that the PMQ holds promise, with considerable future refinement, as a self report screening measure for risk of opioid misuse."	Development of 26-item opioid screening questionnaire, Pain Medication Questionnaire.
Holmes 2006 Dallas, Texas, USA Work supported in part by 3 NIH Grants. No COIs disclosed.	II	Prospective, convenience sample from inter-disciplinary pain program	October 2001 – May 2003	N = 271 with heterogeneous mix of different pain diagnoses. Ages 17-70; 64.7%female; 85.8% white; 68% taking prescribed opioids. Study pursued 2 goals: replicate findings of Pain Medication Questionnaire (PMQ), and examine scores vs. outcomes and functioning at post discharge using one-way and repeated measures ANOVAs.	Four 1-way ANOVAs analysis demonstrated that High-PMQ group had significantly greater distress compared to lower-scoring PMQ ($p \leq 0.01$). Pair sample t-test revealed decrease in PMQ mean scores from pre- to post-treatment ($p <0.001$). After 6 months, not significant differences in improvement on physical and psychological distress among PMQ groups (p value no mentioned).	"[T]he present findings provide further evidence of the clinical utility of the PMQ and justify its clinical use and further validation."	Small sample sizes regarding completers.
Dowling 2007 Texas, USA	II	Clinical study; 2 groups: treatment group received medical, behavioral, psychiatric,	Diagnosed with pain and medical plan for treatment developed.	N = 388 pain center patients who completed PMQ (convenience sample).	High PMQ group 6.4x more likely to be referred for misuse vs. low PMQ group ($p <0.01$). High PMQ group reported worse function vs. low PMQ group ($p = 0.04$).	"[T]he PMQ will aide in the identification of specific problematic behaviors and beliefs at the outset of treatment that may hinder successful treatment of a	Data suggest PMQ 25+ associated with problematic opioid use.

		and physical therapy component vs. medical treatment only				patients pain condition."	
Buelow 2009 Texas, USA	II	Consecutive case series with longitudinal follow-up	Medication use. Study aimed to determine PMQ's predictive accuracy of risk for medication misuse.	N = 1,813 who completed PMQ and took part in an interdisciplinary treatment program (including physical therapy, psychiatric, medical, and psychosocial components). Mean age 51.89.	PMQ predictive accuracy was found to be 85.5%.	"This revised, shortened PMQ can aid physicians in assessing for potential medication misuse, allowing them to more closely monitor at-risk patients during pain management treatment."	Large sample size. Abbreviated PMQ reported to have 85.5% accuracy. Correlation between PMQ and Million visual analog scale 0.24, ODI 0.22 and VAS pain scale 0.08.
Højsted 2011 Denmark	III	Cross-sectional. PMQ administered twice to same group (2 weeks apart).	Long-term opioid therapy.	N = 381 (>18 years) with chronic non-cancer or cancer-related pain. PMQ used to assess addiction.	Pearson's correlation between PMQ and opioid doses ($p < 0.001$), alcohol consumption (0.042), tobacco smoking ($p = 0.012$), anxiety (<0.001), and depression scores ($p < 0.001$). Re-test comparison of PMQ showed correlation = 0.861 ($p < 0.001$).	"The PMQ may assist physicians in addiction risk assessment and stratification when treating chronic pain patients with opioids. PMQ is not a diagnostic tool and should only be used as an indicator for possible addiction problems."	Study of PMQ in Danish version. Sensitivity 82% and specificity 56%.
Morasco 2013 Portland, USA	III	Cross-sectional	Prescription for opioids.	N = 284 meeting diagnostic criteria for current or past substance use disorder (SUD), had current chronic pain, and received prescription for opioid within prior 90 days.	High PMQ group more likely to meet diagnostic criteria for SUD vs. moderate and low PMQ groups ($p = 0.009$).	"Among patients with SUD histories, those with higher risk for prescription opioid misuse reported more pain and impairment, symptoms of depression, and were more likely to have current SUD, relative to patients with lower risk for prescription opioid misuse. In adjusted analyses, pain catastro-phizing was significantly associated with risk for prescription opioid	Pain severity ratings associated with higher PMQ scores. Also, reported higher interference of pain and catastrophizing.

						misuse, but current SUD status was not a significant predictor."	
Opioid Risk Tool							
Jones 2013 No sponsorships or COIs disclosed.	II	Longitudinal case series	Participants received a psycho-logical opioid risk assessment used to complete Brief Risk Interview (BRI) rating scale and given ORT and SOAPP-R assessments to complete. Follow-up after 6 months to determine if medication aberrant behavior had occurred.	N = 196, age 22-91, mean 50.2 years, referred at pain practice for opioid treatment and received long-acting or short-acting opioids. Failure to complete any assessments resulted in exclusion.	BRI, ORT, and SOAPP-R showed 73%, 48%, and 53% accuracy in identifying patients who would engage in medication aberrant behavior, respectively. Specificity in not engaging in aberrant behavior was 0.54, 0.62, and 0.43 for BRI, ORT, and SOAPP-R, respectively. Indicating SOAPP-R had highest accuracy. No p-values reported.	"The BRI shows superior predictive ability in identifying patients who later engage in medication aberrant behavior."	Data suggest best sensitivity for Brief Risk Interview (73%), but lowest specificity (43%). Se/SP for ORT 58/54% and SOAPP-R 53/62%.
Webster 2005 Utah, USA No mention of industry sponsorship or COIs.	III	Consecutive case series from one pain clinic	1 year follow-up after risk tool administered January 2000 – May 2001	N = 185 completed Opioid Risk Tool. Categorized as low, medium, high risk. Tool includes personal/FHx substances abuse, age, sexual abuse, psychological diseases (ADD, OCD, bipolar, schizophrenia, depression).	Higher percentage of high risk in low back group (52%/35%/33%). Risk of displaying an aberrant behavior (presumably over coming year) was low/medium/high: 5.6/9.1/28%.	"[A]mong patients prescribed opioids for chronic pain, the ORT exhibited a high degree of sensitivity and specificity for determining which individuals are at risk for opioid-related, aberrant behaviors. Further studies in a variety of pain and nonpain settings are needed to determine the ORT's universal applicability."	Data suggest questionnaire can reveal higher risks. Some study details absent. Unclear if toxicology studies used.
Witkin 2013 No sponsorships or COIs disclosed.	III	Retrospectiv e review of prospectivel y collected data	Participants given patient-completed Opioid Risk Tool (ORT) and had physician-completed ORT performed after	N = 125; mean age 51, 41.6% female. Patients had to receive opioids as part of pain therapy for minimum of 2 months and attend 2 visits over that course of time.	Patient-completed ORT predicted 4 of 11 (36.4%) moderate risk and 3 of 6 (50%) high risk ADRB participants. Physician-completed ORT predicted 8 of 14 (57.1%) and 4 of 5	"Neither the patient-completed nor the physician-completed ORT was strongly predictive of moderate-to-severe ADRB in patients receiving chronic	ORT – 38.7% low, 57.1% moderate, 80% high with aberrant drug-related behavior. 42.4% with aberrant drug behavior 7.8

			evaluation. Medical records then reviewed for evidence of aberrant drug-related behavior (ADRB).	125 physician-completed ORTs performed; 87 patient-completed ORTs were returned.	(80%) who were high risk ADRB participants. Correlation coefficient between patient-completed and physician-completed ORT = 0.61.	opioid therapy for the treatment of noncancer pain in our pain center."	months (60.4% of them by urine drug screen alone).
Current Opioid Misuse Measure							
Meltzer 2011 Boston, MA, USA No mention of sponsorship or COIs.	II	Cross-sectional study	Analgesic medication users with chronic pain.	N = 238 primary care patients on opioids for chronic pain >3 months, mean age 47 +/-8 years. Prescription drug use disorder (PDD) defined by DSM-IV as social, physical, or legal consequences from use. Dependence defined as compulsive use, health consequences, and physical dependence. Current Opioid Misuse Measure (COMM) administered.	Overall, 11% (n = 27) met criteria for current PDD. Mean COMM score if current PDD was 20.4 (SD 10.8) vs. those without current PDD (8.4 SD 7.5; p <0.0001) and current other substance use disorders (SUD) (13.0 SD 7.4), p <0.00001.	"[T]he COMM is a unique clinical tool that demonstrates utility for PC clinicians. Not only does it serve as a validated measure for assessing PDD, but it also provides a means of tracking these behaviors to identify patients at-risk for prescription opioid misuse."	COMM scores if prescription drug use disorder: 20.4±10.8 vs. 8.4±7.5 (p <0.00010). Data suggest COMM valid.
Parhami 2012 Los Angeles, CA, USA Study supported by research grant from National Institute on Drug Abuse and the Annenberg Foundation. No mention of conflict of interest.	II	Cross-sectional study	Workers' compensation (WC) patients.	N = 92 consecutive new patients in private WC clinic. Inclusion criteria: 18 years or older, presenting to WC for first time. Mean age 49.7 (range 22-83). 53% (n = 49) had history of psychiatric disorder, 45% (n = 41) had documented opioid prescription.	Almost half (46%; n = 42) scored 9 or higher on COMM, indicating high risk for Rx opioid misuse. Average COMM score 11.83±11.8; range 0-46). Participants that screened positive for prescription opioid misuse not more likely to have documented prescription for opioids (OR = 1.26; 95% CI 0.55 to 2.87) than those who screened negative.	"[O]nly 8% of participants screened positive for opioid misuse according to the WHO-ASSIST (requiring some form of intervention), while the COMM found that 46% of our sample misused prescription opiates… While the WHO-ASSIST is a systematic brief interview directly asking about substance use, the COMM is a self-administered questionnaire indirectly inquiring about the symptoms of prescription misuse."	Workers' compensation setting. 46% scored high on COMM. Anti-depressant prescription more likely (OR = 3.29), and intervention for sedative use (OR = 3.07). Data suggest correlation between opioid misuse and depression.

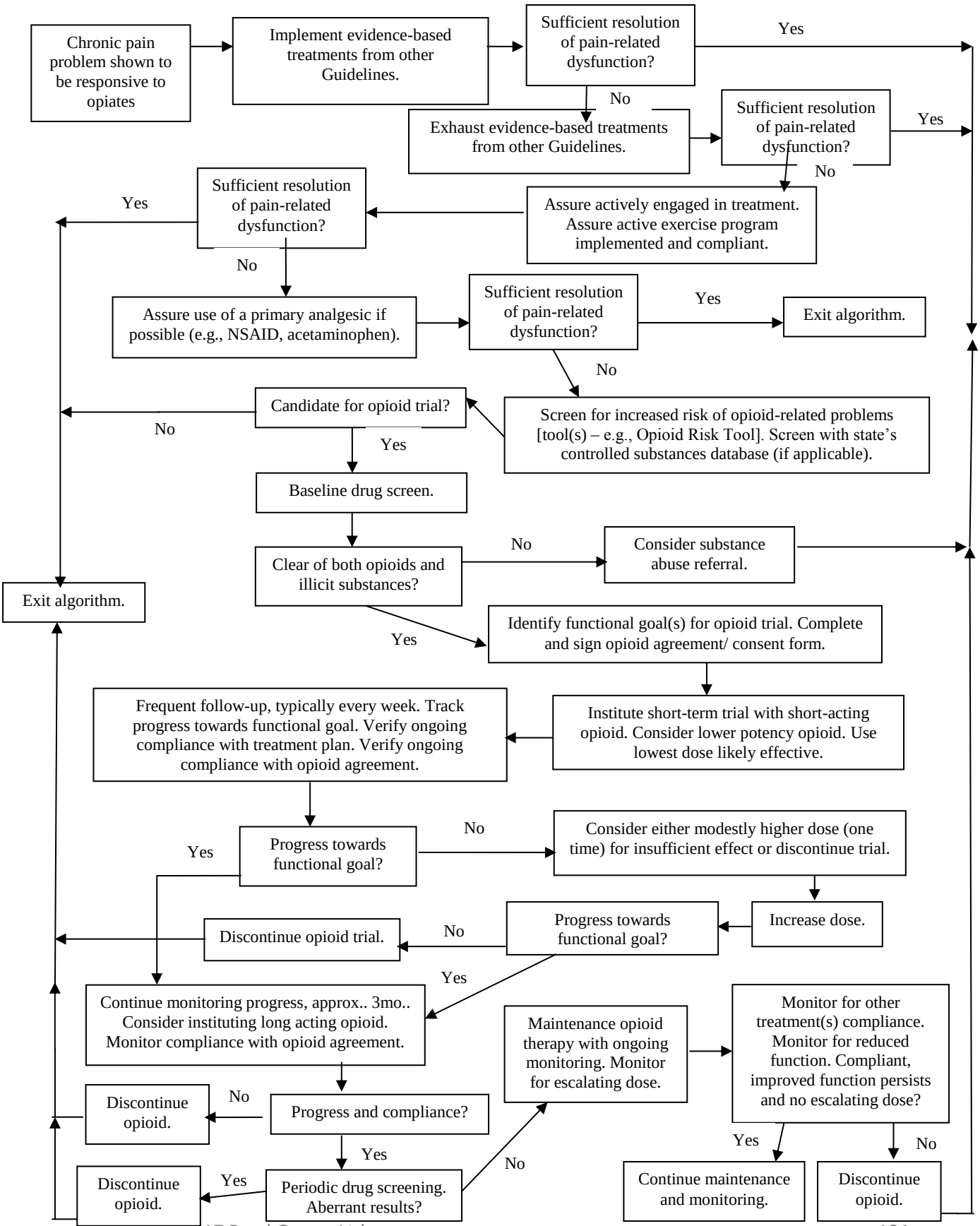
Butler 2010 Boston, MA Toledo, OH Allentown, PA Indianapolis, IN Lebanon, NH, USA Research supported in part by grants from National Institutes of Health, Bethesda, MD, and by unrestricted grant to Inflexxion, Inc. from Endo Pharmaceuticals, Chadds Ford, PA.	II	Longitudinal case series	Patients from pain management centers.	N = 226 chronic non-cancer pain patients prescribed opioids from 5 pain management centers.	Internal consistency for cross validation had a coefficient alpha = 0.83, which is comparable to the original study (alpha = 0.86).	"Cross validation of the COMM yielded promising results. While there was "shrinkage" in the values, which is expected when moving to a completely new sample of patients, the predictive validity as measured by the AUC remained highly significant."	25% dropouts. 41.6% had positive COMM (score 9+). Internal consistency 0.83 vs. 0.86 in original study.
Wasan 2007 Boston, MA, USA Supported in part by a grant from National Institutes of Health, Bethesda, MD (DA015617, Butler, PI) and by an unrestricted grant to Inflexxion, Inc., from Endo Pharmaceuticals, Chadds Ford, PA.	II	Observational study	Patients from 3 pain management centers (Women's Hospital, Boston, MA; Lehigh Valley, PA.; PainCare of Northwest Indiana)	N = 228 taking long-term opioid for chronic non-cancer pain. Average age 50.5 (SD = 12.9; range, 21- 89). Brief Pain Inventory (BPI) administered. SOAPP administered to measure risk potential for future drug-related behavior COMM administered to help track current medication-related behaviors during opioid treatment. Prescription Drug Use Questionnaire (PDUQ) used to assess chronic pain patients. Prescription Opioid Therapy Questionnaire (POTQ) to assess misuse of opioids. Marlowe-Crowne Social Desirability Scale-Short Form (M-C) to measure social desirability. Urine toxicology administered at 5 and 6 month follow-up.	SOAPP scores showed 46.9% with score of $\geq$8 (mean = 8.36; SD = 5.91; range, 0-41). COMM scores averaged 10.12 (SD = 7.53; range, 0-42), and 48.8% of patients scored greater than 8. Total scores on SOAPP and COMM were positively correlated (r = 0.48), and 27.5% of patients had positive scores on both SOAPP and COMM; 13.9% of patients had positive score on POTQ. Urine toxicology screens showed 50.3% of samples normal, 31.8% positive for marijuana, 2.6% positive for cocaine and/or heroin, 8.7% had no evidence of opioids, and 6.7% with no definitive result.	"Psychiatric factors, such as a history of mood disorder, psychologic problems, and psychosocial stressors, may place patients at risk for misuse of prescription opioids. Future studies to elucidate the risk of medication misuse and aberrant drug behavior among this patient population are needed."	Data suggest associations between psychological stress/ problems and opioid use. High Psych group also had higher SOAPP and COMM scores.

Butler 2007 Boston, MA, USA Research supported in part by a grant awarded to first author from the National Institutes of Health, Bethesda, and by an unrestricted grant to Inflexxion, Inc. from Endo Pharmaceutical, Chadds Ford, PA. No conflict of interest was mentioned.	III	Validity and reliability study	Analgesic medication users with chronic pain.	N = 227 chronic pain patients, mean age 50.8 +/-12.4 years, mean years taking opioids 5.7 +/- 9.2 (range 5 months to 66 years). Current Opioid Misuse Measure (COMM) administered. Questionnaire items with a test-retest Intraclass Correlation (ICC) score over 0.50 considered with correlation of Aberrant Drug Behavior Index (ABDI) over 0.20.	17 questions with test-retest ICC over 0.50 (coefficient alpha = 0.86; 95% CI 0.77 to 0.92) and a correlation with ADBI over 0.20 (item correlation score = 0.51). Cohen's D effect size for total COMM score was 1.25 (ICC and ABDI).	"…A 40-item questionnaire was developed using input from a panel of experts and concept mapping analyses. Seventeen of the items of the COMM were found to show good reliability and adequate validity in identifying which chronic pain patients currently on long-term opioid therapy would show evidence of medication misuse or abuse after an extensive assessment process… The development of the COMM may offer clinicians a way to monitor misuse behaviors and to develop treatment strategies designed to minimize continued misuse."	Data suggest COMM of use in detecting prescription opioid misuse. Study not a full validation.
DIRE							
Moore 2009 Knoxville, Tennessee, USA No mention of industry sponsorship or COIs.	II	Longitudinal case series, convenience sample from Pain Clinic	November 2006-2007	N = 48 underwent risk assessment and completed questionnaires. Age Range: 18+ (mean 43.9). SOAPP, Opioid Risk Tool (ORT), and/or Diagnosis, Intractability, Risk, and Efficacy inventory (DIRE) used to measure risks for aberrant behavior related with drug-use.	N = 37 received medium or high in Clinical Interview at baseline (p = 0.77); 35 received high risk in SOAPP [>6 in a scale from 0-56] (p = 0.73). 21 in ORT medium or high [>4in a range from 0-26] (p = 0.45). 8 high risk DIRE [<14 in a scale from 7-21] (p = 0.17). From 13 patients classified as low by SOAPP, 5 classified as medium or high by DIRE or ORT; 11 classified as high by SOAPP were classified as low in ORT and DIRE.	"Among patients who were discontinued from opioids for aberrant drug-related behaviors, the clinical interview and the SOAPP were most effective at predicting risk at baseline."	Modest sample size. Data suggest after clinical interview (Se = 0.77), SOAPP screening and history had highest apparent sensitivity (0.72) to predict aberrant drug-related behavior, then ORT (0.45) and DIRE (0.17). Modest sample size and lack of analysis of "normals" limits conclusions.

Belgrade 2006 Minneapolis, MN, USA	III	Retrospective study	Patients treated with opioids a pain center	N = 61 from outpatient pain management center's opioid prescription database; 44 females and 21 males; mean age for females 44, and males 44.3; age range 18-77. Assessed DIRE score.	Sensitivity for DIRE 94% and specificity 87%.	"The DIRE Score was shown to be valid and reliable. The DIRE Score showed very good correlation with patient compliance with opioid analgesia; and moderate correlation with overall efficacy of opioid therapy (from the treating clinician's perspective) in patients with chronic noncancer pain."	High sensitivity and specificity reported. However, sample size modest and retrospective methods limit conclusions.
Other							
Atluri 2004 USA No external funding in preparation of this manuscript and no declared COIs.	II	Case-control study	Pain center population from 1998-2001.	N = 210 (107 who were dismissed from clinic due to inappropriate opioid use; 103 who did not exhibit inappropriate use of opioid prescriptions. Patients 18+ years who had >6 months with chronic pain, completed a questionnaire followed by a urine drug screen (UDS) used to create a 6 points clinical criteria.	77% of patients in inappropriate opioid use group had score of >3 (high risk on scale from 0-6). Control group had 16% (p value not mentioned). 23% of inappropriate opioid use scored ≤3 and 84% in control group (p value no mentioned).	"[T]his study resulted in the development of a screening tool which may prove to be reliable in chronic pain management."	Cases dismissed from clinic due to aberrant opioid/substances use. No systematic testing of controls other than questionnaire. Data suggest possible association between disability and aberrant opioid/ substances use. Highest risks for opioid misuse: focus on opioids, opioid overuse, other substance use, nonfunctional status, unclear etiology of pain and exaggeration of pain.
Michna 2004 Boston, Massachusetts, USA No mention of industry sponsorship or COIs.	II	Survey study, consecutive cases from Pain Management Center.	January 2000-January 2002	N = 145 prescribed opioids for chronic pain; age 21-69; 52.1% women; 31.5% reported lower back pain. "Substance abuse history" interview consisting of 3 questions, physician	Males had greater positive urine results than women (p <0.05). Greater patient pain, less likely opioids problem reported by family (p <0.05). Patients grouped as high risk (2-3 "yes" interview answers, 69%) had fewer	"[T]he results of this study suggest that questions regarding substance abuse and legal history can be useful in predicting problems with opioid use for patients with	Data suggest substance abuse history predicts aberrant opioid/substance use. Most associated question was regarding positive

				questionnaire, and chart review on urine toxicology to determine aberrant drug-related behavior.	physical symptoms related to opioids; low-risk group had fewer problem behaviors (p <0.05).	chronic noncancer pain."	family history including among grandparents, aunts or uncles.
Compton 1998 USA No mention of funding or COIs.	III	Case series	No exposure mentioned. Data collected over 3-year period.	N = 52 (34 who met criteria for severe diagnosis for substance abuse; 18 with no substance disorder). Age range: 20-66; 60% female; 65% suffered from more than one painful condition. Goal to evaluate ability of screen tools for addictive disease.	No significant differences in patients with/without substance use disorders in daily life activities (p value not mentioned). Addicted patients more likely to seek more prescriptions and obtain opioid from street sources (p value not mentioned). Questionnaire scores ranged from 6-28 (non-addicted: 6-15; substance abusing subjects: 11-25; substance dependant: 15-28), and those who scored above 15 also met diagnostic criteria for substance disorder (p value not mentioned).	"[A]lthough the questionnaire appears promising in its ability to screen for addictive disease in this clinical population, it is not intended to be used in isolation."	Prevalence of psychiatric morbidity 67%. Strongest predictors of misuse: drug seeking behavior, substance abuse, prior opioid abuse/detox, family obtains analgesic, alcohol/psychoactive drug supplementation, increases in dose/frequency, patient/MD/family members believe addicted. Suggests better correlated questions are more directly related to addiction.
Manchikanti 2004 Kentucky, USA No funding in preparation of manuscript. No COIs disclosed.	III	Retrospective, case-control study	No exposure mentioned. Interventional pain management practice.	N = 150 who underwent random urine testing, and were divided into 4 groups based on controlled substance use. Age mean: 44.75; 64% female. Purpose of study was to create a screening control tool that would identify illicit drug use.	Groups with no controlled substance abuse and no illicit drugs (I) and no controlled substance abuse with positive illicit drug (II) where scored <2, showing excellent correlation between groups (p value not mentioned). Groups with positive controlled substance abuse with no illicit drugs (III) and controlled substance abuse plus illicit drug use (IV) where scored ≥2 showing positive correlation between these groups (p value not mentioned).	"This study failed to validate screening criteria previously shown to be useful for identifying controlled substance abuse for the selective detection of illicit drug use. However, these criteria were useful in identifying drug abuse, confirming the previous evaluations."	Retrospective study, methods sparse. Case and control selection criteria unclear, with denominators especially unclear. Article suggests risks of substance use, doctor shopping, deception. Weaknesses limit interpretation.

Algorithm. Opioid Use for Subacute/Chronic Pain



APPENDIX 1: TOOLS

Opioid Risk Tool©

Date _____

Patient Name _____

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

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

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

Opioid Treatment Functional Goal(s)

Name:_____ Date:_____

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

Opioid Treatment Agreement

Patient Name (Print): _____

Prescriber Name (Print):

_____

Medical Condition requiring Opioid:

_____

Planned Opioid Medication: _____

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

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

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

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

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

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

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

Table 1a. Adverse Opioid Effects by Organ System

System	Effect	Secondary Effect
Cardiovascular	Myocardial infarction	Heart attack
	Orthostatic hypotension (dizziness on standing up)	Fainting on standing up
	Abnormal heart rhythm (QT prolongation) (methadone)	Sudden death
Gastrointestinal	Gastroparesis (slow gut movement)	Nausea, weight loss
	Reduced colon motility; spasm	Constipation, bowel obstruction
	Biliary spasm	Stomach pain
Genitourinary	Exacerbation of prostate problems	Urinary retention
Endocrine	Suppression of testosterone	Impotence or reduced sex drive and erectile dysfunction, osteoporosis, feminization, reduced muscle mass, reduced strength
	Suppression of LH, FSH	Abnormal menstrual periods
	Adrenal suppression	Fatigue, low blood pressure, electrolyte changes
Immune		

	Allergic reactions to medication	Rash, shortness of breath, itchy skin, edema
Neurological/ Psychiatric	Impairment of thinking or executive function	Outbursts, inappropriate behavior, limit testing, violence, reduced impulse control
	Frontal lobe atrophy	Alterations in executive function, emotional response
	Brain damage from overdose or apnea induced hypoxia	Slight to severe impairments if an overdose occurs
	Cognitive impairment	Problems thinking clearly
	Increased CNS pressure	Headache
	Hyperalgesia	Increased pain sensitivity, increasing doses of opioids/dose escalation
	Altered sense of taste	Reduced pleasure in eating, weight loss
	Reduced seizure threshold	Seizures
	Confusion, Impaired concentration	Increased accident risks and unclear thoughts
	Drowsiness, somnolence	Crash risk and reduced functioning
	Increased reaction time	Unsafe operation of machinery, motor vehicles, motor vehicle crashes
	Impaired coordination	Unsafe operation of machinery, falls
	Non-medical use	Overdose, death
	Mood elevation, euphoria	Mistaken judgment, changed interactions with other people
	Reduction in anxiety; tranquility	Mistaken judgment, changed interactions with other people
	Depression	Altered mood, depressed feelings, suicidal
Reproductive	Birth defects	Birth defects, miscarriage
	Neonatal withdrawal	Newborn babies of mothers on opioids go through opioid withdrawal
Respiratory	Respiratory depression	Death
	Central sleep apnea	Reduced ability to breath during sleep; daytime sleepiness; death
	Obstructive sleep apnea	New or increased problems with obstructive sleep apnea; daytime sleepiness; death
	Pneumonia	Pneumonia
	Hypoventilation	Worsening asthma and chronic obstructive pulmonary disease (COPD)
Vestibular	Reduced balance	Falls, fractures

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

Goal for improved function: _____

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

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

_____ Increased motor vehicle crashes have been reported in many studies among those taking opioids on a chronic basis. Especially for this reason, workers performing safety sensitive jobs (e.g., driving, operating heavy machinery, transporting goods or people, using overhead cranes, working at elevated heights, making complex judgments) are recommended to be precluded from performing safety sensitive jobs while taking

opioids. If I am employed in a safety sensitive job, I will check with my employer to make sure this medication does not prevent me from working.

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

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

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

I agree to the following (initial each):

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

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

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

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

_____

_____

_____

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

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

_____

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

_____	_____
Patient Signature	Date
_____	_____
Prescriber Signature	Date

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

APPENDIX 2: Drug Interactions between Methadone or Buprenorphine and other Medications

HIV Medications	Methadone	Buprenorphine
AZT (Zidovudine)[1]	Increase in AZT concentrations; possible AZT toxicity[(918)] (McCance-Katz 98)	No clinically significant interaction[(919)] (McCance-Katz 01)
Didanosine[2] (in tablet form)	Significant decrease in Didanosine concentrations[(920)] (Rainey 00)	
Stavudine[2]	Significant decrease in Stavudine concentrations[(920)] (Rainey 00)	
Delavirdine[2]	Increased methadone (and LAAM) concentrations; no cognitive impairment[(921)] (McCance-Katz 06)	Increased buprenorphine concentrations; no cognitive impairment
Atazanavir[2]	Not associated with increased levels of methadone[(922)] (Atazanavir Product Label)	Significant increases in buprenorphine and report of cognitive dysfunction[(923)] (Freimuth 96)
Darunavir[2]	Opiate withdrawal may occur[(924)] (Darunavir Product Label)	
Efavirenz[2]	Opiate withdrawal may occur[(925-929)] (Back 03; McCance-Katz 02; Boffito 02; McCance-Katz 03; McCance-Katz 05)	No clinically significant interaction[(930-932)] (McCance-Katz 06; McCance-Katz 06b; McCance-Katz in press)
Fosamprenavir[1]	Data suggest that the PK interaction is not clinically relevant; however, patients should be monitored for opiate withdrawal symptoms[(933)] (Fosamprenavir Product Label)	
Nelfinavir[1]	Methadone levels are decreased. Opiate withdrawal may occur.[(934)] (Nelfinavir Product Label)	No clinically significant interaction[(930-932)] (McCance-Katz 06; McCance-Katz 06b; McCance-Katz in press)
Nevirapine[2]	Opiate withdrawal may occur[(925-929)] (Back 03; McCance-Katz 02; Boffito 02; McCance-Katz 03; McCance-Katz 05)	No clinically significant interaction[(930-932)](McCance-Katz 06; McCance-Katz 06b; McCance-Katz in press)
Tuberculosis Medications		
Rifampin[2]	Opiate withdrawal may occur[(935)] (McCance-Katz 09)	Opiate withdrawal may occur[(935)] (McCance-Katz 09)
Rifabutin[2]	Not clinically significant interaction[(936)] (Brown 96)	Not studied
Hepatitis C		
Interferon	Not clinically significant interaction[(937, 938)] (Berk 07; Gupta 07)	
Ribavirin[2]	Not studied	
Other Infections		
Fluconazole[2]	Increased methadone plasma concentrations[(939)] (Physician's Desk Reference 05)	
Voriconazole[2]	Increased methadone plasma concentrations[(939)] (Physician's Desk Reference 05)	
Ciprofloxacin[2]	Increased methadone plasma concentrations[(940)] (Karin 00)	
Biaxin, Clarithromycin[2]	Increased methadone plasma concentrations[(939)] (Physician's Desk Reference 09)	
Antidepressants		
Fluoxetine[2]	Not associated with increased levels of methadone[(941)] (Bertschy 96)	
Fluvoxamine[2]	May cause increased methadone plasma levels and discontinuation has been associated with onset of opioid withdrawal[(942)] (Bertschy 94)	
Sertraline[2]	No associated adverse drug interaction[(943)] (Hamilton 00)	No clinically significant interaction[(943)] (Hamilton 00)
Citalopram[2]	No clinically significant interaction[(944)] (Dvir 08)	No clinically significant interaction[(944)] (Dvir 08)
Mirtazepine[2]	No clinically significant interaction	

Duloxetine[2]	Potentially lead to increased duloxetine exposure[(945)] (Gore 08)	
Amitriptyline[2]	Could be associated with increases in plasma methadone concentrations[(946)] (Bomsien 07)	
St. John's Wort[3]	Increased metabolism and elimination of methadone[(947)] (Di 08)	Increased metabolism and elimination of buprenorphine[(947)] (Di 08)
Desipramine[1]	Associated with increased Desipramine levels[(948)] (Maany 89)	
Dextromethorphan[2]	Associated with delirium[(949)] (Lotrich 05)	
Antipsychotics		
Quetiapine[2]	Increased plasma methadone concentrations[(950)] (Uehlinger 07)	
Risperidone[2]	No clinically significant interaction	No clinically significant interaction
Clozapine[2]	No clinically significant interaction	No clinically significant interaction
Aripiprazole[2]	No clinically significant interaction	No clinically significant interaction
Olanzapine[2]	No clinically significant interaction	No clinically significant interaction
Ziprasidone[2]	No clinically significant interaction	No clinically significant interaction
Anticonvulsants		
Carbamazepine[2]	Associated with opiate withdrawal[(951)] (Perucca 06)	Not studied
Phenytoin[2]	Associated with opiate withdrawal[(951)] (Perucca 06)	Not studied
Phenobarbital[2]	Associated with opiate withdrawal[(951)] (Perucca 06)	Not studied
Oxcarbazepine[2]	No clinically significant interaction	No clinically significant interaction
Lamotrigine[2]	No clinically significant interaction	No clinically significant interaction
Topiramate[2]	No clinically significant interaction	
Psychostimulant Medications		
Methylphenidate[2]	No clinically significant interaction	No clinically significant interaction
Pemoline[2]	No clinically significant interaction	No clinically significant interaction
Modafinil[2]	No c clinically significant interaction	No clinically significant interaction
Antihistamines		
Promethazine[2]	May have synergistic depressant effect[(952)] (Sharma 03)	
Diphenhydramine[2]	May have synergistic depressant effect[(952)] (Sharma 03)	
Cardiac and Pulmonary Disease Medications		
Digoxin[2]	Not studied	Not studied
Quinidine[2]	Not studied	Not studied
Verapamil	Not studied	Not studied
Heparin[1]	Not studied	Not studied
Theophylline[2]	Not studied	Not studied
Aspirin[2]	No clinically significant interaction	
Psychostimulants		
Cocaine[2]	Decrease in trough methadone concentrations[(953)] (McCance-Katz 10)	Increased metabolism and diminished plasma concentrations[(954-957)] (McCance-Katz 10; Pellinen 96; Lopez 05; Madden 95)
Methamphetamine[2]	No clinically significant interaction	
Alcohol[2]	Severe adverse events including death,[(958)] (Kreek 84) alcohol appears to be eliminated more frequently.[(959)] (Kreek 81)	Not studied

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

APPENDIX 3: Cytochrome P450 3A4 (2D6) Inhibitors and Inducers

CYP3A4 Inducers Expected to Reduce Opioid Medication Levels				
Carbamazepine Dexamethasone Ethosuximide Primidone Rifabutin Troglitazone	*Statins* Atorvastatin Fluvastatin Lovastatin Simvastatin *Antiretroviral Agents* Efavirenz Lopinavir Nevirapine	*Anticonvulsant Agents* Carbamazepine Oxcarbazepine Phenobarbital Phenytoin Primidone Valproic acid	*Food* Cafestol (caffeine)	*Hypnotic agent* Pentobarbital
CYP3A4 Inhibitors Expected To Increase Opioid Medication Levels				
Amiodarone Cannabinoids Clarithromycin Erythromycin Grapefruit juice Indinavir Norfloxacin Omeprazole (slight) Quinine Saquinavir Troleandomycin Zafirlukast Itraconazole Ketoconazole Metronidazole Mibefradil Miconazole Nefazodone	*CCBs* Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Verapamil *Statin* Simvastatin *Antiarrhythmic Agents* Amiodarone Quinidine *Phosphodiesterase Inhibitor* Tadalafil *Psychiatric Drugs* Bromocriptine Clonazepam Desipramine Fluoxetine Fluvoxamine Haloperidol Nefazodone Norclomipramine Nortriptyline Sertraline	*Chemotherapeutic agents* 4-Ipomeanol Imatinib Irinotecan Tamoxifen *Hormonal therapies* Ethinyl estradiol Levonorgestrel Raloxifene *Other drugs* Cimetidine Disulfiram Methylprednisolone Phenelzine *Foods* Bergamottin (grapefruit juice) Star fruit	*Antibiotics* Ciprofloxacin Clarithromycin Erythromycin Josamycin Norfloxacin Oleandomycin Roxithromycin Telithromycin *Azole Antifungal Agents* Clotrimazole Fluconazole Itraconazole Ketoconazole Miconazole Voriconazole	*Antiretroviral Agents* Amprenavir Atazanavir Delavirdine Efavirenz Indinavir Lopinavir Ritonavir Nelfinavir Nevirapine Saquinavir Tipranavir
Cytochrome P450 2D6 Inducers Expected To Reduce Opioid Medication Levels				
Antibiotic Rifampin	*Glucocorticoid* Dexamethasone			
Cytochrome P450 2D6 Inhibitors Expected To Reduce Opioid Medication Levels				
Antiarrhythmic agents Amiodarone Quinidine *Antipsychotic agents* Chlorpromazine Reduced haloperidol Levomepromazine *SNRI* Duloxetine	*Tricyclic* Clomipramine *Other antidepressant/ antianxiolytic agents* Bupropion Moclobemide *Antihistamine* Chlorpheniramine	*Other drugs* Celecoxib Doxorubicin Ritonavir Terbinafine	*Histamine H2 receptor antagonists* Cimetidine Ranitidine	*SSRIs* Citalopram Escitalopram Fluoxetine Paroxetine Sertraline

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

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

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

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

Acute/Chronic Pain

Author/Year Study Type Potential Conflict of Interest	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Rauck 2006 RCT Funding provided by Ligand Pharmaceuticals Inc. and Organon Pharmaceuticals USA, Inc., in equal parts. Other COIs included consultant and employment positions among 50% of authors.	I(3.5)	N = 392 with chronic moderate to severe chronic LBP, including neuropathic.	Morphine sulfate extended-release capsules (A-MQD) once daily (n = 203) vs. OxyContin extended-release (O-ER) twice a day (n = 189). Adjusted doses. After 3 to 6 weeks of titration phase, subjects entered 8-week evaluation phase, divided into two 4-week periods.	Overall, 32% dropped out. At 6-, 9-, and 12-hour post medication, A-MQD group had decreased absolute pain scores vs. O-ER (p = 0.03, p = 0.005, p = 0.002). Both groups improved sleep scores from baseline, however, A-MQD was significantly improved (p = 0.013) vs. O-ER.	"[T]he ACTION trial demonstrated that SROs are effective agents for the symptomatic management of the majority of patients with chronic, moderate to severe low back pain."	Baseline differences of uncertain significance. Adjusted doses. High dropout (93/203 vs. 79/189). Many weaknesses.
Goebel 2008 RCT Internally funded. No industry sponsorship or COIs.	I(3.5)	N = 18 patients who suffered from chronic pain defined as pain of ≥3 months and with an intensity >3 on standard visual analogue scale.	Patients randomly treated with an injection of buprenorphine plus intramuscular saline (GLOA) or with injection of saline plus intramuscular buprenorphine (SSB). All patients returned after 7 day washout to receive other injection.	No significant differences found between injection types in respect to median relative pin intensities over 8 hours and 6 days.	"In summary, our study designed to test if a clinically observed pain relief after GLOA was in the examined patients related to a specific effect of buprenorphine at the stellate sympathetic ganglion. This was not the case."	Details sparse.
Morley 2003 RCT Funded by grant from the Stanely Thomas Johnson Foundation.	I(3.5)	N = 19 who reported a continuous pattern of pain of central nervous system or peripheral nervous	10mg Methadone vs. placebo (Phase 1) N = 18 for phase 1. Patients received packages containing 2 capsules of 5mg Methadone or matching placebo.	There were statistically significant improvements in three outcomes in Phase 2 of the trial when 20mg of methadone was self administered orally. (1) There was a	"The results of our controlled trial are of interest in that they confirm that methadone does demonstrate an analgesic effect in neuropathic pain, giving some support to our	Small sample size. Many details sparse. Short-term trial.

		system origin. N = 18 patients finished phase 1. N = 17 patients entered phase 2 and only N = 11 patients included in final analysis	20mg Methadone vs. Placebo (Phase 2) N = 11. Patients received packages containing 2 capsules of 10mg or matching placebo. Subjects took pills every other day for 20 days.	VAS reduction in maximum pain intensity of 16.0 (p = 0.013). (2) VAS reduction of average pain intensity of 11.5 (p = 0.02). (3.) Increase in VAS pain relief of 2.16 (p = 0.015). Not the case in Phase 1. No significant improvements on days when 10mg methadone orally administered. In Phase 2 (but not Phase 1) significant analgesic effects also seen on days when participants not orally administering methadone. (1) Lowering of VAS score for maximum pain intensity by 12.02 (p = 0.010). (2) Lowering of VAS score for average pain intensity by 10.46 (p = 0.026). (3.) Increase in VAS score for pain relief of 0.94 (p = 0.025).	rationale for using methadone as an alternative strong opioid in chronic cancer pain."	
Norrbrink 2009 RCT Funded by Norrbacka-Eugenia Foundation. No other mention of industry sponsorship or conflict of interest.	I(3.5)	N = 35 patients with neuropathic pain from spinal cord injury (SCI).	Tramadol 50 mg (n = 23) vs. placebo (n = 12). Study duration, 4 weeks	Adverse events in 21 (91%) in tramadol group and 7 (58%) in placebo (p = 0.02). Tramadol group had significantly improved scores in present pain, general pain, and worst pain (p <0.05) compared to placebo. Compared to placebo, tramadol group had statistically significant improvements regarding global life satisfaction, anxiety, and sleep quality (p < 0.05).	"[P]atients with SCI and neuropathic pain who were randomized to treatment with tramadol significantly improved regarding pain intensity ratings and anxiety ratings compared with those randomized to placebo."	Small sample size. Many details sparse.

Sindrup 1999 RCT Sponsored by Grünenthal GmbH.	I(3.5)	N = 45 patients with poly-neuropathy present for 6 months or longer.	Tramadol titration vs. placebo for 8 weeks.	Side effects were reported in the tramadol group more often than placebo ($p < 0.001$). Pain scores were significantly improved in the tramadol group compared to placebo ($p < 0.001$).	"In the present study, it is unlikely that tramadol side effects had a major influence on results. Side effects were more common during tramadol, but some patients also experienced side effects on placebo and one patient dropped out due to side effects during placebo."	Study includes only polyneuropathy patients.
Wilder-Smith 2005 RCT Sponsorship by Grünenthal GmbH.	I(3.5)	N = 94 patients experiencing pain after amputation.	Tramadol 100mg slow-release (n = 33) vs. Amitriptyline 25mg (n = 30) vs. placebo (n = 31) for 4 weeks.	Change in pain intensity from pretreatment to 1 month not significant between groups for phantom pain or stump pain. Mean (95% CI) from baseline to 1-month for phantom pain in tramadol -40 (-43 to -38), amitriptyline -38 (-39 to -36), and placebo -34 (-54 to -14) and for stump pain, tramadol -38 (-40 to -35), amitriptyline -35 (-38 to -32), and placebo -39 (-66 to -12).	"…Limb pain was almost completely inhibited after initial treatment in 67% of those receiving tramadol, in 83% of those receiving amitriptyline, and in only 3% of those receiving placebo. In the remaining initial nonresponders, similarly good pain relief was achieved after switching to the alternative analgesic."	Data suggest tramadol and amitriptyline comparable.
Zin 2010 RCT Supported by research grant from The Gallipoli Research Trust Foundation, Greenslopes Private Hospital.	I(3.5)	N = 62 with postherpetic neuralgia (PHN) or painful diabetic neuropathy (PDN).	Oxycodone 10mg/day (n = 29) vs. placebo (n = 33) in combination with pregabalin for 4 weeks.	Adverse events in oxycodone (n = 27) and placebo (n = 30) similar. Oxycodone group had significant improvements in cold pain ($p = 0.035$), but placebo showed difference in sharp ($p = 0.035$) and hot pain ($p = 0.042$). No difference between groups in overall concomitant rescue medication of paracetamol ($p > 0.05$).	"[N]o significant difference when a low dose of oxycodone 10mg/day was added to pregabalin. Although a low dose of oxycodone at 10mg/day has been shown to be effective in the treatment of nociceptive pain when combined with other analgesics, there was no apparent additional benefit when administered in combination with pregabalin for the treatment of neuropathic pain in the present study."	Data suggest relatively weak differences.

Thorne 2008 RCT Supported by grant from Purdue Pharma, Canada.	I(3.5)	N = 100 with moderate pain due to hip and/or knee osteoarthritis	Controlled-release tramadol 150 mg, 200mg, 100mg, 400mg (n = 50) vs. placebo (n = 50) for 4 weeks, plus another 4 weeks cross-over.	Total pain/disability scores significantly improved for tramadol group (22.8+/-14.5 (compared to placebo (27.2+/-14.8; p = 0.0004). Overall pain and sleep scores improved from baseline for both tramadol (42.9%; p = 0.0001) and placebo (21.8%; p = 0.0023).	"…Tramadol produced significantly lower scores than placebo in primary and secondary assessments of pain intensity (VAS and ordinal scales, pain intensity questionnaire, WOMAC pain subscale)."	Data suggest lower pain score with tramadol..
Hale 2007a RCT Study protocol was developed by Knoll Pharmaceutical Company; conduct of study supported by Alza Corporation; scientific staff from PharmaGenesis assisted in preparing the first draft of the manuscript and implemented author revisions; 3 of the authors affiliated with Alza Corporation. No COIs declared.	I(3.5)	N = 140 age 18 years and older who met ACR clinical criteria for OA of knee or hip for ≥3 months with a mean daily pain rating at affect joint of moderate to severe despite chronic use of NSAIDs (at least 30 days with no regimen change).	Once-daily controlled-release formulation of OROS hydromorphone taken each morning. OROS hydromorphone started at lowest available dose (8mg); dose increased every 2 days (first to 16mg and then 24, 32, 48, and 64mg) to achieve balance between pain relief and adverse events (n = 71) vs. twice daily extended release (ER) oxycodone taken every 12 hours (8am and 8pm); initial dose 10mg BID (10/10mg) with dose increasing every 2 days (first to 10/20mg then 20/20, 20/30, 30/40, 40/50, 60/60, and 80/80mg) (n = 69). Maximum duration of dose-titration and stabilization phase 14 days. Those who achieved moderate to complete pain relief with final titrated dose for at least 3 days who required ≤64mg a day of OROS hydromorphone or ≤160mg/day of ER	Medical Outcomes Study (MOS) Sleep Problems Index I: less sleep disruption and daytime somnolence in the OROS hydromophone groups (25.7±17.82) vs. ER oxycodone group (35.3±22.56), p <0.012; change from baseline – OROS hydromorphone (-13.3±21.10) vs. ER oxycodone (-5.2±22.09), p<0.045.	"In these patients with chronic pain associated with OA of the knee or hip, once-daily OROS hydromorphone and twice-daily ER oxycodone were associated with comparable relief of chronic moderate to severe pain."	High dropouts. Data suggest comparable efficiency but greater dropouts in hydromorphone.

			oxycodone entered into 28 day maintenance phase. Study 6 weeks.			
Richards 2013 RCT - Open-label 5-center, 3-arm, multiple dose No industry sponsorship. No COIs declared.	I(3.5)	N = 72 ASA physical status I or II patients undergoing major abdominal or orthopedic surgery.	Morphine/ Oxycodone, 3mg/2mg to 24mg/16mg, 1 to 2 tablets (n = 14) vs. Morphine/ Oxycodone, Flexible Dose 3 mg/2 mg, 1 to 2 tablets (n = 15) vs. Oxycodone/ Acetaminophen, 5mg/325mg for up to 24 hours (n = 15). Follow-up time period, 48-72 hours.	Sum of pain intensity scores similar. Brief pain inventory-short form BPI-SF score for pain interfering with general activity significantly lower with morphine/oxycodone than oxycodone/ acetaminophen 5mg/325mg group at 48 hours/early termination, p = 0.023.	"Flexible dose morphine / oxycodone was superior to low-dose morphine / oxycodone and comparable to oxycodone/ acetaminophen."	High dropouts. Short terms trial. Data suggest flexible dose is better. States no COI but 1st 4 and 5 authors employed at Pharmacological Co.
Vevelstad 2009 RCT No industry sponsorship and no disclosed COIs.	I(3.0)	N = 29 with Acute Back Pain.	24-hour treatment C/P (codeine 60mg + paracetamol 1000mg) vs. same regime + L+C/P (levomepromazine 5+5+5+10mg) 4 times daily genotype related EM/HEM for CYP2D6 (n = 12) genotype *1/*4(n = 10/all).	EM/HEM O-demethylation ration (C/P 0.092, 0.041-0.096 vs. L+C/P 0.031, 0.009-0.042; p = 0.016)/(C/P 0.024, 0.011-0.042 vs. 0.026, 0.009-0.041, p = 1.00) combined C/P & L+C/P (p = 0.122) vs. only L+C/P p = 0.011	"No significant difference could be detected in HEM or in the mixed and heterogeneous group of EM/HEM."	Lack of study details. Data suggest codeine not metabolized to morphine in some population when used in conjunction with levomepromazine. Analgesic of this effect is unknown from this study.
Eckhardt 2000 RCT Funding from the Robert Bosch Foundation, Stuttgart; internal standard supplied by Gödecke Parke Davis.	I(3.0)	N = 12 healthy male volunteers	All patients received placebo or active drug followed by washout period and then crossover.	No significant difference between placebo-only group and placebo + GBP (18.9% x h, 95% CI: -2.5 to 40.3). Significant difference between placebo-only groups when compared to morphine + GBP (75.5% x h, 95% CI: 54.0 to 96.9) and morphine + placebo (40.6% x h, 95% CI: 19.2 to 62.0).	"…1) GBP has no analgesic effect on its own after a single oral dose of 600mg in comparison to placebo; 2) GBP significantly enhances the analgesic effects of morphine; and 3) GBP pharmacokinetics, and not morphine pharmaco-kinetics, and metabolism are significantly altered when GBP and morphine are co-administered."	Did not use chronic pain patients, but healthy volunteers. Small sample size crossover study, treatments unclear 1) morphine+gbp, 2) placebo+gbp, 3) placebo+placebo, and 4) morphine+gbp stated in one place, but 4) morphine+placebo stated in another).
Gustin 2010 RCT No industry sponsorship or conflict of interests disclosed.	I(3.0)	N = 20 patients (8 male, 12 female) with a minimum of 6 months pain duration	All patients had minimum wash out period of 2 days. All treated with morphine orally from day 1 to 5 with an intake increase from 10mg to 30mg.	Analysis of Variance (ANOVA) resulted in significant interaction of MEDICATION and TIME for habitual ($F(1,18) = 3.08$, $p < 0.05$) and	"[O]ur data suggest that a combination of morphine with an NMDA-receptor antagonist is more effective for the therapy of neuropathic pain after chronic CRPS	Details sparse.

Funded by a grant from Bundesministerium für Forschung BMBF.		and a pain intensity of at least 3 on a visual analogue scale.	Intake held constant for additional 51 days. On day 8, treatment group (TG, n = 10) received memantine and control group (PG, n = 10) received placebo to be taken orally for total of 49 days. Memantine titrated from 5 to 40mg over 15 days and maintained at 40mg for next 34 days.	movement pain ($F(1,18) = 15.94$, $p < 0.001$). Post-hoc comparisons revealed significant pain decrease for TG with respect to Habitual pain (5.47 to 1.40, $t(9) = 5.31$, $p < 0.001$) and movement pain (8.03 to 2.84, $t(9) = 2.55$, $p < 0.05$). Post-hoc comparisons also showed significant pain decrease for CG with respect for Habitual pain (6.76 to 4.66, $t(9) = 2.55$, $p < 0.05$) but not movement pain.	than morphine alone."	
Max 1988 RCT No mention of industry sponsorship or COIs.	I(2.5)	N = 40 included in this study had daily pain of a least moderate severity that had persisted for 3 months or more, normal cognitive ability to communicate and absence of other pain as severe as PHN	All patients given each of 4 oral treatments. Each treatment given on separate day, at least 48 hours after previous study drug. Patients received all 4 treatments within a 2 to 4 week period. Patients monitored for 6 hours each time they were given a treatment drug. 4 treatment drugs: 0.2mg of clonidine, 120mg of codeine, 800mg of ibuprofen, and 250mg of lactose placebo	ANOVA-RM of hourly scores and 6-hour totals demonstrated significant drug effect ($p < 0.05$) for category relief, category pain, visual analog relief, McGill, and verbal descriptor unpleasantness scales. No significant drug time interactions observed. Newman-Keul's comparison of 6 hour summed scores showed clonidine to be superior to placebo on category of relief and visual analog relief scales ($p < 0.01$) and category pain scale ($p < 0.05$). Clonidine superior to codeine on category relief scale and verbal descriptor unpleasantness scale ($p < 0.05$); 6 hour total relief scores for codeine and ibuprofen did not differ from those for placebo. Normalized average of 6-hour summed relief scores for all 8 scales showed clonidine superior to	"According to the standard procedures used in clinical trials, the outcome is clear: clonidine was superior to placebo in relieving pain, where as codeine and ibuprofen were ineffective."	High dropout rate. Many details sparse.

				placebo (P<0.01) and codeine (P<0.05). Side effects more frequent with clonidine (74%) and codeine (69%) than ibuprofen or placebo. Severity of side effects substantial; >50% described symptoms as moderate or severe after clonidine vs. 8% after placebo.		
Nicholson 2006 RCT Publication support for manuscript from Alpharma Branded Products Division Inc. grant. "Editorial support" provided by Medical Action Communications	I(2.5)	N = 112 with chronic non-malignant moderate to severe pains with VAS pain score ≥4.	Polymer-coated extended-release morphine sulfate (P-ERMS) (n = 53) vs. controlled-released oxycodone HCl (CRO) (n = 59); 6 month treatment period with mail-in questionnaire 3 months post-study.	46% (n = 23) in P-ERMS and 50% (n = 29) in CRO completed study. Both treatment groups had significant decline in pain from baseline to 24 weeks (p <0.05). Mean sleep scores significantly improved in both treatment groups from baseline to 24 weeks (p<0.05). However, comparing the two groups, P-ERMS group significantly better than CRO (p = 0.05).	"[B]oth P-ERMS and CRO were efficacious and well tolerated when used to relieve nonmalignant pain in this community-based population over a 24-week period. Patients demonstrated significant improvements in most quality-of-life, pain and sleep scores, and both patients and clinicians indicated increased satisfaction compared with prior therapy."	High rate of adverse events.
Palangio 2000 RCT Study supported by Knoll Pharmaceutical Company. Apparently all authors employees.	I(2.5)	N = 469 with chronic pain.	Hydrocodone and ibuprofen (7.5mg/200mg) and placebo tablet (HI1) vs. 2 tablets of Hydrocodone and ibuprofen (15mg/400mg) (HI2) vs. 2 tablets codeine and acetaminophen (60mg/600mg) (CA); 4 week study.	All groups had similar discontinuations and adverse events. No differences in overall and weekly pain rating averages between HI1 and CA groups. Average pain rating greater in HI2 group than CA group by end point (p = 0.003).	"2-tablet doses of combination Hydrocodone 7.5mg and ibuprofen 200mg may be more effective than 1-tablet doses off this combination and 2-tablet doses of combination codeine 30mg and acetaminophen 300mg."	Data suggest no differences between groups other than high dose hydrocodone group.
Perruchoud 2011 RCT No mention of industry sponsorship or COIs.	I(2.5)	N = 20 on stable intrathecal therapy for chronic pain. (6 had degenerative spine disease; 5 failed back surgery; 5 peripheral	Three period crossover study: same daily dose was administered at single, double, or quadruple flow rates in randomized sequence, followed by 1 week stabilization.	Mean baseline VAS score 5.1 ± 2.8. No statistical differences on mean pain VAS in 2x flow rate (-6%, 95% confidence interval -18% to 5%; p = 0.29) and 4x's flow rate (0.5%, -20% to 26%; P =	"Despite the impression of many clinicians as well as supporting data from animal experiments showing an increased drug spread with increased flow rate, we have been unable to	Small sample size. Data suggest poor relationship between infusion rate and pain relief.

		neuropathy; 2 CRPS; 1 multiple sclerosis; 1 syringomyelia		0.96) vs.1x's flow rate.	demonstrate an improvement in pain relief that would be expected to occur as a consequence of improved drug spread in the spinal canal."	
Katz 2010 RCT Supported by King Pharmaceuticals, Inc. NK served as a consultant and received research from King Pharmaceuticals, Inc. DM is an employee of WebbWrites, LLC and has provided consulting services to King Pharmaceuticals, Inc. JS was employed, owned stock in, and has a patent pending with Alpharma Pharmaceuticals, LLC a wholly owned subsidiary of King Pharmaceuticals, Inc.	I(2.5)	N = 547 patients (n = 344 who responded to open-label dose titration) who had 0A of hip or knee, required treatment of chronic joint pain within last 90 days and unable to consistently control joint pain with either non-opioid analgesics, tramadol or another opioid at dose equivalent to ≤ 40mg/day of oral morphine.	Patients were randomized into one of two groups. Group 1 (MS-sNT, n = 171) were treated with morphine sulfate and naltrexone hydrochloride extended release capsules for 12 weeks, and were treated with a minimum of 20 mg twice per day. Group 2 (placebo, n = 173) were treated with a dosage titration down to placebo for 12 weeks.	Significant difference between groups with respect to mean change (from baseline) in average-pain scores (Placebo: 0.3 ± 2.1 vs. MS-sNT: -0.2 ± 1.9, p = 0.045), worst pain (Placebo: 0.9 ± 2.0 vs. MS-sNT: 0.3 ± 2.0, p = 0.003), least pain (Placebo: 0.8 ± 1.8 vs. MS-sNT: 0.3 ± 1.8, p = 0.036), average pain (Placebo: 0.9 ± 1.9 vs. MS-sNT: 0.4 ± 2.0, p = 0.026), in-clinic pain (Placebo: 0.7 ± 1.5 vs. MS-sNT: 0.1 ± 1.4, p = 0.001), WOMAC: Composite Index (Placebo: 5.8 ± 16.8 vs. MS-sNT: 1.6 ± 18.0, p = 0.031), and WOMAC: Pain (Placebo: 5.7 ± 17.1 vs. MS-sNT: 1.4 ± 18.9, p = 0.023). After screening, patients entered 1-7 day washout period. Eligible patients entered titration period lasting max 45 days. Maintenance period lasted 12 weeks, those who completed maintenance entered 2-week tapering period.	"In summary, this study demonstrated that 12 weeks of treatment with MS-sNT is significantly more effective than placebo in maintaining pain relief provided by initial dosing of MS-sNT in patients with chronic, moderate-to-severe pain due to OA of the hip of knee."	Details sparse. High dropout, study followed enriched-enrollment randomization study design.
Ashburn 2011 Double-blind crossover RCT Study sponsored by Cephalon, Inc. MA is a shareholder and part-time	I(2.0)	N= 323 with chronic pain >3 months and opioid-tolerant (on stable dose of opioid analgesia >7 days	Fentanyl buccal (FTB) (200, 400, 600, 800mcg) followed by oxycodone (15, 30, 45, 60mg) (n = 183) vs. oxycodone followed by fentanyl buccal (OxyIR) (n = 183)	162 (51%) reported 1+ adverse event and 39 discontinued participation (12%). Only 180 completed both double-blind periods. FBT had significantly improved pain intensity compared to OxyIR from 10	"In this study of opioid-tolerant patients with chronic pain, treatment with FBT for BTP was associated with a more rapid onset of analgesia compared with oxycodone.	No placebo group. Details sparse. High dropout rates despite requirement of opioid-tolerance for enrollment.

employee of ZARS Pharma. JM and FX are employees of Cephalon, Inc.		prior to study).	for treatment of breakthrough pain (BTP). Study included screening period (1-21 days); 2 open-label titration periods (each up to 10 days); and 2 treatment periods (each up to 21 days).	minutes to 60 minutes after administration (p <0.0001).	Differences between FBT and oxycodone were observed in PID (pain intensity difference) from 5 minutes through 60 minutes posttreatment (p<0.05) and in PR (pain relief) from 10 minutes through 60 minutes (p<0.05)."	
Glynn 1988 Crossover RCT No mention of industry sponsorship or COIs.	I(2.0)	N = 20 patients with chronic pain.	Epidural morphine (5mg in 5ml NS) vs. epidural clonidine (150µg in 5 ml NS). Three days later received other solution.	No significant differences found between 2 epidural solutions with respect to analgesic parameters and mood visual analogue scales.	"Thus the evidence from this study and those previously published suggest that epidural clonidine may have a role in the treatment of patients with chronic pain."	Details sparse. Data suggest comparability.
de Beer 2005 RCT Authors AD, GD, LP, JR, ZH, are full-time employees of Purdue Pharma and PM is a past employee and is a paid consultant for Purdue Pharma.	I(1.0)	N = 194 elective primary unilateral total knee or hip replacement secondary to osteoarthritis.	Phase 1 (N = 70; 67.0±9.7 years): controlled release (CR) oxycodone vs. Phase 2 (N = 101; 66.2±9.5 years): standard analgesics, per physician's written orders. Most common regimen acetaminophen plus codeine 300mg/ 30mg; 93 enrolled in Phase 1 and 70 completed study.	Phase 1 VAS scores on day 2 and weeks 1, 2, and 3 (23.8, 31.0, 24.7, and 18.6mm) reduced from baseline (63.3) (p <0.001). VAS scores for phase 1 not different from phase 2 (day 2 and weeks 1, 2, and 3: 37.3, 32.3, 21.2, and 15.6mm) (p = 0.080, p = 0.638, p = 0.252, and p = 0.262).	"CR oxycodone every 12 hours is as effective as ST in treating postoperative pain but length of hospital stay was shorter and analgesic administration in the hospital was used less frequently."	Sparse details. Combined 2 studies in 1 report. Neither well described. Data suggest comparable clinical efficacy. Suggest more efficient with reduced costs.
Friedmann 2011 Long-term safety trial Conflicts of Interest: N. Friedmann and V. Klutzaritz employed by, and L. Webster was Principal Investigator for, trial support Pain Therapeutics, Inc. Writing support by others including one with apparent	III	N = 823 with moderate to severe hip and/or knee pain caused by osteoarthritis or persistent moderate to severe low back pain.	All received Remoxy 5mg (extended-released oxycodone).	Use of other opioid and pain medications prohibited. Patients could take analgesics (NSAIDs or acetaminophen) PRN. Only 380 (46.1%) completed 12-month trial. Large number, 92.7% (n = 723), reported adverse event, with GI distress (n = 823 events) most common. Pain intensity reduced vs. baseline (p < 0.001).	"This open-label study indicates that long-term use of Remoxy (oxycodone extended release) is safe and generally well tolerated in patients with chronic, moderate to severe pain from osteoarthritis of the hip and/or knee or chronic low back pain."	Not randomized, no control group, high dropout rate, and only one study drug used. 443/823 discontinued altogether.

industry employment.						
Breckenridge 2003 Retro-spective comparative study No mention of industry sponsorship or COIs.	III	N = 200 with chronic LBP.	Group N-long term NSAID (n = 100) vs. Group O-long-term opioids (n = 100) at least once per-month for at least 5 of 6 months both groups.	Group O vs. N active prescriptions 14.3±5.8 vs. 12.0±8.1. Substance abuse / personality disorder and age; (p <0.001) / (p = 0.09 & 0.06).	"Regression analysis was performed, which resulted in the identification of 4 variables of age, depression, personality disorder, and history of substance abuse as being closely linked to the use of opioids for the treatment of back pain in preference to non-steroidal anti-inflammatory drugs alone."	Non-randomized comparative study. Data suggest opioids associated with substance abuse and personality disorders.

Adverse Events

Name/Year Location Potential Conflict of Interest	Score (0-11)	Study Design	Exposure	Population Age Range Dropout Rate Case Definition	Results	Conclusion	Comments
Depression/Anxiety							
Emrich 1982 Germany No mention of industry sponsorship or COIs.	I(2.5)	N = 10 severely depressed patients, in a crossover double-blind clinical trial.	Buprenorphine (B) vs. placebo (A1 and A2). A1: 1-7 days; B: 5-8 days; A2: 0-4 days. A 4 day wash-out period preceded the trial.	N = 10 who met the research diagnostic criteria for major depressive disorder, and were free from thymoleptic drugs. Psychological evaluation was performed every 2 days using IMPS and the Hamilton scale of depression.	Hamilton scores during B1-B3 (buprenorphine phases) were strongly reduced in comparison with phases A1 (placebo before buprenorphine), and to a lesser degree to A2 (placebo after buprenorphine) ($p \leq 0.02$). 50% responded very strongly to buprenorphine and 50% did not respond.	"[T]he mixed opiate agonist/antagonist buprenorphine exhibits anti-depressant properties in cases not responding to conventional thymoleptic therapy."	Sparse details. Small sample size.
Post-operative Sleep Disturbances							
Cronin 2001 RCT Supported by the Anesthesia Patient Safety Foundation and the General Clinical Research Center at the Hershey Medical Center.	I(3.5)	Post-operative sleep disturbance	Fentanyl group (n = 6) vs. Bupivacaine (n = 4). No drop-outs.	N = 10 female patients ages 29-39 with benign gynecologic disease requiring surgery via low abdominal incision. Test hypothesis that opioids independently contribute to post-operative sleep disturbance.	Differences in % REM (6.5% vs. 8.9%) and % Slow Wave Sleep (SWS) (10.6% vs. 18.8%) on pre-operative night between fentanyl and bupivacaine, respectively. No significant change in subjective sleep quality.	"REM sleep and SWS were reduced in the early postoperative period."	Small sample size. Pilot study data suggest differences in REM sleep with fentanyl vs. bupivacaine.

APPENDIX 5: Randomized Controlled Trials with Malignant Pain

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

Author/Year Study Type Potential Conflict of Interest	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Ahmedzai 2011 RCT Study and editorial assistance funded by Mundipharma Research GmbH & Co. SA received research funding, honoraria, provided consultancies and participated in advisory boards for Archimedes, Cephalon, Grunenthal, Janssen Cilag, Mundipharma, Pfizer, Prostrakan and Wyeth. FN received honoraria, provided consultancies and/or participated in advisory boards for Archimedes, Cephalon, Grünenthal, Janssen, Mundipharma, Nycomed, Sanofi-Aventis and Wyeth. MH, PL, and BB are employees of Mundipharma Research GmbH & Co.	I(3.5)	N = 185 patients with chronic cancer pain.	120mg/day oxycodone/naloxone prolonged-release (OXN PR) (n = 92) vs. oxycodone prolonged-release tablets (OxyPR) (n = 92). Trial lasted 4 weeks.	High dropout rates for both groups OXN PR (n=26; 28%) and OxyPR (n=25; 27%). Both groups had similar adverse events. Patient assessment of constipation was significantly better in the OXN PR group compared to OxyPR ($p<0.01$).	"[O]XN PR provides comparable analgesia to OxyPR for patients with moderate/severe cancer pain, whilst significantly improving bowel function and reducing symptoms of constipation."	Study did not measure pain, but constipation, safety, and efficacy.
Mercadante 2000 RCT No mention of industry sponsorship.	I(3.5)	N = 10 cancer patients whose pain was unrelieved by morphine and a Krnofsky	On 3 separate days at least 2 days apart subjects received each of the three treatment drugs considered as a slow intravenous	Wilcoxon signed-rank test used to compare pain intensity, symptom intensity scores and MMSE. Friedman test used to compare pain intensity, symptom intensity	"In conclusion, ketamine improves morphine analgesia in difficult pain syndromes, namely neuropathic pain."	Small sample size, high adverse events.

		status for 50 or more	bolus administered in about 30 minutes. 3 treatment drugs: 0.25mg/kg Ketamine Hydrochloride, 0.50mg/kg Ketamine Hydrochloride, Placebo.	scores and MMSE in different treatments. A highly significant decrease in pain intensity found when comparing Ketamine to saline. Those treated with 0.50mg/kg Ketamine had more relevant analgesic effect than patient who received 0.25mg/kg ($p < 0.05$) Both 0.5mg/kg and 0.25mg/kg Ketamine injections produced central adverse effects in 4 of 10 subjects.		
Arai 2010 RCT No mention of industry sponsorship or COIs.	I(3.0)	N = 52 cancer patients with neuro-pathic pain	Gabapentin 200mg and imipramine 10mg every 12 hours (G400-1 group) (n = 14) vs. gabapentin 200mg every 12 hours (G400 group) (n = 14) vs. gabapentin 400mg every 12 hours (G800 group) vs. imipramine 10mg every 12 hours (I group) (n = 12). 7 day trial.	No difference between groups for adverse events, except for the G800 group (n = 15 dizziness; $p < 0.01$). The G400-I group had significantly less opioid rescue doses compared to the other groups ($p = 0.008$) and significantly lower pain scores ($p < 0.05$).	"[T]he combination of low-dose gabapentin and imipramine more effectively alleviated cancer pain than gabapentin or imipramine alone. Furthermore, gabapentin 200mg and imipramine 10mg every 12 h were more effective than gabapentin 400mg every 12 h."	No placebo group. Few details, only among cancer patients with chronic pain.
Slatkin 2007 RCT Study was supported by Cephalon, Inc.	I(2.5)	N = 129 with cancer-related break-through pain (BTP) and a life expect-ancy of 2 months	Randomized into 1 of 18 prespecified sequences with 10 tablets: 7 Fentanyl buccal tablet (FBT) plus 3 placebos taken in consecutive order. Titration phase approximately 7 days. Patients were allowed up to 3 weeks to complete treatment phase.	BPT episodes with improvement in pain intensity scores was significantly better in the FBT group compared to placebo for every time point after administration except for 5-minutes ($p<0.05$). By 120 minutes post-administration, the FBT group had greater pain relief ($p<0.0001$).	"[T]he efficacy and tolerability of FBT in the management of opioid-tolerant patients with BTP associated with chronic cancer pain. It is the first study to demonstrate relief of BTP at 10 minutes that is sustained up to 2 hours post dose, providing evidence for the rapid onset of action and sustained effect of	Cancer pain study of break-through pain.

					FBT in this patient population."	
Rodriguez 2008 RCT Supported by a research grant from the Universidad Libre Seccional Cali. Drugs supplied by Grünenthal and Librapharma.	I(1.5)	N = 118 with moderate to severe chronic cancer pain	Hydrocodone/ Acetaminophen (n = 62): group received 2500mg/day of hydrocodone/ Acetaminophen Tramadol Chlorohydrate (n = 56): group received 200mg a day of tramadol chlorohydrate. 23 day study period.	Pain relief experienced by 73% of patients who received tramadol and 71% using hydrocodone/APA. Differences in pain relief not significant between 2 groups (X^2 = 0.07 and p = 0.786). Participants receiving a starting dose of tramadol presented a significant increase in side effects when compared to patients receiving starting dose of hydrocodone. (See Table 2 for p values of specific side effects).	"This study showed analgesic effects of the studied drugs are similar with some important differences in their collateral effects nausea, vomiting, dizziness, loss of appetite, and weakness."	Cancer pain with comparable pain relief.
Stambaugh 1987 RCT/Cross-over Supported by a grant from Wyeth Laboratories. No other COIs disclosed.	I(1.5)	N = 43 with moderate to severe chronic pain from primary or metastatic malig-nancy of bone or major organs.	Four-way crossover randomized into: Ciramadol 30mg (n = 43) vs. ciramadol 90mg (n = 43) vs. codeine (60mg) (n = 43) vs. placebo (n = 43). Single-dose study.	Ciramadol 90mg had significantly greater pain relief compared to placebo (p <0.01) and codeine and ciramadol 30mg (p <0.05). The codeine and ciramadol 30mg groups had similar pain relief and both were significantly better than placebo (p<0.05).	"[C]iramadol appears to have single-dose efficacy in relieving chronic moderate to severe pain of cancer. The 30mg dose of ciramadol was equivalent to 60mg of codeine, and 90mg of ciramadol was superior, indicating that the drug may be alternative to long-term use of opioid drugs in these patients."	Cancer pain. Higher dose had greater pain relief.

APPENDIX 6: PICO Questions

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

Appendix 7: List of Abbreviations

BTP Break-Through Pain

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

CLIA Clinical Laboratory Improvement Amendments

CNS Central Nervous System

COMM Current Opioid Misuse Measure

COPD Chronic Obstructive Pulmonary Disease

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

ECG Electro-Cardiogram (same as EKG, electrokardiogram)

GC/MS Gas Chromatography Mass Spectrometry

GCPS Graded Chronic Pain Scale

LC/MS Liquid Chromatography Mass Spectrometry

MED Morphine Equivalent Dose (equivalent to MME)

MME Morphine Milligram Equivalents (equivalent to MED)

NSAID Nonsteroidal Anti-Inflammatory Drug

ORT Opioid Risk Tool

PCA Patient-Controlled Analgesia

PDMP Prescription Drug Monitoring Program

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

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

PNS Periphernal Nervous System

POC Point of Care

POMI Prescription Opioid Misuse Index

PTSD Post-Traumatic Stress Disorder

RCT Randomized Controlled Trial

SIMP Structured Intensive Multidisciplinary Program

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

UDS Urine Drug Screen (same as UDT)

UDT Urine Drug Test (same as UDS)

WHYMPI West Haven-Yale Multidimensional Pain Inventory

References

1. Food and Drug Administration. Letter to Dr. Andrew Kolodny in Response to the Citizen Petition Submitted by Physicians for Responsible Opioid Prescribing. 2013.
2. International Association for the Study of Pain. Definition of pain. 1994.
3. Melhorn J, Talmage J, Ackerman III W, Hyman M. *AMA Guides® to the Evaluation of Disease and Injury Causation, second edition*. Chicago, IL: American Medical Association; 2014.
4. Center for the Evaluative Clinical Sciences. Spine surgery. A Report by the Dartmouth Atlas of Health Care. CMS-FDA Collaborative. 2006.
5. Centers for Disease Control and Prevention. Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. *MMWR*. 2011;60(43):1487-92.
6. Centers for Disease Control and Prevention (CDC). Vital signs: risk of overdose from methadone used for pain relief-United States, 1999-2010. *MMWR*. 2012;61:493-7.
7. The AGREE Research Trust. Appraisal of Guidelines for Research & Evaluation II (AGREE II) Instrument. 2009.
8. American College of Occupational and Environmental Medicine. Methodology for the Update of the Occupational Medicine Practice Guidelines. Available at: www.acoem.org/uploadedFiles/Knowledge_Centers/Practice_Guidelines/ACOEM%20Practice%20Guidelines%20Methodology.pdf. 2006.
9. Harris JS, Sinnott PL, Holland JP, et al. Methodology to update the practice recommendations in the American College of Occupational and Environmental Medicine's Occupational Medicine Practice Guidelines, second edition. *J Occup Environ Med*. 2008;50(3):282-95.
10. American College of Occupational and Environmental Medicine. Summary: Methodology for Updates to the ACOEM Practice Guidelines. Available at: www.acoem.org/guidelines_summary.aspx. 2006.
11. Talmage J, Andersson G, Carragee E, et al. Chapter 8: Cervical and thoracic spine disorders. In: Hegmann K, ed. *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery in Workers, 3rd ed*. Elk Grove Village, Ill: American College of Occupational and Environmental Medicine; 2011.
12. Talmage J, Belcourt R, Galper J, et al. Chapter 9: Low back disorders. In: Hegmann K, ed. *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery in Workers, 3rd ed*. Elk Grove Village, Ill: American College of Occupational and Environmental Medicine; 2011.
13. Genovese E, Korevaar W, Mueller K, Aronoff G, Bruns D, et al. Chapter 10: Chronic pain. In: Hegmann K, ed. *ACOEM's Occupational Medicine Practice Guidelines, 3rd ed*. Elk Grove Village, IL: American College of Occupational and Environmental Medicine; 2011.
14. Kaufman L, Green A, Haas N, et al. Chapter 11: Shoulder disorders. In: Hegmann K, ed. *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery in Workers, 3rd ed*. Elk Grove Village, Ill: American College of Occupational and Environmental Medicine; 2011.
15. Hoffman H, Belcourt R, Byrne K, et al. Chapter 12: Elbow disorders. In: Hegmann K, ed. *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery in Workers, 3rd ed*. Elk Grove Village, Ill: American College of Occupational and Environmental Medicine; 2011.
16. Melhorn J, Arbesman M, Franzblau A, et al. Chapter 13: Hand, wrist, and forearm disorders. In: Hegmann K, ed. *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery in Workers, 3rd ed*. Elk Grove Village, Ill: American College of Occupational and Environmental Medicine; 2011.
17. McKenzie J, Jacobs J, Caruso G, et al. Chapter 14: Hip and groin disorders. In: Hegmann K, ed. *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery in Workers,3rd ed*. Elk Grove Village, Ill: American College of Occupational and Environmental Medicine; 2011.
18. Lichtblau E, Coward D, Howell S, et al. Chapter 15: Knee disorders. In: Hegmann K, ed. *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery in Workers,3rd ed*. Elk Grove Village, Ill: American College of Occupational and Environmental Medicine; 2011.
19. Haas N, Beecher P, Easly M, et al. Chapter 16: Ankle and foot disorders. In: Hegmann K, ed. *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery in Workers, 3rd ed*. Elk Grove Village, Ill: American College of Occupational and Environmental Medicine; 2011.
20. Institute of Medicine. Standards for Developing Trustworthy Clinical Practice Guidelines. Available at: http://www.iom.edu/~/media/Files/Report%20Files/2011/Clinical-Practice-Guidelines-We-Can-Trust/Clinical%20Practice%20Guidelines%202011%20Insert.pdf. 2011.
21. Rogak L, Starr T, Kirsh K, Passik S. Chapter 32. The psychology of addiction. In: Fishman S, Ballantyne J, Rathmell J, eds. *Bonica's Management of Pain, Fourth Edition*. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.
22. Corsini E, Zacharoff K. Definitions related to aberrant drug-related behavior: Is there correct terminology. Available at: http://www.painedu.org/articles_timely.asp?ArticleNumber=58. 2011.
23. WebMD. Drug Abuse, Addiction, and the Brain. Available at: http://www.webmd.com/mental-health/drug-abuse-addiction. 2012.
24. Goodman A. Addiction: definition and implications. *Br J Addict*. 1990;85(11):1403-8.

25. Lynch N, Clay R, Hegmann K, Greaves W, Gold J. Advocagenic illness: a new name for an old phenomenon. *Legal Med Perspectives*. 1998;5(4):1-2.
26. Dugdale D, Zieve D. Drug dependence. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002490/. *Pub Med Health*. 2010.
27. Merriam-Webster Dictionary. Iatrogenesis. Available at: http://www.merriam-webster.com/ medical/ iatrogenesis.
28. Illich I. Chapter 2. The medicalization of life. *Medical Nemesis: The Expropriation of Health* 1982.
29. Moynihan R, Heath I, Henry D. Selling sickness: the pharmaceutical industry and disease mongering. *BMJ*. 2002;324(7342):886-91.
30. Merriam-Webster Dictionary. Medicalize. Available at: http://www.merriam-webster.com/dictionary/medicalize.
31. U. S. Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse. NIH Publication Number 11-4881- Research Report Series: Prescription Drugs: Abuse and Addiction. Available at: http://www.drugabuse.gov/sites/default/files/rrprescription.pdf. October 2011.
32. Stayner RS, Copenhaver DJ. Opioids, pain management and the law. *Curr Opin Anaesthesiol*. 2012;25(5):566-71.
33. Portenoy R, Foley K. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain*. 1986;25(2):171-86.
34. Bannwarth B. Risk-benefit assessment of opioids in chronic noncancer pain. *Drug Safety*. 1999;21(4):283-96.
35. Bovill JG. Which potent opioid? Important criteria for selection. *Drugs*. 1987;33(5):520-30.
36. Rupp T, Delaney KA. Inadequate analgesia in emergency medicine. *Ann Emerg Med*. 2004;43(4):494-503.
37. State of Oregon Board of Medical Examiners vs. Paul Andre Bilder M. Stipulated Order. 1999.
38. Hoffmann D, Tarzian A. Achieving the right balance in oversight of physician opioid prescribing for pain: the role of State Medical Boards. *J Law Med Ethics*. 2003;3121-40.
39. 27 T. Jefferson L. Rev. 133 2004-2005.
40. Garcia AM. State laws regulating prescribing of controlled substances: balancing the public health problems of chronic pain and prescription painkiller abuse and overdose. *J Law Med Ethics*. 2013;41 Suppl 142-5.
41. Department of Veterans Affairs. Pain as the 5th Vital Sign Toolkit. Washington, DC; 2000.
42. Merboth M, Barnason S. Managing pain: the fifth vital sign. *Nursing Clin North Am*. 2000;35(2):375-83.
43. Berry PH, Dahl JL. The new JCAHO pain standards: implications for pain management nurses. *Pain Manag Nurs*. 2000;1(1):3-12.
44. Joint Commission for the Accreditation of Healthcare Organizations. www.jointcommission.org/pain_management/. 2013.
45. Utah Department of Health. *Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain*. Salt Lake City, UT: Utah Department of Health; 2009.
46. Yamaguchi T, Shima Y, Morita T, Hosoya M, Matoba M. Clinical guideline for pharmacological management of cancer pain: the Japanese society of palliative medicine recommendations. *Jpn J Clin Oncol*. 2013;43(9):896-909.
47. Abdulla A, Adams N, Bone M, et al. Guidance on the management of pain in older people. *Age Ageing*. 2013;42 Suppl 1i1-57.
48. Furlan A, Reardon R, Weppler C. Opioids for chronic noncancer pain: a new Canadian practice guideline *Cmaj*. 2010;doi:10.1503/cmaj.100187.
49. Washington State Department of Labor & Industries, Washington Agency Medical Directors' Group. Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain: An educational aid to improve care and safety with opioid therapy, 2010 Update. 2010.
50. Medical Board of California, Department of Consumer Affairs. Guidelines for Prescribing Controlled Substances for Pain. 2007.
51. Canada: National Opioid Use Guideline Group (NOUGG). Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain. Available at: http://nationalpaincentre.mcmaster.ca/opioid/. 2010.
52. Hawkins EJ, Malte CA, Imel ZE, Saxon AJ, Kivlahan DR. Prevalence and trends of benzodiazepine use among Veterans Affairs patients with posttraumatic stress disorder, 2003-2010. *Drug Alcohol Depend*. 2012;124(1-2):154-61.
53. Warner EA. Opioids for the treatment of chronic noncancer pain. *Am J Med*. 2012;125(12):1155-61.
54. Turk DC, O'Connor AB, Dworkin RH, et al. Research design considerations for clinical studies of abuse-deterrent opioid analgesics: IMMPACT recommendations. *Pain*. 2012;153(10):1997-2008.
55. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res* 2012;64(4):465-74.
56. Peppin JF, Passik SD, Couto JE, et al. Recommendations for urine drug monitoring as a component of opioid therapy in the treatment of chronic pain. *Pain Med*. 2012;13(7):886-96.
57. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol*. 2012;13(2):e58-68.
58. Fallon M, Reale C, Davies A, et al. Efficacy and safety of fentanyl pectin nasal spray compared with immediate-release morphine sulfate tablets in the treatment of breakthrough cancer pain: a multicenter, randomized, controlled, double-blind, double-dummy multiple-crossover study. *J Support Oncol*. 2011;9(6):224-31.

59. Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2--guidance. *Pain Physician*. 2012;15(3 Suppl):S67-116.
60. Manchikanti L, Helm Sn, Fellows B, et al. Opioid epidemic in the United States. *Pain Physician*. 2012;15(3 Suppl):ES9-38.
61. Office of The Army Surgeon General, Pain Management Task Force. Providing a Standardized DoD and VHA Vision and Approach to Pain Management to Optimize the Care for Warriors and their Families. 2010.
62. American Society of Anesthesiologists Task Force on Chronic Pain Management. 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. *Anesthesiology*. 2010;112(4):1-24.
63. The Royal Australasian College of Physicians. Prescription Opioid Policy: Improving management of chronic non-malignant pain and prevention of problems associated with prescription opioid use. 2009.
64. U.S. Veterans Affairs Administration. Clinical Practice Guideline: Management of Opioid Therapy for Chronic Pain. Available at: http://www.healthquality.va.gov/COT_312_Full-er.pdf. 2010.
65. Washington State Department of Labor & Industries. Guideline for Prescribing Opioids to Treat Pain in Injured Workers. 2013.
66. Albert S, Brason II F, Sanford C, et al. Project Lazarus: Community-based overdose prevention in rural North Carolina. *Pain Med*. 2011;12 (Suppl s2):S77-S85.
67. Kahan M, Mailis-Gagnon A, Wilson L, Srivastava A. Canadian guidelines for safe and effective use of opioids for chronic noncancer pain. Clinical summary for family physicians. Part 1: general population. *Canadian Family Physician*. 2011;57(11):1257-66.
68. Kahan M, Wilson L, Mailis-Gagnon A, Srivastava A. Canadian guideline for safe and effective use of opioids for chronic noncancer pain. Clinical summary for family physicians. Part 2: special populations. *Canadian Family Physician*. 2011;57(11):1269-76.
69. Bril V, England J, Franklin GM, et al. 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. *Neurology*. 2011;76(20):1758-65.
70. Chapman CR, Lipschitz DL, Angst MS, et al. Opioid pharmacotherapy for chronic non-cancer pain in the United States: a research guideline for developing an evidence-base. *J Pain*. 2010;11(9):807-29.
71. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10(2):113-30.
72. Federation of State Medical Boards. Model Policy on the Use of Opioid Analgesics in the Treatment of Chronic Pain. 2013.
73. Caudill-Slosberg MA, Schwartz LM, Woloshin S. Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 vs. 2000. *Pain*. 2004;109(3):514-9.
74. Franklin GM, Mai J, Wickizer T, Turner JA, Fulton-Kehoe D, Grant L. Opioid dosing trends and mortality in Washington State workers' compensation, 1996-2002. *Am J Ind Med*. 2005;48(2):91-9.
75. Volkow N, McLellan T. Curtailing diversion and abuse of opioid analgesics without jeopardizing pain treatment *Jama*. 2011;305(13):1346-7.
76. Parsells Kelly J, Cook SF, Kaufman DW, Anderson T, Rosenberg L, Mitchell AA. Prevalence and characteristics of opioid use in the US adult population. *Pain*. 2008;138(3):507-13.
77. Substance Abuse and Mental Health Services Administration. Federal Guidelines for Opioid Treatment. 2013.
78. Centers for Disease Control and Prevention. Adult Use of Prescription Opioid Pain Medications - Utah, 2008. *MMWR*. 2010;59(6):153-7.
79. Centers for Disease Control and Prevention. Emergency department visits involving nonmedical use of selected prescription drugs - United States, 2004-2008. *MMWR*. 2010;59(23):705-9.
80. Coben JH, Davis SM, Furbee PM, Sikora RD, Tillotson RD, Bossarte RM. Hospitalizations for poisoning by prescription opioids, sedatives, and tranquilizers. *Am J Prev Med*. 2010;38(5):517-24.
81. Kress HG, Kraft B. Opioid medication and driving ability. *Eur J Pain*. 2005;9(2):141-4.
82. Gomes T, Redelmeier DA, Juurlink DN, Dhalla IA, Camacho X, Mamdani MM. Opioid dose and risk of road trauma in Canada: a population-based study. *JAMA Intern Med*. 2013;173(3):196-201.
83. Gibson JE, Hubbard RB, Smith CJ, Tata LJ, Britton JR, Fogarty AW. Use of self-controlled analytical techniques to assess the association between use of prescription medications and the risk of motor vehicle crashes. *Am J Epidemiol*. 2009;169(6):761-8.
84. Engeland A, Skurtveit S, Morland J. Risk of road traffic accidents associated with the prescription of drugs: a registry-based cohort study. *Ann Epidemiol*. 2007;17(8):597-602.
85. Dubois S, Bedard M, Weaver B. The association between opioid analgesics and unsafe driving actions preceding fatal crashes. *Accid Anal Prev*. 2010;42(1):30-7.
86. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Res Ther*. 2005;7(5):R1046-51.
87. Howard ME, Desai AV, Grunstein RR, et al. Sleepiness, sleep-disordered breathing, and accident risk factors in commercial vehicle drivers. *Am J Respir Crit Care Med*. 2004;170(9):1014-21.

88. Talmage J, Melhorn J, Hyman M. Chapter 9. Medications, Driving, and Work. In: Talmage J, Melhorn J, Hyman M, eds. *AMA Guides (TM) to the Evaluation of Work Ability and Return to Work Second Edition*. Chicago, IL: American Medical Association; 2011.
89. Warner M, Chen L, Makuc D, Anderson R, Minino A. Drug poisoning deaths in the United States, 1980-2008. *NCHS Data Brief*. 2011;No. 81.
90. Rosenblatt RA, Catlin M. Opioids for chronic pain: first do no harm. *Ann Fam Med*. 2012;10(4):300-1.
91. Campbell CI, Weisner C, Leresche L, et al. Age and gender trends in long-term opioid analgesic use for noncancer pain. *Am J Public Health*. 2010;100(12):2541-7.
92. Kuehn B. Safety plan for opioids meets resistance opioid-linked deaths continue to soar. *Jama*. 2010;303(6):495-7.
93. Piercefield E, Archer P, Kemp P, Mallonee S. Increase in unintentional medication overdose deaths: Oklahoma, 1994-2006. *Am J Prev Med*. 2010;39(4):357-63.
94. Al-Asmari AI, Anderson RA. The role of dihydrocodeine (DHC) metabolites in dihydrocodeine-related deaths. *J Anal Toxicol*. 2010;34(8):476-90.
95. Al-Asmari AI, Anderson RA, Cooper GA. Oxycodone-related fatalities in the west of Scotland. *J Anal Toxicol*. 2009;33(8):423-32.
96. Dhalla IA, Mamdani MM, Sivilotti ML, Kopp A, Qureshi O, Juurlink DN. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *Cmaj*. 2009;181(12):891-6.
97. Porucznik CA, Johnson EM, Sauer B, Crook J, Rolfs RT. Studying adverse events related to prescription opioids: the Utah experience. *Pain Med*. 2011;12 Suppl 2S16-25.
98. Tanne JH. Deaths from prescription opioids soar in New York. *BMJ*. 2013;346f921.
99. Centers for Disease Control and Prevention. Alcohol and Other Drug Use Among Victims of Motor-Vehicle Crashes–West Virginia, 2004-2005. *MMWR*. 2006;55(48):1293-6.
100. Warner M, Chen L, Makuc D. Increase in Fatal Poisonings Involving Opioid Analgesics in the United States, 1999–2006. *NCHS Data Brief*. 2009;22.
101. Kuehn BM. Methadone overdose deaths rise with increased prescribing for pain. *Jama*. 2012;308(8):749-50.
102. Hall A, Logan J, Toblin R, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *Jama*. 2008;300(22):2613-20.
103. Mack K, Jones C, Paulozzi L. Vital Signs: Overdoses of Prescription Opioid Pain Relievers and Other Drugs Among Women - United States, 1999-2010. *MMWR*. 2013;62(26):537-42.
104. Wunsch M, Nakamoto K, Behonick G, Massello W. Opioid deaths in rural Virginia: a description of the high prevalence of accidental fatalities involving prescribed medications. *Am J Addict*. 2009;18(1).
105. Green TC, Grau LE, Carver HW, Kinzly M, Heimer R. Epidemiologic trends and geographic patterns of fatal opioid intoxications in Connecticut, USA: 1997-2007. *Drug Alcohol Depend*. 2011;115(3):221-8.
106. Ohio Department of Health, Violence and Injury Prevention Program. Epidemic of Prescription Drug Overdose in Ohio. Available at:

http://www.healthy.ohio.gov/vipp/data/~/media/B36238B3B2C746308AA51232575613DD.ashx. Accessed November 7, 2013.
107. Lanier W. Prescription opioid overdose deaths - Utah, 2008-2009. *Presented at the 59th Annual Epidemic Intelligence Service Conference Atlanta, GA, April 19-23, 2010*.
108. Paulozzi L, Baldwin G, Franklin G, et al. CDC Grand Rounds: Prescription Drug Overdoses-a U.S. Epidemic. *MMWR*. 2012;61(1):10-3.
109. Cheng M, Sauer B, Johnson E, Porucznik C, Hegmann K. Comparison of opioid-related deaths by work-related injury. *Am J Industrial Med*. 2013;56308-16.
110. Bernacki EJ, Yuspeh L, Lavin R, Tao XG. Increases in the use and cost of opioids to treat acute and chronic pain in injured workers, 1999 to 2009. *J Occup Environ Med*. 2012;54(2):216-23.
111. Vogt M, Kwoh K, Cope D, Osial T, Culyba M, Starz T. Analgesic usage for low back pain: impact on health care costs and service use. *SPINE*. 2005;30(9):1075-81.
112. Volinn E, Fargo JD, Fine PG. Opioid therapy for nonspecific low back pain and the outcome of chronic work loss. *Pain*. 2009;142(3):194-201.
113. Birnbaum H, White A, Schiller M, et al. Societal costs of opioid abuse, dependence, and misuse in the United States. *Pain Med*. 2011;12(4):657–67.
114. Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. *Pain Med*. 2005;6(2):107-12.
115. International Association of Industrial Accident Boards and Commissions. Reducing Inappropriate Opioid Use in Treatment of Injured Workers. A Policy Guide. 2013.
116. Webster LR. Eight principles for safer opioid prescribing. *Pain Med*. 2013;14(7):959-61.
117. Jovey RD. Use of opioid analgesics for the treatment of chronic noncancer pain--a consensus statement and guidelines from the Canadian Pain Society, 2002. *Pain Res Manag*. 2002;Spring(8):3A-28A.
118. Mahowald ML, Singh JA, Majeski P. Opioid use by patients in an orthopedics spine clinic. *Arthritis Rheum*. 2005;52(1):312-21.
119. Saper J, Lake III A. Sustained opioid therapy should rarely be administered to headache patients: clinical observations, literature review, and proposed guidelines. *Headache Currents*. 2006;3(3):67-70.

120. Reneman MF, Jorritsma W, Schellekens JM, Goeken LN. Concurrent validity of questionnaire and performance-based disability measurements in patients with chronic nonspecific low back pain. *J Occup Rehabil*. 2002;12(3):119-29.
121. Graziotti P, Goucke R, for the Directors of the Australian Pain Society. *The use of oral opioids in patients with chronic nonmalignant pain: Management strategies*. Perth, Australia: Australian Pain Society; 2002.
122. Majdzadeh R, Feiz-Zadeh A, Rajabpour Z, et al. Opium consumption and the risk of traffic injuries in regular users: a case-crossover study in an emergency department. *Traffic Inj Prev*. 2009;10(4):325-9.
123. Meuleners LB, Duke J, Lee AH, Palamara P, Hildebrand J, Ng JQ. Psychoactive medications and crash involvement requiring hospitalization for older drivers: a population-based study. *J Am Geriatr Soc*. 2011;59(9):1575-80.
124. Leveille SG, Buchner DM, Koepsell TD, McCloskey LW, Wolf ME, Wagner EH. Psychoactive medications and injurious motor vehicle collisions involving older drivers. *Epidemiology*. 1994;5(6):591-8.
125. Ray WA, Fought RL, Decker MD. Psychoactive drugs and the risk of injurious motor vehicle crashes in elderly drivers. *Am J Epidemiol*. 1992;136(7):873-83.
126. Bramness JG, Skurtveit S, Morland J, Engeland A. An increased risk of motor vehicle accidents after prescription of methadone. *Addiction*. 2012;107(5):967-72.
127. Morland J, Steentoft A, Simonsen KW, et al. Drugs related to motor vehicle crashes in northern European countries: a study of fatally injured drivers. *Accid Anal Prev*. 2011;43(6):1920-6.
128. Mura P, Kintz P, Ludes B, et al. Comparison of the prevalence of alcohol, cannabis and other drugs between 900 injured drivers and 900 control subjects: results of a French collaborative study. *Forensic Sci Int*. 2003;133(1-2):79-85.
129. Linnoila M, Hakkinen S. Effects of diazepam and codeine, alone and in combination with alcohol, on simulated driving. *Clin Pharmacol Ther*. 1974;15(4):368-73.
130. Galski T, Williams JB, Ehle HT. Effects of opioids on driving ability. *J Pain Symptom Manage*. 2000;19(3):200-8.
131. Sabatowski R, Schwalen S, Rettig K, Herberg KW, Kasper SM, Radbruch L. Driving ability under long-term treatment with transdermal fentanyl. *J Pain Symptom Manage*. 2003;25(1):38-47.
132. Menefee L, Frank E, Crerand C, et al. The effects of transdermal fentanyl on driving, cognitive performance, and balance in patients with chronic nonmalignant pain conditions. *Pain Med*. 2004;5(1):42-9.
133. Verster JC, Veldhuijzen DS, Volkerts ER. Effects of an opioid (oxycodone/paracetamol) and an NSAID (bromfenac) on driving ability, memory functioning, psychomotor performance, pupil size, and mood. *Clin J Pain*. 2006;22(5):499-504.
134. Kelly E, Darke S, Ross J. A review of drug use and driving: epidemiology, impairment, risk factors and risk perceptions. *Drug Alcohol Rev*. 2004;23(3):319-44.
135. Lenne M, Dietze P, Rumbold G, Redman J, Triggs T. Opioid dependence and driving ability: a review in the context of poposed legislative change in Victoria. *Drug Alcohol Rev*. 2000;19427-39.
136. Lenne MG, Dietze P, Rumbold GR, Redman JR, Triggs TJ. The effects of the opioid pharmacotherapies methadone, LAAM and buprenorphine, alone and in combination with alcohol, on simulated driving. *Drug Alcohol Depend*. 2003;72(3):271-8.
137. Schindler SD, Ortner R, Peternell A, Eder H, Opgenoorth E, Fischer G. Maintenance therapy with synthetic opioids and driving aptitude. *Eur Addict Res*. 2004;10(2):80-7.
138. Berghaus G, Friedel B. Methadone and driver fitness. *Euro-methwork*. 1998;135-6.
139. Byas-Smith MG, Chapman SL, Reed B, Cotsonis G. The effect of opioids on driving and psychomotor performance in patients with chronic pain. *Clin J Pain*. 2005;21(4):345-52.
140. Hill JL, Zacny JP. Comparing the subjective, psychomotor, and physiological effects of intravenous hydromorphone and morphine in healthy volunteers. *Psychopharmacology (Berl)*. 2000;152(1):31-9.
141. Dellemijn PL, van Duijn H, Vanneste JA. Prolonged treatment with transdermal fentanyl in neuropathic pain. *J Pain Symptom Manage*. 1998;16(4):220-9.
142. McNicol E, Horowicz-Mehler N, Fisk RA, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. *J Pain*. 2003;4(5):231-56.
143. Jamison RN, Schein JR, Vallow S, Ascher S, Vorsanger GJ, Katz NP. Neuropsychological effects of long-term opioid use in chronic pain patients. *J Pain Symptom Manage*. 2003;26(4):913-21.
144. Vainio A, Ollila J, Matikainen E, Rosenberg P, Kalso E. Driving ability in cancer patients receiving long-term morphine analgesia. *Lancet*. 1995;346(8976):667-70.
145. Larsen B, Otto H, Dorscheid E, Larsen R. Effects of long-term opioid therapy on psychomotor function in patients with cancer pain or non-malignant pain. *Anaesthesist*. 1999;48(9):613-24.
146. Lorenz J, Beck H, Bromm B. Cognitive performance, mood and experimental pain before and during morphine-induced analgesia in patients with chronic non-malignant pain. *Pain*. 1997;73(3):369-75.
147. Gaertner J, Radbruch L, Giesecke T, et al. Assessing cognition and psychomotor function under long-term treatment with controlled release oxycodone in non-cancer pain patients. *Acta Anaesthesiol Scand*. 2006;50(6):664-72.
148. Strumpf M, Kohler A, Zenz M, Willweber-Strumpf A, Dertwinkel R, Donner B. Opioids and driving ability. *Schmerz*. 1997;11(4):233-40.
149. Kendall SE, Sjogren P, Pimenta CA, Hojsted J, Kurita GP. The cognitive effects of opioids in chronic non-cancer pain. *Pain*. 2010;150(2):225-30.

150. Gruber SA, Silveri MM, Yurgelun-Todd DA. Neuropsychological consequences of opiate use. *Neuropsychol Rev*. 2007;17(3):299-315.
151. Zacny J. A review of the effects of opioids on psychomotor and cognitive functioning in humans. *Exp Clin Psychopharmacol*. 1995;3(4):432-66.
152. Iezzi T, Duckworth MP, Vuong LN, Archibald YM, Klinck A. Predictors of neurocognitive performance in chronic pain patients. *Int J Behav Med*. 2004;11(1):56-61.
153. Berryman C, Stanton TR, Jane Bowering K, Tabor A, McFarlane A, Lorimer Moseley G. Evidence for working memory deficits in chronic pain: a systematic review and meta-analysis. *Pain*. 2013;154(8):1181-96.
154. Hart RP, Martelli MF, Zasler ND. Chronic pain and neuropsychological functioning. *Neuropsychol Rev*. 2000;10(3):131-49.
155. Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: a review of clinical and preclinical research. *Prog Neurobiol*. 2011;93(3):385-404.
156. Kreitler S, Niv D. Cognitive impairment in chronic pain. *Pain Clin Updates*. 2007;15(4):1-4.
157. Fishbain DA, Cutler RB, Rosomoff HL, Rosomoff RS. Can patients taking opioids drive safely? A structured evidence-based review. *J Pain Palliat Care Pharmacother*. 2002;16(1):9-28.
158. Fishbain D, Cutler R, Rosomoff H, Rosomoff R. Are opioid-dependent/tolerant patients impaired in driving-related skills? A structured evidence-based review. *J Pain Symptom Manage*. 2003;25(6):559-77.
159. Zacny JP. Should people taking opioids for medical reasons be allowed to work and drive? *Addiction*. 1996;91(11):1581-4.
160. Dassanayake T, Michie P, Carter G, Jones A. Effects of benzodiazepines, antidepressants and opioids on driving: a systematic review and meta-analysis of epidemiological and experimental evidence. *Drug Saf*. 2011;34(2):125-56.
161. Orriols L, Salmi LR, Philip P, et al. The impact of medicinal drugs on traffic safety: a systematic review of epidemiological studies. *Pharmacoepidemiol Drug Saf*. 2009;18(8):647-58.
162. Strand MC, Fjeld B, Arnestad M, Morland J. Can patients receiving opioid maintenance therapy safely drive? A systematic review of epidemiological and experimental studies on driving ability with a focus on concomitant methadone or buprenorphine administration. *Traffic Inj Prev*. 2013;14(1):26-38.
163. Leung SY. Benzodiazepines, opioids and driving: an overview of the experimental research. *Drug Alcohol Rev*. 2011;30(3):281-6.
164. Bachs LC, Engeland A, Morland JG, Skurtveit S. The risk of motor vehicle accidents involving drivers with prescriptions for codeine or tramadol. *Clin Pharmacol Ther*. 2009;85(6):596-9.
165. Corsenac P, Lagarde E, Gadegbeku B, et al. Road traffic crashes and prescribed methadone and buprenorphine: a French registry-based case-control study. *Drug Alcohol Depend*. 2012;123(1-3):91-7.
166. Movig KL, Mathijssen MP, Nagel PH, et al. Psychoactive substance use and the risk of motor vehicle accidents. *Accid Anal Prev*. 2004;36(4):631-6.
167. Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain*. 2006;125(1-2):172-9.
168. Atluri S, Sudarshan G. Development of a screening tool to detect the risk of inappropriate prescription opioid use in patients with chronic pain. *Pain Physician*. 2004;7(3):333-8.
169. Shah NG, Lathrop SL, Reichard RR, Landen MG. Unintentional drug overdose death trends in New Mexico, USA, 1990-2005: combinations of heroin, cocaine, prescription opioids and alcohol. *Addiction*. 2008;103(1):126-36.
170. Webster L, Cochella S, Dasgupta N, et al. An analysis of the root causes for opioid-related overdose deaths in the United States. *Pain Med*. 2011;12(Suppl 2):S26-35.
171. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med*. 2010;152(2):85-92.
172. Paulozzi LJ, Logan JE, Hall AJ, McKinstry E, Kaplan JA, Crosby AE. A comparison of drug overdose deaths involving methadone and other opioid analgesics in West Virginia. *Addiction*. 2009;104(9):1541-8.
173. Grattan A, Sullivan M, Saunders K, Campbell C, Von Korff M. Depression and prescription opioid misuse among chronic opioid therapy recipients with no history of substance abuse. *Annals Fam Med*. 2012;10(4):304-11.
174. Manchikanti L, Damron KS, McManus CD, Barnhill RC. Patterns of illicit drug use and opioid abuse in patients with chronic pain at initial evaluation: a prospective, observational study. *Pain Physician*. 2004;7(4):431-7.
175. Nyhlen A, Fridell M, Backstrom M, Hesse M, Krantz P. Substance abuse and psychiatric co-morbidity as predictors of premature mortality in Swedish drug abusers: a prospective longitudinal study 1970-2006. *BMC Psychiatry*. 2011;11122.
176. Hadidi MS, Ibrahim MI, Abdallat IM, Hadidi KA. Current trends in drug abuse associated fatalities - Jordan, 2000-2004. *Forensic Sci Int*. 2009;186(1-3):44-7.
177. Wysowski DK, Governale LA, Swann J. Trends in outpatient prescription drug use and related costs in the US: 1998-2003. *Pharmacoeconomics*. 2006;24(3):233-6.
178. Wysowski DK. Surveillance of prescription drug-related mortality using death certificate data. *Drug Saf*. 2007;30(6):533-40.
179. Toblin RL, Paulozzi LJ, Logan JE, Hall AJ, Kaplan JA. Mental illness and psychotropic drug use among prescription drug overdose deaths: a medical examiner chart review. *J Clin Psychiatry*. 2010;71(4):491-6.
180. Centers for Disease Control and Prevention. Unintentional deaths from drug poisoning by urbanization of area — New Mexico, 1994–2003. *MMWR*. 2005;54(35):870-3.

181. Fareed A, Casarella J, Roberts M, et al. High dose versus moderate dose methadone maintenance: is there a better outcome? *J Addict Dis*. 2009;28(4):399-405.
182. Deyo RA, Smith DH, Johnson ES, et al. Opioids for back pain patients: primary care prescribing patterns and use of services. *J Am Board Fam Med*. 2011;24(6):717-27.
183. Goodridge D, Lawson J, Rocker G, Marciniuk D, Rennie D. Factors associated with opioid dispensation for patients with COPD and lung cancer in the last year of life: A retrospective analysis. *Int J Chron Obstruct Pulmon Dis*. 2010;599-105.
184. Dean M. Opioids in renal failure and dialysis patients. *J Pain Symptom Manage*. 2004;28(5):497-504.
185. Seal KH, Shi Y, Cohen G, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. *Jama*. 2012;307(9):940-7.
186. Mills K, Teesson M, Ross J, Darke S, Shanahan M. The costs and outcomes of treatment for opioid dependence associated with posttraumatic stress disorder. *Psychiatr Serv*. 2005;56(8):940-5.
187. Walter SR, Thein HH, Amin J, et al. Trends in mortality after diagnosis of hepatitis B or C infection: 1992-2006. *J Hepatol*. 2011;54(5):879-86.
188. Cifuentes M, Webster B, Genevay S, Pransky G. The course of opioid prescribing for a new episode of disabling low back pain: opioid features and dose escalation. *Pain*. 2010;151(1):22-9.
189. Dersh J, Mayer T, Gatchel R, Polatin P, Theodore B, Mayer E. Prescription opioid dependence is associated with poorer outcomes in disabling spinal disorders. *SPINE*. 2008;33(20):2219-27.
190. Veenema K, Leahey N, S. S. Ketorolac versus meperidine: ED treatment of severe musculoskeletal low back pain. *Am J Emerg Med*. 2000;18(4):404-7.
191. Innes GD, Croskerry P, Worthington J, Beveridge R, Jones D. Ketorolac versus acetaminophen-codeine in the emergency department treatment of acute low back pain. *J Emerg Med*. 1998;16(4):549-56.
192. Swinkels-Meewisse IE, Roelofs J, Oostendorp RA, Verbeek AL, Vlaeyen JW. Acute low back pain: pain-related fear and pain catastrophizing influence physical performance and perceived disability. *Pain*. 2006;120(1-2):36-43.
193. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *Jama*. 2011;305(13):1315-21.
194. Church CA, Stewart Ct, TJ OL, Wallace D. Rofecoxib versus hydrocodone/acetaminophen for postoperative analgesia in functional endoscopic sinus surgery. *Laryngoscope*. 2006;116(4):602-6.
195. Nussmeier NA, Whelton AA, Brown MT, et al. Safety and efficacy of the cyclooxygenase-2 inhibitors parecoxib and valdecoxib after noncardiac surgery. *Anesthesiology*. 2006;104(3):518-26.
196. Legeby M, Sandelin K, Wickman M, Olofsson C. Analgesic efficacy of diclofenac in combination with morphine and paracetamol after mastectomy and immediate breast reconstruction. *Acta Anaesthesiol Scand*. 2005;49(9):1360-6.
197. Dirks J, Fredensborg BB, Christensen D, Fomsgaard JS, Flyger H, Dahl JB. A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy. *Anesthesiology*. 2002;97(3):560-4.
198. Pettersson PH, Jakobsson J, Owall A. Intravenous acetaminophen reduced the use of opioids compared with oral administration after coronary artery bypass grafting. *J Cardiothorac Vasc Anesth*. 2005;19(3):306-9.
199. Wininger SJ, Miller H, Minkowitz HS, et al. A randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of two intravenous acetaminophen dosing regimens for the treatment of pain after abdominal laparoscopic surgery. *Clin Ther*. 2010;32(14):2348-69.
200. Buchler MW, Seiler CM, Monson JR, et al. Clinical trial: alvimopan for the management of post-operative ileus after abdominal surgery: results of an international randomized, double-blind, multicentre, placebo-controlled clinical study. *Aliment Pharmacol Ther*. 2008;28(3):312-25.
201. Wolff BG, Michelassi F, Gerkin TM, et al. Alvimopan, a novel, peripherally acting mu opioid antagonist: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial of major abdominal surgery and postoperative ileus. *Ann Surg*. 2004;240(4):728-34; discussion 34-5.
202. Dierking G, Duedahl TH, Rasmussen ML, et al. Effects of gabapentin on postoperative morphine consumption and pain after abdominal hysterectomy: a randomized, double-blind trial. *Acta Anaesthesiol Scand*. 2004;48(3):322-7.
203. Pizzi LT, Toner R, Foley K, et al. Relationship between potential opioid-related adverse effects and hospital length of stay in patients receiving opioids after orthopedic surgery. *Pharmacotherapy*. 2012;32(6):502-14.
204. Christensen KS, Cohen AE, Mermelstein FH, et al. The analgesic efficacy and safety of a novel intranasal morphine formulation (morphine plus chitosan), immediate release oral morphine, intravenous morphine, and placebo in a postsurgical dental pain model. *Anesth Analg*. 2008;107(6):2018-24.
205. Nader A, Kendall MC, Wixson RL, Chung B, Polakow LM, McCarthy RJ. A randomized trial of epidural analgesia followed by continuous femoral analgesia compared with oral opioid analgesia on short- and long-term functional recovery after total knee replacement. *Pain Med*. 2012;13(7):937-47.
206. Belknap SM, Moore H, Lanzotti SA, et al. Application of software design principles and debugging methods to an analgesia prescription reduces risk of severe injury from medical use of opioids. *Clin Pharmacol Ther*. 2008;84(3):385-92.
207. Webster LR, Johnson FK, Stauffer J, Setnik B, Ciric S. Impact of intravenous naltrexone on intravenous morphine-induced high, drug liking, and euphoric effects in experienced, nondependent male opioid users. *Drugs R D*. 2011;11(3):259-75.

208. Gross DP, Battie MC. Construct validity of a kinesiophysical functional capacity evaluation administered within a worker's compensation environment. *J Occup Rehabil*. 2003;13(4):287-95.
209. Reneman MF, Schiphorts Preuper HR, Kleen M, Geertzen JH, Dijkstra PU. Are pain intensity and pain related fear related to functional capacity evaluation performances of patients with chronic low back pain? *J Occup Rehabil*. 2007;17(2):247-58.
210. Brouwer S, Dijkstra PU, Stewart RE, Goeken LN, Groothoff JW, Geertzen JH. Comparing self-report, clinical examination and functional testing in the assessment of work-related limitations in patients with chronic low back pain. *Disabil Rehabil*. 2005;27(17):999-1005.
211. Buelow AK, Haggard R, Gatchel RJ. Additional validation of the pain medication questionnaire in a heterogeneous sample of chronic pain patients. *Pain Pract*. 2009;9(6):428-34.
212. Schiphorst Preuper H, Reneman M, Boonstra A, et al. Relationship between psychological factors and performance-based and self-reported disability in chronic low back pain. *Eur Spine J*. 2008;17(11):1448-56.
213. Smeets RJ, van Geel AC, Kester AD, Knottnerus JA. Physical capacity tasks in chronic low back pain: what is the contributing role of cardiovascular capacity, pain and psychological factors? *Disabil Rehabil*. 2007;29(7):577-86.
214. Morasco BJ, Cavanagh R, Gritzner S, Dobscha SK. Care management practices for chronic pain in veterans prescribed high doses of opioid medications. *Fam Pract*. 2013.
215. Fox CD, Steger HG, Jennison JH. Ratio scaling of pain perception with the submaximum effort tourniquet technique. *Pain*. 1979;7(1):21-9.
216. Hartrick CT, Kovan JP, Shapiro S. The numeric rating scale for clinical pain measurement: a ratio measure? *Pain Pract*. 2003;3(4):310-6.
217. Lund I, Lundeberg T, Sandberg L, Budh CN, Kowalski J, Svensson E. Lack of interchangeability between visual analogue and verbal rating pain scales: a cross sectional description of pain etiology groups. *BMC Med Res Methodol*. 2005;531.
218. Von Korff M, Merrill JO, Rutter CM, Sullivan M, Campbell CI, Weisner C. Time-scheduled vs. pain-contingent opioid dosing in chronic opioid therapy. *Pain*. 2011;152(6):1256-62.
219. Cifuentes M, Powell R, Webster B. Shorter time between opioid prescriptions associated with reduced work disability among acute low back pain opioid users. *J Occup Environ Med*. 2012;54(4):491-6.
220. Hartrick C, Gatchel R, Conroy S. Identification and management of pain medication abuse and misuse: current state and future directions. *Expert Rev Neurother*. 2012;12(5).
221. Kidner CL, Gatchel RJ, Mayer TG. MMPI disability profile is associated with degree of opioid use in chronic work-related musculoskeletal disorders. *Clin J Pain*. 2010;26(1):9-15.
222. Naliboff BD, Wu SM, Schieffer B, et al. A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. *J Pain*. 2011;12(2):288-96.
223. Starrels JL, Becker WC, Alford DP, Kapoor A, Williams AR, Turner BJ. Systematic review: treatment agreements and urine drug testing to reduce opioid misuse in patients with chronic pain. *Ann Intern Med*. 2010;152(11):712-20.
224. Wiedemer N, Harden P, Arndt I, Gallagher R. The opioid renewal clinic: a primary care, managed approach to opioid therapy in chronic pain patients at risk for substance abuse. *Pain Med*. 2007;8(7):573-84.
225. Goldberg K, Simel D, Oddone E. Effect of an opioid management system on opioid prescribing and unscheduled visits in a large primary care clinic. *JCOM*. 2005;12(12):621-8.
226. Manchikanti L, Cash K, Damron K, Manchukonda R, Pampati V, McManus C. Controlled substance abuse and illicit drug use in chronic pain patients: an evaluation of multiple variables. *Pain Physician*. 2006;9(3):215-25.
227. Manchikanti L, Manchukonda R, Damron KS, Brandon D, McManus CD, Cash K. Does adherence monitoring reduce controlled substance abuse in chronic pain patients? *Pain Physician*. 2006;9(1):57-60.
228. Chelminski PR, Ives TJ, Felix KM, et al. A primary care, multi-disciplinary disease management program for opioid-treated patients with chronic non-cancer pain and a high burden of psychiatric comorbidity. *BMC Health Serv Res*. 2005;5(1):3.
229. Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res*. 2006;646.
230. Hariharan J, Lamb GC, Neuner JM. Long-term opioid contract use for chronic pain management in primary care practice. A five year experience. *J Gen Intern Med*. 2007;22(4):485-90.
231. Compton PA, Wu SM, Schieffer B, Pham Q, Naliboff BD. Introduction of a self-report version of the Prescription Drug Use Questionnaire and relationship to medication agreement noncompliance. *J Pain Symptom Manage*. 2008;36(4):383-95.
232. Burchman S, Pagel P. Implementation of a formal treatment agreement for outpatient management of chronic nonmalignant pain with opioid analgesics. *J Pain Symptom Manage*. 1995;10(7):556-63.
233. Vaglienti RM, Huber SJ, Noel KR, Johnstone RE. Misuse of prescribed controlled substances defined by urinalysis. *W V Med J*. 2003;99(2):67-70.
234. Lees R, Kingston R, Williams TM, Henderson G, Lingford-Hughes A, Hickman M. Comparison of ethyl glucuronide in hair with self-reported alcohol consumption. *Alcohol Alcohol*. 2012;47(3):267-72.
235. Politi L, Zucchella A, Morini L, Stramesi C, Polettini A. Markers of chronic alcohol use in hair: comparison of ethyl glucuronide and cocaethylene in cocaine users. *Forensic Sci Int*. 2007;172(1):23-7.

236. Lamoureux F, Gaulier JM, Sauvage FL, Mercerolle M, Vallejo C, Lachatre G. Determination of ethyl-glucuronide in hair for heavy drinking detection using liquid chromatography-tandem mass spectrometry following solid-phase extraction. *Anal Bioanal Chem*. 2009;394(7):1895-901.
237. Cooper GA, Kronstrand R, Kintz P. Society of Hair Testing guidelines for drug testing in hair. *Forensic Sci Int*. 2012;218(1-3):20-4.
238. Kulaga V, Velazquez-Armenta Y, Aleksa K, Vergee Z, Koren G. The effect of hair pigment on the incorporation of fatty acid ethyl esters (FAEE). *Alcohol Alcohol*. 2009;44(3):287-92.
239. Appenzeller BM, Agirman R, Neuberg P, Yegles M, Wennig R. Segmental determination of ethyl glucuronide in hair: a pilot study. *Forensic Sci Int*. 2007;173(2-3):87-92.
240. Auerbach K. Drug testing methods. In: Lessenger J, Roper G, eds. *Drug Courts: A New Approach to Treatment and Rehabilitation*. New York, NY: Springer Science+Business Media; 2007:215-33.
241. Jortani S, Stauble E, Wong S. Chapter 1. Pharmacogenetics in clinical and forensic toxicology: opioid overdoses and deaths. In: Mozayani A, Raymon L, eds. *Handbook of Drug Interactions A Clinical and Forensic Guide*. New York, NY: Humana Press; 2012:3-22.
242. Heit H, Gourlay D. Urine drug testing in pain medicine. *J Pain Symptom Manage*. 2004;27(3):260-7.
243. Kjaersgaard-Andersen P, Nafei A, Skov O, et al. Codeine plus paracetamol versus paracetamol in longer-term treatment of chronic pain due to osteoarthritis of the hip. A randomised, double-blind, multi-centre study. *Pain*. 1990;43(3):309-18.
244. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112(3):372-80.
245. Webster LR, Butera PG, Moran LV, Wu N, Burns LH, Friedmann N. Oxytrex minimizes physical dependence while providing effective analgesia: a randomized controlled trial in low back pain. *J Pain*. 2006;7(12):937-46.
246. Hale ME, Dvergsten C, Gimbel J. Efficacy and safety of oxymorphone extended release in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study. *J Pain*. 2005;6(1):21-8.
247. Hale M, Khan A, Kutch M, Li S. Once-daily OROS hydromorphone ER compared with placebo in opioid-tolerant patients with chronic low back pain. *Curr Med Res Opin*. 2010;26(6):1505-18.
248. Peloso PM, Fortin L, Beaulieu A, Kamin M, Rosenthal N. Analgesic efficacy and safety of tramadol/ acetaminophen combination tablets (Ultracet) in treatment of chronic low back pain: a multicenter, outpatient, randomized, double blind, placebo controlled trial. *J Rheumatol*. 2004;31(12):2454-63.
249. Ruoff GE, Rosenthal N, Jordan D, Karim R, Kamin M. Tramadol/acetaminophen combination tablets for the treatment of chronic lower back pain: a multicenter, randomized, double-blind, placebo-controlled outpatient study. *Clin Ther*. 2003;25(4):1123-41.
250. Schnitzer TJ, Gray WL, Paster RZ, Kamin M. Efficacy of tramadol in treatment of chronic low back pain. *J Rheumatol*. 2000;27(3):772-8.
251. Simpson D, Messina J, Xie F, Hale M. Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther*. 2007;29(4):588-601.
252. Breckenridge J, Clark J. Patient characteristics associated with opioid versus nonsteroidal anti-inflammatory drug management of chronic low back pain. . *J Pain*. 2003;4(6):344-50.
253. Bourgeois FT, Murthy S, Mandl KD. Outcome reporting among drug trials registered in ClinicalTrials.gov. *Ann Intern Med*. 2010;153(3):158-66.
254. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *Jama*. 2003;289(4):454-65.
255. Shah RV, Albert TJ, Bruegel-Sanchez V, Vaccaro AR, Hilibrand AS, Grauer JN. Industry support and correlation to study outcome for papers published in Spine. *SPINE*. 2005;30(9):1099-104; discussion 105.
256. Steinbrook R. Peer review and federal regulations. *N Engl J Med*. 2004;350(2):103-4.
257. Buvanendran A, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. *Anesth Analg*. 2010;110(1):199-207.
258. Pavelka K, Pelisková Z, Stehlíková H, Ratcliffe S RC. Intraindividual differences in pain relief and functional improvement in osteoarthritis with diclofenac or tramadol. *Clin Drug Investig*. 1998;16(6):421-9.
259. Matsumoto A, Babul N, Ahdieh H. Oxymorphone extended-release tablets relieve moderate to severe pain and improve physical function in osteoarthritis: results of a randomized, double-blind, placebo- and active-controlled phase III trial. *Pain Med*. 2005;6(5):357-66.
260. Rosenthal NR, Silverfield JC, Wu SC, Jordan D, Kamin M. Tramadol/acetaminophen combination tablets for the treatment of pain associated with osteoarthritis flare in an elderly patient population. *J Am Geriatr Soc*. 2004;52(3):374-80.
261. Freeman R, Raskin P, Hewitt DJ, et al. Randomized study of tramadol/acetaminophen versus placebo in painful diabetic peripheral neuropathy. *Curr Med Res Opin*. 2007;23(1):147-61.
262. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database Syst Rev*. 2013;8CD004959.
263. Gammaitoni AR, Galer BS, Lacouture P, Domingos J, Schlagheck T. Effectiveness and safety of new oxycodone/acetaminophen formulations with reduced acetaminophen for the treatment of low back pain. *Pain Med*. 2003;4(1):21-30.

264. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med*. 2007;146(2):116-27.
265. Maruta T, Swanson DW, Finlayson RE. Drug abuse and dependency in patients with chronic pain. *Mayo Clin Proc*. 1979;54(4):241-4.
266. Chabal C, Erjavec MK, Jacobson L, Mariano A, Chaney E. Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors. *Clin J Pain*. 1997;13(2):150-5.
267. Butler S, Fernandez K, Benoit C, Budman S, Jamison R. Validation of the revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R). *J Pain*. 2008;9(4):360-72.
268. Michna E, Ross E, Hynes W, et al. Predicting aberrant drug behavior in patients treated for chronic pain: importance of abuse history. *J Pain Symptom Manage*. 2004;28(3):250-8.
269. Ekman EF, Ruoff G, Kuehl K, et al. The COX-2 specific inhibitor valdecoxib versus tramadol in acute ankle sprain: a multicenter randomized, controlled trial. *Am J Sports Med*. 2006;34(6):945-55.
270. Clark E, Plint AC, Correll R, Gaboury I, Passi B. A randomized, controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma. *Pediatrics*. 2007;119(3):460-7.
271. Lovell SJ, Taira T, Rodriguez E, Wackett A, Gulla J, Singer AJ. Comparison of valdecoxib and an oxycodone-acetaminophen combination for acute musculoskeletal pain in the emergency department: a randomized controlled trial. *Acad Emerg Med*. 2004;11(12):1278-82.
272. Brown FL, Jr., Bodison S, Dixon J, Davis W, Nowoslawski J. Comparison of diflunisal and acetaminophen with codeine in the treatment of initial or recurrent acute low back strain. *Clin Ther*. 1986;9 (Suppl C):52-8.
273. Muncie HL, Jr., King DE, DeForge B. Treatment of mild to moderate pain of acute soft tissue injury: diflunisal vs acetaminophen with codeine. *J Fam Pract*. 1986;23(2):125-7.
274. Chang DJ, Desjardins PJ, King TR, Erb T, Geba GP. The analgesic efficacy of etoricoxib compared with oxycodone/acetaminophen in an acute postoperative pain model: a randomized, double-blind clinical trial. *Anesth Analg*. 2004;99(3):807-15, table of contents.
275. Baratta R. A double-blind comparative study of carisoprodol, propoxyphene, and placebo in the management of low back syndrome. *Curr Ther Res Clin Exp*. 1976;20(3):233-40.
276. Ordog GJ. Transcutaneous electrical nerve stimulation versus oral analgesic: a randomized double-blind controlled study in acute traumatic pain. *Am J Emerg Med*. 1987;5(1):6-10.
277. Chang AK, Bijur PE, Meyer RH, Kenny MK, Solorzano C, Gallagher EJ. Safety and efficacy of hydromorphone as an analgesic alternative to morphine in acute pain: a randomized clinical trial. *Ann Emerg Med*. 2006;48(2):164-72.
278. Chang AK, Bijur PE, Campbell CM, Murphy MK, Gallagher EJ. Safety and efficacy of rapid titration using 1mg doses of intravenous hydromorphone in emergency department patients with acute severe pain: the "1+1" protocol. *Ann Emerg Med*. 2009;54(2):221-5.
279. Chang AK, Bijur PE, Davitt M, Gallagher EJ. Randomized clinical trial comparing a patient-driven titration protocol of intravenous hydromorphone with traditional physician-driven management of emergency department patients with acute severe pain. *Ann Emerg Med*. 2009;54(4):561-7 e2.
280. Chang AK, Bijur PE, Davitt M, Gallagher EJ. Randomized clinical trial of an intravenous hydromorphone titration protocol versus usual care for management of acute pain in older emergency department patients. *Drugs Aging*. 2013;30(9):747-54.
281. Chang AK, Bijur PE, Gallagher EJ. Randomized clinical trial comparing the safety and efficacy of a hydromorphone titration protocol to usual care in the management of adult emergency department patients with acute severe pain. *Ann Emerg Med*. 2011;58(4):352-9.
282. Chang AK, Bijur PE, Lupow JB, Gallagher EJ. Randomized clinical trial of the 2 mg hydromorphone bolus protocol versus the "1+1" hydromorphone titration protocol in treatment of acute, severe pain in the first hour of emergency department presentation. *Ann Emerg Med*. 2013;62(4):304-10.
283. Chang AK, Bijur PE, Lupow JB, John Gallagher E. Randomized clinical trial of efficacy and safety of a single 2-mg intravenous dose of hydromorphone versus usual care in the management of acute pain. *Acad Emerg Med*. 2013;20(2):185-92.
284. Turturro MA, Paris PM, Larkin GL. Tramadol versus hydrocodone-acetaminophen in acute musculoskeletal pain: a randomized, double-blind clinical trial. *Ann Emerg Med*. 1998;32(2):139-43.
285. Turturro MA, Paris PM, Yealy DM, Menegazzi JJ. Hydrocodone versus codeine in acute musculoskeletal pain. *Ann Emerg Med*. 1991;20(10):1100-3.
286. Jalili M, Fathi M, Moradi-Lakeh M, Zehtabchi S. Sublingual buprenorphine in acute pain management: a double-blind randomized clinical trial. *Ann Emerg Med*. 2012;59(4):276-80.
287. Bounes V, Barthelemy R, Diez O, Charpentier S, Montastruc JL, Ducasse JL. Sufentanil is not superior to morphine for the treatment of acute traumatic pain in an emergency setting: a randomized, double-blind, out-of-hospital trial. *Ann Emerg Med*. 2010;56(5):509-16.
288. Marco CA, Plewa MC, Buderer N, Black C, Roberts A. Comparison of oxycodone and hydrocodone for the treatment of acute pain associated with fractures: a double-blind, randomized, controlled trial. *Acad Emerg Med*. 2005;12(4):282-8.
289. Webster B, Verma S, Gatchel R. Relationship between early opioid prescribing for acute occupational low back pain and disability duration, medical costs, subsequent surgery and late opioid use. *SPINE*. 2007;32(19):2127-32.

290. Franklin GM, Rahman EA, Turner JA, Daniell WE, Fulton-Kehoe D. Opioid use for chronic low back pain: A prospective, population-based study among injured workers in Washington state, 2002-2005. *Clin J Pain*. 2009;25(9):743-51.
291. Trevino CM, deRoon-Cassini T, Brasel K. Does opiate use in traumatically injured individuals worsen pain and psychological outcomes? *J Pain*. 2013;14(4):424-30.
292. Gora-Harper M, Record K, Darkow T, Tibbs P. Opioid analgesics versus ketorolac in spine and joint procedures: impact on healthcare resources. *Ann Pharmacother*. 2001;35(11):1320-6.
293. Silvanto M, Lappi M, Rosenberg PH. Comparison of the opioid-sparing efficacy of diclofenac and ketoprofen for 3 days after knee arthroplasty. *Acta Anaesthesiol Scand*. 2002;46(3):322-8.
294. Sell S, Phillips O, Handel M. No difference between two doses of diclofenac in prophylaxis of heterotopic ossifications after total hip arthroplasty. *Acta Orthop Scand*. 2004;75(1):45-9.
295. Gimbel JS, Brugger A, Zhao W, Verburg KM, Geis GS. Efficacy and tolerability of celecoxib versus hydrocodone/acetaminophen in the treatment of pain after ambulatory orthopedic surgery in adults. *Clin Ther*. 2001;23(2):228-41.
296. Dahl V, Raeder JC, Drosdal S, Wathne O, Brynildsrud J. Prophylactic oral ibuprofen or ibuprofen-codeine versus placebo for postoperative pain after primary hip arthroplasty. *Acta Anaesthesiol Scand*. 1995;39(3):323-6.
297. Ittichaikulthol W, Prachanpanich N, Kositchaiwat C, Intapan T. The post-operative analgesic efficacy of celecoxib compared with placebo and parecoxib after total hip or knee arthroplasty. *J Med Assoc Thai*. 2010;93(8):937-42.
298. O'Donnell JB, Ekman EF, Spalding WM, Bhadra P, McCabe D, Berger MF. The effectiveness of a weak opioid medication versus a cyclo-oxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drug in treating flare-up of chronic low-back pain: results from two randomized, double-blind, 6-week studies. *J Int Med Res*. 2009;37(6):1789-802.
299. Parr G, Darekar B, Fletcher A, CJ. B. Joint pain and quality of life; results of a randomised trial. *Br J Clin Pharmacol*. 1989;27(2):235-42.
300. Jamison RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain. A randomized prospective study. *SPINE*. 1998;23(23):2591-600.
301. Khoromi S, Cui L, Nackers L, Max M. Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. . *Pain*. 2007;130(1-2):66-75.
302. Siddall PJ, Molloy AR, Walker S, Mather LE, Rutkowski SB, Cousins MJ. The efficacy of intrathecal morphine and clonidine in the treatment of pain after spinal cord injury. *Anesth Analg*. 2000;91(6):1493-8.
303. Li C, Ni J, Wang Z, et al. Analgesic efficacy and tolerability of flupirtine vs. tramadol in patients with subacute low back pain: a double-blind multicentre trial*. *Curr Med Res Opin*. 2008;24(12):3523-30.
304. Moulin D, Iezzi A, Amireh R, Sharp WK, Boyd D, H. M. Randomised trial of oral morphine for chronic non-cancer pain. *Lancet*. 1996;347(8995):143-7.
305. Wu CL, Agarwal S, Tella PK, et al. Morphine versus mexiletine for treatment of postamputation pain: a randomized, placebo-controlled, crossover trial. *Anesthesiology*. 2008;109(2):289-96.
306. Edwards RR, Wasan AD, Michna E, Greenbaum S, Ross E, Jamison RN. Elevated pain sensitivity in chronic pain patients at risk for opioid misuse. *J Pain*. 2011;12(9):953-63.
307. Joranson D, Berger J. Regulatory issues in pain management. *J Am Pharm Assoc*. 2000;40(5 Suppl 1):S60-1.
308. Gilson A, Ryan KM, Joranson DE, JL. D. A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control: 1997-2002. *J Pain Symptom Manage*. 2004;28(2):176-88.
309. Fishbain D, Cole B, Lewis J, Rosomoff H, Rosomoff R. 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. *Pain Med*. 2008;9(4):444-59.
310. Hojsted J, Sjogren P. Addiction to opioids in chronic pain patients: a literature review. *Eur J Pain*. 2007;11(5):490-518.
311. Noble M, Tregear SJ, Treadwell JR, Schoelles K. Long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and safety. *J Pain Symptom Manage*. 2008;35(2):214-28.
312. Furlan A, Sandoval JA, Mailis-Gagnon A, E. T. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *Cmaj*. 2006;174(11):1589-94.
313. Michna E, Jamison R, Pham L, et al. . Urine toxicology screening among chronic pain patients on opioid therapy: frequency and predictability of abnormal findings. *Clin J Pain*. 2007;23(2):173-9.
314. Davies E, Green C, Taylor S, Williamson P, Mottram D, Pirmohamed M. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. *PLoS ONE*. 2009;4(2):e4439.
315. Oderda G, Said Q, Evans R, et al. Opioid-related adverse drug events in surgical hospitalizations: impact on costs and length of stay. *Ann Pharmacother*. 2007;41(3):400-6.
316. Choiniere M. Efficacy and costs of patient-controlled analgesia versus regularly administered intramuscular opioid therapy. *Anesthesiology*. 1998;89.
317. Rittenhouse B, Choiniere M. An economic evaluation of pain therapy after hysterectomy. Patient-controlled analgesia versus regular intramuscular opioid therapy. *Intl J Technology Assessment Health Care*. 1999;15(3):548-62.
318. Vojtassak J, Vojtassak J, Jacobs A, Rynn L, Waechter S, Richarz U. A Phase IIIb, Multicentre, Randomised, Parallel-Group, Placebo-Controlled, Double-Blind Study to Investigate the Efficacy and Safety of OROS

Hydromorphone in Subjects with Moderate-to-Severe Chronic Pain Induced by Osteoarthritis of the Hip or the Knee. *Pain Res Treat*. 20111-9.
319. Hewitt DJ, Todd KH, Xiang J, Jordan DM, Rosenthal NR. Tramadol/acetaminophen or hydrocodone/acetaminophen for the treatment of ankle sprain: a randomized, placebo-controlled trial. *Ann Emerg Med*. 2007;49(4):468-80.
320. Lemming D, Sorensen J, Graven-Nielsen T, Arendt-Nielsen L, Gerdle B. The responses to pharmacological challenges and experimental pain in patients with chronic whiplash-associated pain. *Clin J Pain*. 2005;21(5):412-21.
321. Lemming D, Sorensen J, Graven-Nielsen T, Lauber R, Arendt-Nielsen L, Gerdle B. Managing chronic whiplash associated pain with a combination of low-dose opioid (remifentanil) and NMDA-antagonist (ketamine). *Eur J Pain*. 2007;11(7):719-32.
322. Wasan AD, Davar G, Jamison R. The association between negative affect and opioid analgesia in patients with discogenic low back pain. *Pain*. 2005;117(3):450-61.
323. Gross DP, Bhambhani Y, Haykowsky MJ, Rashiq S. Acute opioid administration improves work-related exercise performance in patients with chronic back pain. *J Pain*. 2008;9(9):856-62.
324. Silverfield JC, Kamin M, Wu SC, Rosenthal N. Tramadol/acetaminophen combination tablets for the treatment of osteoarthritis flare pain: a multicenter, outpatient, randomized, double-blind, placebo-controlled, parallel-group, add-on study. *Clin Ther*. 2002;24(2):282-97.
325. Caldwell J, Hale M, Boyd R, et al. . Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. *J Rheumatol*. 1999;26(4):862-9.
326. Mullican WS, Lacy JR. Tramadol/acetaminophen combination tablets and codeine/acetaminophen combination capsules for the management of chronic pain: a comparative trial. *Clin Ther*. 2001;23(9):1429-45.
327. de Craen AJ, Lampe-Schoenmaeckers AJ, Kraal JW, Tijssen JG, Kleijnen J. Impact of experimentally-induced expectancy on the analgesic efficacy of tramadol in chronic pain patients: a 2 x 2 factorial, randomized, placebo-controlled, double-blind trial. *J Pain Symptom Manage*. 2001;21(3):210-7.
328. Musclow SL, Bowers T, Vo H, Glube M, Nguyen T. Long-acting morphine following hip or knee replacement: a randomized, double-blind and placebo-controlled trial. *Pain Res Manag*. 2012;17(2):83-8.
329. Yeom JH, Chon MS, Jeon WJ, Shim JH. Peri-operative ketamine with the ambulatory elastometric infusion pump as an adjuvant to manage acute postoperative pain after spinal fusion in adults: a prospective randomized trial. *Korean J Anesthesiol*. 2012;63(1):54-8.
330. Foss NB, Kristensen MT, Kristensen BB, Jensen PS, Kehlet H. Effect of postoperative epidural analgesia on rehabilitation and pain after hip fracture surgery: a randomized, double-blind, placebo-controlled trial. *Anesthesiology*. 2005;102(6):1197-204.
331. Pandey CK, Sahay S, Gupta D, et al. Preemptive gabapentin decreases postoperative pain after lumbar discoidectomy. *CAN J ANAESTH*. 2004;51(10):986-9.
332. Enggaard TP, Poulsen L, Arendt-Nielsen L, et al. The analgesic effect of codeine as compared to imipramine in different human experimental pain models. *Pain*. 2001;92(1-2):277-82.
333. Comelon M, Wisloeff-Aase K, Raeder J, et al. A comparison of oxycodone prolonged-release vs. oxycodone + naloxone prolonged-release after laparoscopic hysterectomy. *Acta Anaesthesiol Scand*. 2013;57(4):509-17.
334. Perrot S, Krause D, Crozes P, Naim C. Efficacy and tolerability of paracetamol/tramadol (325 mg/37.5 mg) combination treatment compared with tramadol (50 mg) monotherapy in patients with subacute low back pain: a multicenter, randomized, double-blind, parallel-group, 10-day treatment study. *Clin Ther*. 2006;28(10):1592-606.
335. Palangio M, Damask MJ, Morris E, et al. Combination hydrocodone and ibuprofen versus combination codeine and acetaminophen for the treatment of chronic pain. *Clin Ther*. 2000;22(7):879-92.
336. Ma K, Jiang W, Zhou Q, Du DP. The efficacy of oxycodone for management of acute pain episodes in chronic neck pain patients. *Int J Clin Pract*. 2008;62(2):241-7.
337. Rashiq S, Koller M, Haykowsky M, Jamieson K. The effect of opioid analgesia on exercise test performance in chronic low back pain. *Pain*. 2003;106(1-2):119-25.
338. Hale ME, Fleischmann R, Salzman R, et al. Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized, double-blind evaluation in patients with chronic back pain. *Clin J Pain*. 1999;15(3):179-83.
339. Hale ME, Ahdieh H, Ma T, Rauck R. Efficacy and safety of OPANA ER (oxymorphone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: a 12-week, randomized, double-blind, placebo-controlled study. *J Pain*. 2007;8(2):175-84.
340. Portenoy RK, Messina J, Xie F, Peppin J. Fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid-treated patients with chronic low back pain: a randomized, placebo-controlled study. *Curr Med Res Opin*. 2007;23(1):223-33.
341. Chu LF, D'Arcy N, Brady C, et al. Analgesic tolerance without demonstrable opioid-induced hyperalgesia: a double-blinded, randomized, placebo-controlled trial of sustained-release morphine for treatment of chronic nonradicular low-back pain. *Pain*. 2012;153(8):1583-92.
342. Allan L, Richarz U, Simpson K, Slappendel R. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naive patients with chronic low back pain. *SPINE*. 2005;30(22):2484-90.

343. Buynak R, Shapiro DY, Okamoto A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. *Expert Opin Pharmacother*. 2010;11(11):1787-804.
344. Gould EM, Jensen MP, Victor TW, Gammaitoni AR, White RE, Galer BS. The pain quality response profile of oxymorphone extended release in the treatment of low back pain. *Clin J Pain*. 2009;25(2):116-22.
345. Kalso E, Simpson KH, Slappendel R, Dejonckheere J, Richarz U. Predicting long-term response to strong opioids in patients with low back pain: findings from a randomized, controlled trial of transdermal fentanyl and morphine. *BMC Med*. 2007;539.
346. Vorsanger GJ, Xiang J, Gana TJ, Pascual ML, Fleming RR. Extended-release tramadol (tramadol ER) in the treatment of chronic low back pain. *J Opioid Manag*. 2008;4(2):87-97.
347. Peniston JH, Gould E. Oxymorphone extended release for the treatment of chronic low back pain: a retrospective pooled analysis of enriched-enrollment clinical trial data stratified according to age, sex, and prior opioid use. *Clin Ther*. 2009;31(2):347-59.
348. Peniston JH, Xiang Q, Gould EM. Factors affecting acceptability of titrated oxymorphone extended release in chronic low back pain - an individual patient analysis. *Curr Med Res Opin*. 2010;26(8):1861-71.
349. Gordon A, Callaghan D, Spink D, et al. Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. *Clin Ther*. 2010;32(5):844-60.
350. Gordon A, Rashiq S, Moulin DE, et al. Buprenorphine transdermal system for opioid therapy in patients with chronic low back pain. *Pain Res Manag*. 2010;15(3):169-78.
351. Etropoliski M. Dose conversion between tapentadol immediate and extended release for low back pain. *Pain Physician*. 2010;13(1):61-70.
352. Vondrackova D, Leyendecker P, Meissner W, et al. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. *J Pain*. 2008;9(12):1144-54.
353. Fleischmann RM, Caldwell JR, Roth SH, Tesser JRP, Olson W, Kamin M. Tramadol for the treatment of joint pain associated with osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Curr Ther Res*. 2001;62(2):113-28.
354. Langford R, McKenna F, Ratcliffe S, Vojtassak J, Richarz U. Transdermal fentanyl for improvement of pain and functioning in osteoarthritis: a randomized, placebo-controlled trial. *Arthritis Rheum*. 2006;54(6):1829-37.
355. Malonne H, Coffiner M, Sonet B, Sereno A, F V. Efficacy and tolerability of sustained-release tramadol in the treatment of symptomatic osteoarthritis of the hip or knee: a multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther*. 2004;26(11):1774-82.
356. Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of Tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clin Drug Investig*. 2010;30(8):489-505.
357. Lerner D, Chang H, Rogers WH, et al. Imputing at-work productivity loss using results of a randomized controlled trial comparing tapentadol extended release and oxycodone controlled release for osteoarthritis pain. *J Occup Environ Med*. 2012;54(8):933-8.
358. Burch F, Fishman R, Messina N, et al. A comparison of the analgesic efficacy of Tramadol Contramid OAD versus placebo in patients with pain due to osteoarthritis. *J Pain Symptom Manage*. 2007;34(3):328-38.
359. Katz N, Sun S, Johnson F, Stauffer J. ALO-01 (morphine sulfate and naltrexone hydrochloride) extended-release capsules in the treatment of chronic pain of osteoarthritis of the hip or knee: pharmacokinetics, efficacy, and safety. *J Pain*. 2010;11(4):303-11.
360. Markenson J, Croft J, Zhang PG, P. R. Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical trial. *Clin J Pain*. 2005;6(21):524-35.
361. Florete OG, Xiang J, Vorsanger GJ. Effects of extended-release tramadol on pain-related sleep parameters in patients with osteoarthritis. *Expert Opin Pharmacother*. 2008;9(11):1817-27.
362. Gana TJ, Pascual ML, Fleming RR, et al. Extended-release tramadol in the treatment of osteoarthritis: a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Curr Med Res Opin*. 2006;22(7):1391-401.
363. Lloyd RS, Costello F, Eves MJ, James IG, Miller AJ. The efficacy and tolerability of controlled-release dihydrocodeine tablets and combination dextropropoxyphene/paracetamol tablets in patients with severe osteoarthritis of the hips. *Curr Med Res Opin*. 1992;13(1):37-48.
364. Kean WF, Bouchard S, Roderich Gossen E. Women with pain due to osteoarthritis: the efficacy and safety of a once-daily formulation of tramadol. *Pain Med*. 2009;10(6):1001-11.
365. Emkey R, Rosenthal N, Wu SC, Jordan D, Kamin M. Efficacy and safety of tramadol/acetaminophen tablets (Ultracet) as add-on therapy for osteoarthritis pain in subjects receiving a COX-2 nonsteroidal antiinflammatory drug: a multicenter, randomized, double-blind, placebo-controlled trial. *J Rheumatol*. 2004;31(1):150-6.
366. Roth SH, Fleischmann RM, Burch FX, et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: placebo-controlled trial and long-term evaluation. *Arch Intern Med*. 2000;160(6):853-60.
367. Schnitzer T, Kamin M, WH. O. Tramadol allows reduction of naproxen dose among patients with naproxenresponsive osteoarthritis pain: a randomized, double-blind, placebo-controlled study. *Arthritis Rheum*. 1999;42(7):1370-7.

368. Roth S. Efficacy and safety of tramadol HCl in breakthrough musculoskeletal pain attributed to osteoarthritis. *J Rheumatol*. 1998;25(7):1358-63.
369. Peloso PM, Bellamy N, Bensen W, et al. Double blind randomized placebo control trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. *J Rheumatol*. 2000;27(3):764-71.
370. Fishman RL, Kistler CJ, Ellerbusch MT, et al. Efficacy and safety of 12 weeks of osteoarthritic pain therapy with once-daily tramadol (Tramadol Contramid OAD). *J Opioid Manag*. 2007;3(5):273-80.
371. James IG, O'Brien CM, McDonald CJ. A randomized, double-blind, double-dummy comparison of the efficacy and tolerability of low-dose transdermal buprenorphine (BuTrans seven-day patches) with buprenorphine sublingual tablets (Temgesic) in patients with osteoarthritis pain. *J Pain Symptom Manage*. 2010;40(2):266-78.
372. Zautra AJ, Smith BW. Impact of controlled-release oxycodone on efficacy beliefs and coping efforts among osteoarthritis patients with moderate to severe pain. *Clin J Pain*. 2005;21(6):471-7.
373. Babul N, Noveck R, Chipman H, Roth SH, Gana T, Albert K. Efficacy and safety of extended-release, once-daily tramadol in chronic pain: a randomized 12-week clinical trial in osteoarthritis of the knee. *J Pain Symptom Manage*. 2004;28(1):59-71.
374. Caldwell J, Rapoport R, Davis J, et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J Pain Symptom Manage*. 2002;23(4):278-91.
375. Munera C, Drehobl M, Sessler NE, Landau C. A randomized, placebo-controlled, double-blinded, parallel-group, 5-week study of buprenorphine transdermal system in adults with osteoarthritis. *J Opioid Manag*. 2010;6(3):193-202.
376. Hartrick C, Van Hove I, Stegmann JU, Oh C, Upmalis D. Efficacy and tolerability of tapentadol immediate release and oxycodone HCl immediate release in patients awaiting primary joint replacement surgery for end-stage joint disease: a 10-day, phase III, randomized, double-blind, active- and placebo-controlled study. *Clin Ther*. 2009;31(2):260-71.
377. Likar R, Schafer M, Paulak F, et al. Intraarticular morphine analgesia in chronic pain patients with osteoarthritis. *Anesth Analg*. 1997;84(6):1313-7.
378. Fancourt GJ, Flavell Matts SG. A double-blind comparison of meptazinol versus placebo in chronic rheumatoid arthritis and osteoarthritis. *Curr Med Res Opin*. 1984;9(3):184-91.
379. Hale M, Upmalis D, Okamoto A, Lange C, Rauschkolb C. Tolerability of tapentadol immediate release in patients with lower back pain or osteoarthritis of the hip or knee over 90 days: a randomized, double-blind study. *Curr Med Res Opin*. 2009;25(5):1095-104.
380. Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology*. 1998;50(6):1837-41.
381. Hanna M, O'Brien C, Wilson MC. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. *Eur J Pain*. 2008;12(6):804-13.
382. Wild JE, Grond S, Kuperwasser B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. *Pain Pract*. 2010;10(5):416-27.
383. Jadad AR, Carroll D, Glynn CJ, Moore RA, McQuay HJ. Morphine responsiveness of chronic pain: double-blind randomised crossover study with patient-controlled analgesia. *Lancet*. 1992;339(8806):1367-71.
384. Peat S, Sweet P, Miah Y, Barklamb M, Larsen U. Assessment of analgesia in human chronic pain. Randomized double-blind crossover study of once daily repro-dose morphine versus MST continus. *Eur J Clin Pharmacol*. 1999;55(8):577-81.
385. Binsfeld H, Szczepanski L, Waechter S, Richarz U, Sabatowski R. A randomized study to demonstrate noninferiority of once-daily OROS((R)) hydromorphone with twice-daily sustained-release oxycodone for moderate to severe chronic noncancer pain. *Pain Pract*. 2010;10(5):404-15.
386. Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch Gen Psychiatry*. 2011;68(12):1238-46.
387. Farrar JT, Messina J, Xie F, Portenoy RK. A novel 12-week study, with three randomized, double-blind placebo-controlled periods to evaluate fentanyl buccal tablets for the relief of breakthrough pain in opioid-tolerant patients with noncancer-related chronic pain. *Pain Med*. 2010;11(9):1313-27.
388. Jones JD, Sullivan MA, Manubay J, Vosburg SK, Comer SD. The subjective, reinforcing, and analgesic effects of oxycodone in patients with chronic, non-malignant pain who are maintained on sublingual buprenorphine/naloxone. *Neuropsychopharmacology*. 2011;36(2):411-22.
389. Sittl R, Griessinger N, Likar R. Analgesic efficacy and tolerability of transdermal buprenorphine in patients with inadequately controlled chronic pain related to cancer and other disorders: a multicenter, randomized, double-blind, placebo-controlled trial. *Clin Ther*. 2003;25(1):150-68.
390. Harke H, Gretenkort P, Ladleif HU, Rahman S, Harke O. The response of neuropathic pain and pain in complex regional pain syndrome I to carbamazepine and sustained-release morphine in patients pretreated with spinal cord stimulation: a double-blinded randomized study. *Anesth Analg*. 2001;92(2):488-95.
391. Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ*. 2008;336(7637):199-201.
392. Keskinbora K, Pekel AF, Aydinli I. Gabapentin and an opioid combination versus opioid alone for the management of neuropathic cancer pain: a randomized open trial. *J Pain Symptom Manage*. 2007;34(2):183-9.

393. Rowbotham MC, Reisner-Keller LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia. *Neurology*. 1991;41(7):1024-8.
394. Keskinbora K, Aydinli I. Perineural morphine in patients with chronic ischemic lower extremity pain: efficacy and long-term results. *J Anesth*. 2009;23(1):11-8.
395. Kuusniemi K, Zollner J, Sjovall S, et al. Prolonged-release oxycodone/naloxone in postoperative pain management: from a randomized clinical trial to usual clinical practice. *J Int Med Res*. 2012;40(5):1775-93.
396. Rothwell MP, Pearson D, Hunter JD, et al. Oral oxycodone offers equivalent analgesia to intravenous patient-controlled analgesia after total hip replacement: a randomized, single-centre, non-blinded, non-inferiority study. *Br J Anaesth*. 2011;106(6):865-72.
397. Kastanias P, Gowans S, Tumber PS, Snaith K, Robinson S. Patient-controlled oral analgesia for postoperative pain management following total knee replacement. *Pain Res Manag*. 2010;15(1):11-6.
398. Hayek SM, Ritchey RM, Sessler D, et al. Continuous femoral nerve analgesia after unilateral total knee arthroplasty: stimulating versus nonstimulating catheters. *Anesth Analg*. 2006;103(6):1565-70.
399. Kerrick JM, Fine PG, Lipman AG, Love G. Low-dose amitriptyline as an adjunct to opioids for postoperative orthopedic pain: a placebo-controlled trial. *Pain*. 1993;52(3):325-30.
400. Mok MS, Lippmann M, Steen SN. Multidose/observational, comparative clinical analgetic evaluation of buprenorphine. *J Clin Pharmacol*. 1981;21(7):323-9.
401. Divella M, Cecconi M, Fasano N, et al. Pain relief after total hip replacement: oral CR oxycodone plus IV paracetamol versus epidural levobupivacaine and sufentanil. A randomized controlled trial. *Minerva Anestesiol*. 2012;78(5):534-41.
402. Aqua K, Gimbel JS, Singla N, Ma T, Ahdieh H, Kerwin R. Efficacy and tolerability of oxymorphone immediate release for acute postoperative pain after abdominal surgery: a randomized, double-blind, active- and placebo-controlled, parallel-group trial. *Clin Ther*. 2007;29(6):1000-12.
403. Jung YS, Kim DK, Kim MK, Kim HJ, Cha IH, Lee EW. Onset of analgesia and analgesic efficacy of tramadol/acetaminophen and codeine/acetaminophen/ibuprofen in acute postoperative pain: a single-center, single-dose, randomized, active-controlled, parallel-group study in a dental surgery pain model. *Clin Ther*. 2004;26(7):1037-45.
404. Barreveld AM, Correll DJ, Liu X, et al. Ketamine decreases postoperative pain scores in patients taking opioids for chronic pain: results of a prospective, randomized, double-blind study. *Pain Med*. 2013;14(6):925-34.
405. Backlund M, Lindgren L, Kajimoto Y, Rosenberg PH. Comparison of epidural morphine and oxycodone for pain after abdominal surgery. *J Clin Anesth*. 1997;9(1):30-5.
406. Wong HY, Parker RK, Fragen R, White PF. Pentamorphone for management of postoperative pain. *Anesth Analg*. 1991;72(5):656-60.
407. Ouellette RD. Buprenorphine and morphine efficacy in postoperative pain: a double-blind multiple-dose study. *J Clin Pharmacol*. 1982;22(4):165-72.
408. Lin FS, Lin WY, Lai CH, et al. Analgesic efficacy of tramadol/acetaminophen and propoxyphene/acetaminophen for relief of postoperative wound pain. *Acta Anaesthesiol Taiwan*. 2012;50(2):49-53.
409. Jamison RN, Edwards RR, Liu X, et al. Relationship of negative affect and outcome of an opioid therapy trial among low back pain patients. *Pain Pract*. 2013;13(3):173-81.
410. Hale ME, Nalamachu SR, Khan A, Kutch M. Effectiveness and gastrointestinal tolerability during conversion and titration with once-daily OROS(R) hydromorphone extended release in opioid-tolerant patients with chronic low back pain. *J Pain Res*. 2013;6319-29.
411. Muller FO, Odendaal CL, Muller FR, Raubenheimer J, Middle MV, Kummer M. Comparison of the efficacy and tolerability of a paracetamol/codeine fixed-dose combination with tramadol in patients with refractory chronic back pain. *Arzneimittelforschung*. 1998;48(6):675-9.
412. Katz N, Rauck R, Ahdieh H, et al. A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naive patients with chronic low back pain. *Curr Med Res Opin*. 2007;23(1):117-28.
413. Steiner D, Munera C, Hale M, Ripa S, Landau C. Efficacy and safety of buprenorphine transdermal system (BTDS) for chronic moderate to severe low back pain: a randomized, double-blind study. *J Pain*. 2011;12(11):1163-73.
414. Miller K, Yarlas A, Wen W, et al. Buprenorphine transdermal system and quality of life in opioid-experienced patients with chronic low back pain. *Expert Opin Pharmacother*. 2013;14(3):269-77.
415. Kivitz A, Ma C, Ahdieh H, Galer BS. A 2-week, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, phase III trial comparing the efficacy of oxymorphone extended release and placebo in adults with pain associated with osteoarthritis of the hip or knee. *Clin Ther*. 2006;28(3):352-64.
416. Rauck R, Rapoport R, Thipphawong J. Results of a double-blind, placebo-controlled, fixed-dose assessment of once-daily OROS(R) hydromorphone ER in patients with moderate to severe pain associated with chronic osteoarthritis. *Pain Pract*. 2013;13(1):18-29.
417. Karlsson M, Berggren AC. Efficacy and safety of low-dose transdermal buprenorphine patches (5, 10, and 20 microg/h) versus prolonged-release tramadol tablets (75, 100, 150, and 200 mg) in patients with chronic osteoarthritis pain: a 12-week, randomized, open-label, controlled, parallel-group noninferiority study. *Clin Ther*. 2009;31(3):503-13.

418. Cruciani RA, Katz N, Portenoy RK. Dose equivalence of immediate-release hydromorphone and once-daily osmotic-controlled extended-release hydromorphone: a randomized, double-blind trial incorporating a measure of assay sensitivity. *J Pain*. 2012;13(4):379-89.
419. de la Iglesia FA, Pace GW, Robinson GL, Huang NY, Stern W, Richards P. Tolerability and efficacy of two synergistic ratios of oral morphine and oxycodone combinations versus morphine in patients with chronic noncancer pain. *J Opioid Manag*. 2012;8(2):89-98.
420. Watson CP, Moulin D, Watt-Watson J, Gordon A, Eisenhoffer J. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain*. 2003;105(1-2):71-8.
421. Hamann S, Sloan P. Oral naltrexone to enhance analgesia in patients receiving continuous intrathecal morphine for chronic pain: a randomized, double-blind, prospective pilot study. *J Opioid Manag*. 2007;3(3):137-44.
422. Richarz U, Waechter S, Sabatowski R, Szczepanski L, Binsfeld H. Sustained safety and efficacy of once-daily hydromorphone extended-release (OROS(R) hydromorphone ER) compared with twice-daily oxycodone controlled-release over 52 weeks in patients with moderate to severe chronic noncancer pain. *Pain Pract*. 2013;13(1):30-40.
423. Wilder-Smith CH, Hill L, Spargo K, Kalla A. Treatment of severe pain from osteoarthritis with slow-release tramadol or dihydrocodeine in combination with NSAID's: a randomised study comparing analgesia, antinociception and gastrointestinal effects. *Pain*. 2001;91(1-2):23-31.
424. Zacny JP, Paice JA, Coalson DW. Subjective and psychomotor effects of carisoprodol in combination with oxycodone in healthy volunteers. *Drug Alcohol Depend*. 2012;120(1-3):229-32.
425. Sorensen J, Kalman S, Tropp H, Bengtsson M. Can a pharmacological pain analysis be used in the assessment of chronic low back pain? *Eur Spine J*. 1996;5(4):236-42.
426. Cloutier C, Taliano J, O'Mahony W, et al. Controlled-release oxycodone and naloxone in the treatment of chronic low back pain: a placebo-controlled, randomized study. *Pain Res Manag*. 2013;18(2):75-82.
427. Rauck RL, Bookbinder SA, Bunker TR, et al. The ACTION study: a randomized, open-label, multicenter trial comparing once-a-day extended-release morphine sulfate capsules (AVINZA) to twice-a-day controlled-release oxycodone hydrochloride tablets (OxyContin) for the treatment of chronic, moderate to severe low back pain. *J Opioid Manag*. 2006;2(3):155-66.
428. Goebel A, Lawson A, Allen S, Glynn C. Buprenorphine injection to the stellate ganglion in the treatment of upper body chronic pain syndromes. *Eur J Pain*. 2008;12(3):266-74.
429. Morley JS, Bridson J, Nash TP, Miles JB, White S, Makin MK. Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. *Palliat Med*. 2003;17(7):576-87.
430. Norrbrink C, Lundeberg T. Tramadol in neuropathic pain after spinal cord injury: a randomized, double-blind, placebo-controlled trial. *Clin J Pain*. 2009;25(3):177-84.
431. Sindrup SH, Andersen G, Madsen C, Smith T, Brosen K, Jensen TS. Tramadol relieves pain and allodynia in polyneuropathy: a randomised, double-blind, controlled trial. *Pain*. 1999;83(1):85-90.
432. Wilder-Smith CH, Hill LT, Laurent S. Postamputation pain and sensory changes in treatment-naive patients: characteristics and responses to treatment with tramadol, amitriptyline, and placebo. *Anesthesiology*. 2005;103(3):619-28.
433. Zin CS, Nissen LM, O'Callaghan JP, Duffull SB, Smith MT, Moore BJ. A randomized, controlled trial of oxycodone versus placebo in patients with postherpetic neuralgia and painful diabetic neuropathy treated with pregabalin. *J Pain*. 2010;11(5):462-71.
434. Thorne C, Beaulieu AD, Callaghan DJ, et al. A randomized, double-blind, crossover comparison of the efficacy and safety of oral controlled-release tramadol and placebo in patients with painful osteoarthritis. *Pain Res Manag*. 2008;13(2):93-102.
435. Richards P, Gimbel JS, Minkowitz HS, Kelen R, Stern W. Comparison of the efficacy and safety of dual-opioid treatment with morphine plus oxycodone versus oxycodone/acetaminophen for moderate to severe acute pain after total knee arthroplasty. *Clin Ther*. 2013;35(4):498-511.
436. Vevelstad M, Pettersen S, Tallaksen C, Brors O. O-demethylation of codeine to morphine inhibited by low-dose levomepromazine. *Eur J Clin Pharmacol*. 2009;65(8):795-801.
437. Eckhardt K, Ammon S, Hofmann U, Riebe A, Gugeler N, Mikus G. Gabapentin enhances the analgesic effect of morphine in healthy volunteers. *Anesth Analg*. 2000;91(1):185-91.
438. Gustin SM, Schwarz A, Birbaumer N, et al. NMDA-receptor antagonist and morphine decrease CRPS-pain and cerebral pain representation. *Pain*. 2010;151(1):69-76.
439. Max MB, Schafer SC, Culnane M, Dubner R, Gracely RH. Association of pain relief with drug side effects in postherpetic neuralgia: a single-dose study of clonidine, codeine, ibuprofen, and placebo. *Clin Pharmacol Ther*. 1988;43(4):363-71.
440. Nicholson B, Ross E, Sasaki J, Weil A. Randomized trial comparing polymer-coated extended-release morphine sulfate to controlled-release oxycodone HCl in moderate to severe nonmalignant pain. *Curr Med Res Opin*. 2006;22(8):1503-14.
441. Perruchoud C, Eldabe S, Durrer A, et al. Effects of flow rate modifications on reported analgesia and quality of life in chronic pain patients treated with continuous intrathecal drug therapy. *Pain Med*. 2011;12(4):571-6.
442. Katz N, Hale M, Morris D, Stauffer J. Morphine sulfate and naltrexone hydrochloride extended release capsules in patients with chronic osteoarthritis pain. *Postgrad Med*. 2010;122(4):112-28.

443. Ashburn MA, Slevin KA, Messina J, Xie F. The efficacy and safety of fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic pain. *Anesth Analg*. 2011;112(3):693-702.
444. Glynn C, Dawson D, Sanders R. A double-blind comparison between epidural morphine and epidural clonidine in patients with chronic non-cancer pain. *Pain*. 1988;34(2):123-8.
445. de Beer Jde V, Winemaker MJ, Donnelly GA, et al. Efficacy and safety of controlled-release oxycodone and standard therapies for postoperative pain after knee or hip replacement. *Can J Surg*. 2005;48(4):277-83.
446. Friedmann N, Klutzaritz V, Webster L. Long-term safety of Remoxy(R) (extended-release oxycodone) in patients with moderate to severe chronic osteoarthritis or low back pain. *Pain Med*. 2011;12(5):755-60.
447. Gustorff B. Intravenous opioid testing in patients with chronic non-cancer pain. *Eur J Pain*. 2005;9(2):123-5.
448. Kalman S, Osterberg A, Sorensen J, Boivie J, Bertler A. Morphine responsiveness in a group of well-defined multiple sclerosis patients: a study with i.v. morphine. *Eur J Pain*. 2002;6(1):69-80.
449. Isiordia-Espinoza MA, Pozos-Guillen AJ, Martinez-Rider R, Herrera-Abarca JE, Perez-Urizar J. Preemptive analgesic effectiveness of oral ketorolac plus local tramadol after impacted mandibular third molar surgery. *Med Oral Patol Oral Cir Bucal*. 2011;16(6):e776-80.
450. Wongyingsinn M, Baldini G, Stein B, Charlebois P, Liberman S, Carli F. Spinal analgesia for laparoscopic colonic resection using an enhanced recovery after surgery programme: better analgesia, but no benefits on postoperative recovery: a randomized controlled trial. *Br J Anaesth*. 2012;108(5):850-6.
451. Ahmedzai SH, Nauck F, Bar-Sela G, Bosse B, Leyendecker P, Hopp M. A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. *Palliat Med*. 2011;26(1):50-60.
452. Arai YC, Matsubara T, Shimo K, et al. Low-dose gabapentin as useful adjuvant to opioids for neuropathic cancer pain when combined with low-dose imipramine. *J Anesth*. 2010;24(3):407-10.
453. Slatkin NE, Xie F, Messina J, Segal TJ. Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. *J Support Oncol*. 2007;5(7):327-34.
454. Rodriguez RF, Castillo JM, Castillo MP, et al. Hydrocodone/acetaminophen and tramadol chlorhydrate combination tablets for the management of chronic cancer pain: a double-blind comparative trial. *Clin J Pain*. 2008;24(1):1-4.
455. Stambaugh JE, Jr., McAdams J. Comparison of the analgesic efficacy and safety oral ciramadol, codeine, and placebo in patients with chronic cancer pain. *J Clin Pharmacol*. 1987;27(2):162-6.
456. American Academy of Pain Medicine NPF, American Pain Foundation, and National Hospice and Palliative Care Organization. Recommendations to Physicians Caring for Katrina Disaster Victims on Chronic Opioids 2005.
457. Kral L. Opioid Tapering: Safely Discontinuing Opioid Analgesics. Available at: http://pain-topics.org/pdf/Safely_Tapering_Opioids.pdf. 2006.
458. American Society of Health-System Pharmacists. 2011 Update to Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing. Available at: http://www.ashp.org/DocLibrary/Bookstore/P1985/2011-Update.aspx. 2011.
459. Eastern Metropolitan Region Palliative Care Consortium (EMRPCC). Opioid Conversion Ratios - Guide to Practice 2010. Available at: http://www.emrpcc.org.au/wp-content/uploads/2013/03/EMRPCC-Opioid-Conversion2010-Final2.pdf. 2010.
460. Agency Medical Directors Group. Opioid Dose Calculator. 2012. Available at http://www.agencymeddirectors.wa.gov/Calculator/DoseCalculator.htm.
461. GlobalRPH Opioid Analgesic Converter. Available at: http://www.globalrph.com/narcoticonv.htm.
462. National Cancer Institute Pain (PDQ). Pharmacologic management. http://www.cancer.gov/cancertopics/pdq/supportivecare/pain/HealthProfessional/page3. (Accessed July 13, 2012).
463. Agency for Healthcare Research and Quality. Morbidity & mortality rounds on the web. Case & commentary. Strassels SA. Miscalculated risk. Hospital medicine. http://webmm.ahrq.gov/case.aspx?caseID=132#table1. (Accessed July 13, 2012). August 2006.
464. American Academy of Hospice and Palliative Medicine. Guidelines for prescribing opiates for hospice and palliative care patients. http://www.aahpm.org/pdf/guidelinesforopioids.pdf. (Accessed July 16, 2012).
465. Federal Drug Administration. Introduction for the FDA blueprint for prescriber education for extended-release and long-acting opioid analgesics. http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf. (Accessed July 14, 2012). July 9, 2012.
466. Martin BC, Fan MY, Edlund MJ, Devries A, Braden JB, Sullivan MD. Long-term chronic opioid therapy discontinuation rates from the TROUP study. *J Gen Intern Med*. 2011;26(12):1450-7.
467. Nilsen HK, Stiles TC, Landro NI, Fors EA, Kaasa S, Borchgrevink PC. Patients with problematic opioid use can be weaned from codeine without pain escalation. *Acta Anaesthesiol Scand*. 2010;54(5):571-9.
468. Murphy JL, Clark ME, Banou E. Opioid cessation and multidimensional outcomes after interdisciplinary chronic pain treatment. *Clin J Pain*. 2013;29(2):109-17.
469. Dreifuss JA, Griffin ML, Frost K, et al. Patient characteristics associated with buprenorphine/naloxone treatment outcome for prescription opioid dependence: Results from a multisite study. *Drug Alcohol Depend*. 2013;131(1-2):112-8.
470. Orman JS, Keating GM. Buprenorphine/naloxone: a review of its use in the treatment of opioid dependence. *Drugs*. 2009;69(5):577-607.

471. Dunn KE, Sigmon SC, Strain EC, Heil SH, Higgins ST. The association between outpatient buprenorphine detoxification duration and clinical treatment outcomes: a review. *Drug Alcohol Depend*. 2011;119(1-2):1-9.
472. Westermeyer J, McCance-Katz EF. Course and treatment of buprenorphine/naloxone withdrawal: an analysis of case reports. *Am J Addict*. 2012;21(5):401-3.
473. Ling W, Hillhouse M, Jenkins J, Miotto K, Torrington M, Chapleo C. Comparisons of analgesic potency and side effects of buprenorphine and buprenorphine with ultra-low-dose naloxone. *J Addict Med*. 2012;6(2):118-23.
474. Farahmand S, Ahmadi O, Dehpour A, Khashayar P. Does adding low doses of oral naltrexone to morphine alter the subsequent opioid requirements and side effects in trauma patients? *Am J Emerg Med*. 2012;30(1):75-8.
475. Webster LR, Bath B, Medve RA, Marmon T, Stoddard GJ. Randomized, double-blind, placebo-controlled study of the abuse potential of different formulations of oral oxycodone. *Pain Med*. 2012;13(6):790-801.
476. Fiellin DA, Barry DT, Sullivan LE, et al. A randomized trial of cognitive behavioral therapy in primary care-based buprenorphine. *Am J Med*. 2013;126(1):74 e11-7.
477. Fiellin DA, Pantalon MV, Chawarski MC, et al. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. *N Engl J Med*. 2006;355(4):365-74.
478. Fudala PJ, Yu E, Macfadden W, Boardman C, Chiang CN. Effects of buprenorphine and naloxone in morphine-stabilized opioid addicts. *Drug Alcohol Depend*. 1998;50(1):1-8.
479. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet*. 2011;377(9776):1506-13.
480. Krupitsky E, Zvartau E, Blokhina E, et al. Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence. *Arch Gen Psychiatry*. 2012;69(9):973-81.
481. Mannelli P, Peindl K, Wu LT, Patkar AA, Gorelick DA. The combination very low-dose naltrexone-clonidine in the management of opioid withdrawal. *Am J Drug Alcohol Abuse*. 2012;38(3):200-5.
482. Chawla JM, Pal H, Lal R, Jain R, Schooler N, Balhara YP. Comparison of efficacy between buprenorphine and tramadol in the detoxification of opioid (heroin)-dependent subjects. *J Opioid Manag*. 2013;9(1):35-41.
483. Gerra G, Zaimovic A, Rustichelli P, et al. Rapid opiate detoxication in outpatient treatment: relationship with naltrexone compliance. *J Subst Abuse Treat*. 2000;18(2):185-91.
484. Lobmaier PP, Kunoe N, Gossop M, Waal H. Naltrexone depot formulations for opioid and alcohol dependence: a systematic review. *CNS Neurosci Ther*. 2011;17(6):629-36.
485. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev*. 2011(4):CD001333.
486. Nosyk B, MacNab YC, Sun H, et al. Proportional hazards frailty models for recurrent methadone maintenance treatment. *Am J Epidemiol*. 2009;170(6):783-92.
487. Nosyk B, Sun H, Evans E, et al. Defining dosing pattern characteristics of successful tapers following methadone maintenance treatment: results from a population-based retrospective cohort study. *Addiction*. 2012;107(9):1621-9.
488. Janiri L, Mannelli P, Persico AM, Serretti A, Tempesta E. Opiate detoxification of methadone maintenance patients using lefetamine, clonidine and buprenorphine. *Drug Alcohol Depend*. 1994;36(2):139-45.
489. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2003(2):CD002207.
490. Howells C, Allen S, Gupta J, Stillwell G, Marsden J, Farrell M. Prison based detoxification for opioid dependence: a randomised double blind controlled trial of lofexidine and methadone. *Drug Alcohol Depend*. 2002;67(2):169-76.
491. Kleber HD. Pharmacologic treatments for opioid dependence: detoxification and maintenance options. *Dialogues Clin Neurosci*. 2007;9(4):455-70.
492. Palmstierna T. Effects of a high-dose fast tapering buprenorphine detoxification program on symptom relief and treatment retention. *J Psychoactive Drugs*. 2004;36(2):273-7.
493. Brigham GS, Amass L, Winhusen T, Harrer JM, Pelt A. Using buprenorphine short-term taper to facilitate early treatment engagement. *J Subst Abuse Treat*. 2007;32(4):349-56.
494. Lintzeris N, Leung SY, Dunlop AJ, et al. A randomised controlled trial of sublingual buprenorphine-naloxone film versus tablets in the management of opioid dependence. *Drug Alcohol Depend*. 2013;131(1-2):119-26.
495. Alford DP, LaBelle CT, Kretsch N, et al. Collaborative care of opioid-addicted patients in primary care using buprenorphine: five-year experience. *Arch Intern Med*. 2011;171(5):425-31.
496. Al-Qadheeb NS, Roberts RJ, Griffin R, Garpestad E, Ruthazer R, Devlin JW. Impact of enteral methadone on the ability to wean off continuously infused opioids in critically ill, mechanically ventilated adults: a case-control study. *Ann Pharmacother*. 2012;46(9):1160-6.
497. Camarasa X, Khazaal Y, Besson J, Zullino DF. Naltrexone-assisted rapid methadone discontinuation: a pilot study. *Eur Addict Res*. 2007;13(1):20-4.
498. Calsyn DA, Malcy JA, Saxon AJ. Slow tapering from methadone maintenance in a program encouraging indefinite maintenance. *J Subst Abuse Treat*. 2006;30(2):159-63.
499. Becker AB, Strain EC, Bigelow GE, Stitzer ML, Johnson RE. Gradual dose taper following chronic buprenorphine. *Am J Addict*. 2001;10(2):111-21.
500. Jan SA. Introduction: landscape of opioid dependence. *J Manag Care Pharm*. 2010;16(1 Suppl B):S4-8.

501. Schottenfeld RS, Pakes J, Ziedonis D, Kosten TR. Buprenorphine: dose-related effects on cocaine and opioid use in cocaine-abusing opioid-dependent humans. *Biol Psychiatry*. 1993;34(1-2):66-74.
502. Middleton LS, Nuzzo PA, Lofwall MR, Moody DE, Walsh SL. The pharmacodynamic and pharmacokinetic profile of intranasal crushed buprenorphine and buprenorphine/naloxone tablets in opioid abusers. *Addiction*. 2011;106(8):1460-73.
503. Bigelow GE, Preston KL, Schmittner J, Dong Q, Gastfriend DR. Opioid challenge evaluation of blockade by extended-release naltrexone in opioid-abusing adults: dose-effects and time-course. *Drug Alcohol Depend*. 2012;123(1-3):57-65.
504. Krabbe PF, Koning JP, Heinen N, Laheij RJ, van Cauter RM, De Jong CA. Rapid detoxification from opioid dependence under general anaesthesia versus standard methadone tapering: abstinence rates and withdrawal distress experiences. *Addict Biol*. 2003;8(3):351-8.
505. Jones HE, O'Grady KE, Malfi D, Tuten M. Methadone maintenance vs. methadone taper during pregnancy: maternal and neonatal outcomes. *Am J Addict*. 2008;17(5):372-86.
506. Cami J, de Torres S, San L, Sole A, Guerra D, Ugena B. Efficacy of clonidine and of methadone in the rapid detoxification of patients dependent on heroin. *Clin Pharmacol Ther*. 1985;38(3):336-41.
507. Perez de los Cobos J, Duro P, Trujols J, et al. Methadone tapering plus amantadine to detoxify heroin-dependent inpatients with or without an active cocaine use disorder: two randomised controlled trials. *Drug Alcohol Depend*. 2001;63(2):187-95.
508. Mitchell SG, Gryczynski J, Schwartz RP, O'Grady KE, Olsen YK, Jaffe JH. A randomized trial of intensive outpatient (IOP) vs. standard outpatient (OP) buprenorphine treatment for African Americans. *Drug Alcohol Depend*. 2013;128(3):222-9.
509. Amass L, Bickel WK, Higgins ST, Hughes JR. A preliminary investigation of outcome following gradual or rapid buprenorphine detoxification. *J Addict Dis*. 1994;13(3):33-45.
510. Ling W, Amass L, Shoptaw S, et al. A multi-center randomized trial of buprenorphine-naloxone versus clonidine for opioid detoxification: findings from the National Institute on Drug Abuse Clinical Trials Network. *Addiction*. 2005;100(8):1090-100.
511. Ling W, Hillhouse M, Domier C, et al. Buprenorphine tapering schedule and illicit opioid use. *Addiction*. 2009;104(2):256-65.
512. Ling W, Casadonte P, Bigelow G, et al. Buprenorphine implants for treatment of opioid dependence: a randomized controlled trial. *Jama*. 2010;304(14):1576-83.
513. Wright NM, Sheard L, Adams CE, et al. Comparison of methadone and buprenorphine for opiate detoxification (LEEDS trial): a randomised controlled trial. *Br J Gen Pract*. 2011;61(593):e772-80.
514. Neumann AM, Blondell RD, Jaanimagi U, et al. A preliminary study comparing methadone and buprenorphine in patients with chronic pain and coexistent opioid addiction. *J Addict Dis*. 2013;32(1):68-78.
515. Blondell RD, Ashrafioun L, Dambra CM, Foschio EM, Zielinski AL, Salcedo DM. A clinical trial comparing tapering doses of buprenorphine with steady doses for chronic pain and co-existent opioid addiction. *J Addict Med*. 2010;4(3):140-6.
516. Nielsen S, Hillhouse M, Thomas C, Hasson A, Ling W. A comparison of buprenorphine taper outcomes between prescription opioid and heroin users. *J Addict Med*. 2013;7(1):33-8.
517. Everly JJ, DeFulio A, Koffarnus MN, et al. Employment-based reinforcement of adherence to depot naltrexone in unemployed opioid-dependent adults: a randomized controlled trial. *Addiction*. 2011;106(7):1309-18.
518. DeFulio A, Everly JJ, Leoutsakos JM, et al. Employment-based reinforcement of adherence to an FDA approved extended release formulation of naltrexone in opioid-dependent adults: a randomized controlled trial. *Drug Alcohol Depend*. 2012;120(1-3):48-54.
519. Strain EC, Bigelow GE, Liebson IA, Stitzer ML. Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial. *Jama*. 1999;281(11):1000-5.
520. Warden D, Subramaniam GA, Carmody T, et al. Predictors of attrition with buprenorphine/naloxone treatment in opioid dependent youth. *Addict Behav*. 2012;37(9):1046-53.
521. Roux P, Sullivan MA, Cohen J, et al. Buprenorphine/naloxone as a promising therapeutic option for opioid abusing patients with chronic pain: Reduction of pain, opioid withdrawal symptoms, and abuse liability of oral oxycodone. *Pain*. 2013;154(8):1442-8.
522. Potter JS, Marino EN, Hillhouse MP, et al. Buprenorphine/naloxone and methadone maintenance treatment outcomes for opioid analgesic, heroin, and combined users: findings from Starting Treatment with Agonist Replacement Therapies (START). *J Stud Alcohol Drugs*. 2013;74(4):605-13.
523. Madlung-Kratzer E, Spitzer B, Brosch R, Dunkel D, Haring C. A double-blind, randomized, parallel group study to compare the efficacy, safety and tolerability of slow-release oral morphine versus methadone in opioid-dependent in-patients willing to undergo detoxification. *Addiction*. 2009;104(9):1549-57.
524. Jain K, Jain R, Dhawan A. A double-blind, double-dummy, randomized controlled study of memantine versus buprenorphine in naloxone-precipitated acute withdrawal in heroin addicts. *J Opioid Manag*. 2011;7(1):11-20.
525. Kirtadze I, Otiashvili D, O'Grady KE, Jones HE. Behavioral treatment + naltrexone reduces drug use and legal problems in the Republic of Georgia. *Am J Drug Alcohol Abuse*. 2012;38(2):171-5.
526. Comer SD, Sullivan MA, Vosburg SK, et al. Abuse liability of intravenous buprenorphine/naloxone and buprenorphine alone in buprenorphine-maintained intravenous heroin abusers. *Addiction*. 2010;105(4):709-18.
527. Ruger JP, Chawarski M, Mazlan M, Ng N, Schottenfeld R. Cost-effectiveness of buprenorphine and naltrexone treatments for heroin dependence in Malaysia. *PLoS ONE*. 2012;7(12):e50673.

528. Coviello DM, Cornish JW, Lynch KG, Alterman AI, O'Brien CP. A randomized trial of oral naltrexone for treating opioid-dependent offenders. *Am J Addict*. 2010;19(5):422-32.
529. Cropsey KL, Lane PS, Hale GJ, et al. Results of a pilot randomized controlled trial of buprenorphine for opioid dependent women in the criminal justice system. *Drug Alcohol Depend*. 2011;119(3):172-8.
530. *New Zealand Clinical Guidelines for the Use of Buprenorphine (with or without Naloxone) in the Treatment of Opioid Dependence* Wellington: Ministry of Health; 2010.
531. Amato JN, Marie S, Lelong-Boulouard V, et al. Effects of three therapeutic doses of codeine/paracetamol on driving performance, a psychomotor vigilance test, and subjective feelings. *Psychopharmacology (Berl)*. 2013;228(2):309-20.
532. Ray LA, Bujarski S, Chin PF, Miotto K. Pharmacogenetics of naltrexone in asian americans: a randomized placebo-controlled laboratory study. *Neuropsychopharmacology*. 2012;37(2):445-55.
533. Krupitsky EM, Burakov AM, Dunaevsky IV, Romanova TN, Slavina TY, Grinenko AY. Single versus repeated sessions of ketamine-assisted psychotherapy for people with heroin dependence. *J Psychoactive Drugs*. 2007;39(1):13-9.
534. O'Brien C, Cornish JW. Naltrexone for probationers and parolees. *J Subst Abuse Treat*. 2006;31(2):107-11.
535. Sullivan MD, Edlund MJ, Zhang L, Unutzer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. *Arch Intern Med*. 2006;166(19):2087-93.
536. Lintzeris N, Lee S, Scopelliti L, Mabbutt J, Haber PS. Unplanned admissions to two Sydney public hospitals after naltrexone implants. *Med J Aust*. 2008;188(8):441-4.
537. Stein MD, Herman DS, Kettavong M, et al. Antidepressant treatment does not improve buprenorphine retention among opioid-dependent persons. *J Subst Abuse Treat*. 2010;39(2):157-66.
538. Lobmaier P, Gossop M, Waal H, Bramness J. The pharmacological treatment of opioid addiction--a clinical perspective. *Eur J Clin Pharmacol*. 2010;66(6):537-45.
539. Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Arch Gen Psychiatry*. 2006;63(2):210-8.
540. Kunoe N, Lobmaier P, Vederhus JK, et al. Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial. *Br J Psychiatry*. 2009;194(6):541-6.
541. Carreno JE, Alvarez CE, Narciso GI, Bascaran MT, Diaz M, Bobes J. Maintenance treatment with depot opioid antagonists in subcutaneous implants: an alternative in the treatment of opioid dependence. *Addict Biol*. 2003;8(4):429-38.
542. Colquhoun R, Tan DY, Hull S. A comparison of oral and implant naltrexone outcomes at 12 months. *J Opioid Manag*. 2005;1(5):249-56.
543. Foster J, Brewer C, Steele T. Naltrexone implants can completely prevent early (1-month) relapse after opiate detoxification: a pilot study of two cohorts totalling 101 patients with a note on naltrexone blood levels. *Addict Biol*. 2003;8(2):211-7.
544. Grusser SM, Thalemann CN, Platz W, Golz J, Partecke G. A new approach to preventing relapse in opiate addicts: a psychometric evaluation. *Biol Psychol*. 2006;71(3):231-5.
545. Hulse G, O'Neil G. Using naltrexone implants in the management of the pregnant heroin user. *Aust N Z J Obstet Gynaecol*. 2002;42(5):569-73.
546. Hulse GK. Behavioural family counselling reduces drug use in opioid-dependent men. *Evid Based Ment Health*. 2003;6(4):123.
547. Hulse GK, Arnold-Reed DE, O'Neil G, Hansson RC. Naltrexone implant and blood naltrexone levels over pregnancy. *Aust N Z J Obstet Gynaecol*. 2003;43(5):386-8.
548. Hulse GK, Morris N, Arnold-Reed D, Tait RJ. Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone. *Arch Gen Psychiatry*. 2009;66(10):1108-15.
549. Hulse GK, O'Neil G, Hatton M, Paech MJ. Use of oral and implantable naltrexone in the management of the opioid impaired physician. *Anaesth Intensive Care*. 2003;31(2):196-201.
550. Hulse GK, O'Neill G. A possible role for implantable naltrexone in the management of the high-risk pregnant heroin user. *Aust N Z J Obstet Gynaecol*. 2002;42(1):93-4.
551. Hulse GK, Tait RJ. A pilot study to assess the impact of naltrexone implant on accidental opiate overdose in 'high-risk' adolescent heroin users. *Addict Biol*. 2003;8(3):337-42.
552. Hulse GK, Low VH, Stalenberg V, et al. Biodegradability of naltrexone-poly(DL) lactide implants in vivo assessed under ultrasound in humans. *Addict Biol*. 2008;13(3-4):364-72.
553. Hulse GK, Tait RJ, Comer SD, Sullivan MA, Jacobs IG, Arnold-Reed D. Reducing hospital presentations for opioid overdose in patients treated with sustained release naltrexone implants. *Drug Alcohol Depend*. 2005;79(3):351-7.
554. Ngo HT, Tait RJ, Arnold-Reed DE, Hulse GK. Mental health outcomes following naltrexone implant treatment for heroin-dependence. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(3):605-12.
555. Ngo HT, Tait RJ, Hulse GK. Comparing drug-related hospital morbidity following heroin dependence treatment with methadone maintenance or naltrexone implantation. *Arch Gen Psychiatry*. 2008;65(4):457-65.
556. Tait RJ, Ngo HT, Hulse GK. Mortality in heroin users 3 years after naltrexone implant or methadone maintenance treatment. *J Subst Abuse Treat*. 2008;35(2):116-24.
557. Brewer C. Serum naltrexone and 6-beta-naltrexol levels from naltrexone implants can block very large amounts of heroin: a report of two cases. *Addict Biol*. 2002;7(3):321-3.

558. Brewer C, Wong VS. Naltrexone: report of lack of hepatotoxicity in acute viral hepatitis, with a review of the literature. *Addict Biol*. 2004;9(1):81-7.
559. Fishman M. Precipitated withdrawal during maintenance opioid blockade with extended release naltrexone. *Addiction*. 2008;103(8):1399-401.
560. Gibson AE, Degenhardt LJ. Mortality related to pharmacotherapies for opioid dependence: a comparative analysis of coronial records. *Drug Alcohol Rev*. 2007;26(4):405-10.
561. Hamilton RJ, Olmedo RE, Shah S, et al. Complications of ultrarapid opioid detoxification with subcutaneous naltrexone pellets. *Acad Emerg Med*. 2002;9(1):63-8.
562. He F, Guan H, Zhao Z, et al. Evaluation of short-term psychological functions in opiate addicts after ablating the nucleus accumbens via stereotactic surgery. *Stereotact Funct Neurosurg*. 2008;86(5):320-9.
563. He L, Kim JA, Whistler JL. Biomarkers of morphine tolerance and dependence are prevented by morphine-induced endocytosis of a mutant mu-opioid receptor. *FASEB J*. 2009;23(12):4327-34.
564. Reece AS. Comparative treatment and mortality correlates and adverse event profile of implant naltrexone and sublingual buprenorphine. *J Subst Abuse Treat*. 2009;37(3):256-65.
565. Reece AS. Diacetylmorphine versus methadone for opioid addiction. *N Engl J Med*. 2009;361(22):2194-5; author reply 5.
566. Reece AS, Davidson P. Deficit of circulating stem--progenitor cells in opiate addiction: a pilot study. *Subst Abuse Treat Prev Policy*. 2007;219.
567. Waal H, Aamodt O, Olsen H. Use of naltrexone in the treatment of young drug addicts. *Tidsskr Nor Laegeforen*. 2003;123(12):1662-4.
568. Waal H, Frogopsahl G, Olsen L, Christophersen AS, Morland J. Naltrexone implants -- duration, tolerability and clinical usefulness. A pilot study. *Eur Addict Res*. 2006;12(3):138-44.
569. Oliver P, Horspool M, Keen J. Fatal opiate overdose following regimen changes in naltrexone treatment. *Addiction*. 2005;100:560-3.
570. Goltz J, Partecke G. Catamnestic outcome of opiate addicts after rapid opiate detoxification under anesthesia, relapse-prophylaxis with naltrexone and psychosocial care. *Suctttherapie*. 2000;1:166-72.
571. Pederson C, Parran L. Opioid tapering in hematopoietic progenitor cell transplant recipients. *Oncol Nurs Forum*. 2000;27(9):1371-80.
572. Parran L, Pederson C. Effects of an opioid taper algorithm in hematopoietic progenitor cell transplant recipients. *Oncol Nurs Forum*. 2002;29(1):41-50.
573. Parran L, Pederson C. Development of an opioid-taper algorithm for hematopoietic cell transplant recipients. *Oncol Nurs Forum*. 2000;27(6):967-74.
574. Fine P, Messina J, Xie F, Rathmell J. Long-term safety and tolerability of fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic pain: an 18-month study. *J Pain Symptom Manage*. 2010;40(5):747-60.
575. Hojsted J, Nielsen P, Eriksen J, Hansen O, Sjøgren P. Breakthrough pain in opioid-treated chronic non-malignant pain patients referred to a multidisciplinary pain centre: a preliminary study. *Acta Anaesthesiol Scand*. 2006;50(10):1290-6.
576. Simmonds M. Management of breakthrough pain due to cancer. *Oncology*. 1999;13(8):1103-8.
577. Rauck R, North J, Finn A. Fentanyl buccal soluble film (FBSF) for breakthrough pain in patients with cancer: a randomized, double-blind, placebo-controlled study. *Ann Oncology*. 2010;21(6):1308-14.
578. Mercadante S, Radbruch L, Davies A, et al. A comparison of intranasal fentanyl spray with oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain: an pen-label, randomised, crossover trial. *Curr Med Res Opinion*. 2009;25(11):2805-15.
579. Hanks G, Conno F, Cherny N, et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer*. 2001;84(5):587-93.
580. Hansen M, Mathiesen O, Trautner S, Dahl J. Intranasal fentanyl in the treatment of acute pain – a systematic review. *Acta Anaesthesiol Scand*. 2012;56(4):407-19.
581. Kress H, Orońska A, Kaczmarek Z, Kaasa S, Colberg T, Nolte T. Efficacy and tolerability of intranasal fentanyl spray 50 to 200 ug for breakthrough pain in patients with cancer: a Phase III, multinational, randomized, double-blind, placebo-controlled, crossover trial with a la-month, open-label extension treatment period. *Clin Ther*. 2009;31(6):1177-91.
582. Zeppetella G. An assessment of the safety, efficacy, and acceptability of intranasal fentanyl citrate in the management of cancer-related breakthrough pain: a pilot study. *J Pain Symptom Manage*. 2000;20(4):253-8.
583. Zeppetella G. Sublingual fentanyl citrate for cancer-related breakthrough pain: a pilot study. *Palliat Med*. 2001;15(4):323-8.
584. Zeppetella G, Messina J, Xie F, Slatkin N. Consistent and clinically relevant effects with fentanyl buccal tablet in the treatment of patients receiving maintenance opioid therapy and experiencing cancer-related breakthrough pain. *Pain Pract*. 2010;10(4):287-93.
585. Zeppetella G, O'Doherty C, Collins S. Prevalence and characteristics of breakthrough pain in cancer patients admitted to a hospice. *J Pain Symptom Manage*. 2000;20(2):87-92.
586. Zeppetella G, O'Doherty CA, Collins S. Prevalence and characteristics of breakthrough pain in patients with non-malignant terminal disease admitted to a hospice. *Palliat Med*. 2001;15(3):243-6.
587. Zeppetella G, Ribeiro M. Opioids for the management of breakthrough (episodic) pain in cancer patients. *Cochrane Database Syst Rev*. 2006(1):CD004311.

588. Portenoy R, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain*. 1999;81(1-2):129-34.
589. William L, Macleod R. Management of breakthrough pain in patients with cancer. *Drugs*. 2008;68(7):913-24.
590. Svendsen K, Andersen S, Arnason S, et al. Breakthrough pain in malignant and non-malignant diseases: a review of prevalence, characteristics and mechanisms. *Eur J Pain*. 2005;9(2):195-206.
591. Vissers D, Lenre M, Tolley K, Jakobsson J, Sendersky V, Jansen J. An economic evaluation of short-acting opioids for treatment of breakthrough pain in patients with cancer. *Value Health*. 2011;14(2):274-81.
592. Pavis H, Wilcock A, Edgecombe J, et al. Pilot study of nasal morphine-chitosan for the relief of breakthrough pain in patients with cancer. *J Pain Symptom Manage*. 2002;24(6):598-602.
593. Smith H. A comprehensive review of rapid-onset opioids for breakthrough pain. *CNS Drugs*. 2012;26(6):509-35.
594. Portenoy R, Bennett D, Rauck R, et al. Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain. *J Pain*. 2006;7(8):583-91.
595. Boezaart A, Eksteen JA, Spuy GV, Rossouw P, M. K. Intrathecal morphine. Double-blind evaluation of optimal dosage for analgesia after major lumbar spinal surgery. . *SPINE*. 1999;24(11):1131-7.
596. Chan JH, Heilpern GN, Packham I, Trehan RK, Marsh GD, Knibb AA. A prospective randomized double-blind trial of the use of intrathecal fentanyl in patients undergoing lumbar spinal surgery. *SPINE*. 2006;31(22):2529-33.
597. France JC, Jorgenson SS, Lowe TG, Dwyer AP. The use of intrathecal morphine for analgesia after posterolateral lumbar fusion: a prospective, double-blind, randomized study. *SPINE*. 1997;22(19):2272-7.
598. O'Neill P, Knickenberg C, Bogahalanda S, Booth AE. Use of intrathecal morphine for postoperative pain relief following lumbar spine surgery. *J Neurosurg*. 1985;63(3):413-6.
599. Coffey RJ, Owens ML, Broste SK, et al. Mortality associated with implantation and management of intrathecal opioid drug infusion systems to treat noncancer pain. *Anesthesiology*. 2009;111(4):881-91.
600. Deer T, Chapple I, Classen A, et al. Intrathecal drug delivery for treatment of chronic low back pain: report from the National Outcomes Registry for Low Back Pain. *Pain Med*. 2004;5(1):6-13.
601. Turner JA, Sears JM, Loeser JD. Programmable intrathecal opioid delivery systems for chronic noncancer pain: a systematic review of effectiveness and complications. *Clin J Pain*. 2007;23(2):180-95.
602. Miele VJ, Price KO, Bloomfield S, Hogg J, Bailes JE. A review of intrathecal morphine therapy related granulomas. *Eur J Pain*. 2006;10(3):251-61.
603. Rauck RL, Wallace MS, Leong MS, et al. A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. *J Pain Symptom Manage*. 2006;31(5):393-406.
604. Raffaeli W, Marconi G, Fanelli G, Taddei S, Borghi GB, Casati A. Opioid-related side-effects after intrathecal morphine: a prospective, randomized, double-blind dose-response study. *Eur J Anaesthesiol*. 2006;23(7):605-10.
605. Hay JL, White JM, Bochner F, Somogyi AA, Semple TJ, Rounsefell B. Hyperalgesia in opioid-managed chronic pain and opioid-dependent patients. *J Pain*. 2009;10(3):316-22.
606. Ram KC, Eisenberg E, Haddad M, Pud D. Oral opioid use alters DNIC but not cold pain perception in patients with chronic pain - new perspective of opioid-induced hyperalgesia. *Pain*. 2008;139(2):431-8.
607. Tarkkila P, Tuominen M, Lindgren L. Comparison of respiratory effects of tramadol and oxycodone. *J Clin Anesth*. 1997;9(7):582-5.
608. Sandler AN, Chovaz P, Whiting W. Respiratory depression following epidural morphine: a clinical study. *Can Anaesth Soc J*. 1986;33(5):542-9.
609. Ladd LA, Kam PC, Williams DB, Wright AW, Smith MT, Mather LE. Ventilatory responses of healthy subjects to intravenous combinations of morphine and oxycodone under imposed hypercapnic and hypoxaemic conditions. *Br J Clin Pharmacol*. 2005;59(5):524-35.
610. Tantucci C, Paoletti F, Bruni B, et al. Acute respiratory effects of sublingual buprenorphine: comparison with intramuscular morphine. *Int J Clin Pharmacol Ther Toxicol*. 1992;30(6):202-7.
611. Bailey PL, Sperry RJ, Johnson GK, et al. Respiratory effects of clonidine alone and combined with morphine, in humans. *Anesthesiology*. 1991;74(1):43-8.
612. Bulow HH, Linnemann M, Berg H, Lang-Jensen T, LaCour S, Jonsson T. Respiratory changes during treatment of postoperative pain with high dose transdermal fentanyl. *Acta Anaesthesiol Scand*. 1995;39(6):835-9.
613. Thompson PI, Joel SP, John L, Wedzicha JA, Maclean M, Slevin ML. Respiratory depression following morphine and morphine-6-glucuronide in normal subjects. *Br J Clin Pharmacol*. 1995;40(2):145-52.
614. White MJ, Berghausen EJ, Dumont SW, et al. Side effects during continuous epidural infusion of morphine and fentanyl. *CAN J ANAESTH*. 1992;39(6):576-82.
615. Olofsen E, van Dorp E, Teppema L, et al. Naloxone reversal of morphine- and morphine-6-glucuronide-induced respiratory depression in healthy volunteers: a mechanism-based pharmacokinetic-pharmacodynamic modeling study. *Anesthesiology*. 2010;112(6):1417-27.
616. Yassen A, Olofsen E, Romberg R, et al. Mechanism-based PK/PD modeling of the respiratory depressant effect of buprenorphine and fentanyl in healthy volunteers. *Clin Pharmacol Ther*. 2007;81(1):50-8.
617. Jungquist C, Flannery M, Perlis M, Grace J. Relationship of chronic pain and opioid use with respiratory disturbance during sleep. *Pain Manage Nurs*. 2012;13(2):70-9.
618. Jungquist CR, Karan S, Perlis ML. Risk factors for opioid-induced excessive respiratory depression. *Pain Manag Nurs*. 2011;12(3):180-7.

619. Talbert RL, Peters JI, Sorrells SC, Simmons RS. Respiratory effects of high-dose butorphanol. *Acute Care*. 1988;12 Suppl 147-56.
620. Caspi J, Klausner JM, Safadi T, Amar R, Rozin RR, Merin G. Delayed respiratory depression following fentanyl anesthesia for cardiac surgery. *Crit Care Med*. 1988;16(3):238-40.
621. Goldberg ME, Torjman M, Bartkowski RR, Mora CT, Boerner T, Seltzer JL. Time-course of respiratory depression after an alfentanil infusion-based anesthetic. *Anesth Analg*. 1992;75(6):965-71.
622. Clemens KE, Quednau I, Klaschik E. Is there a higher risk of respiratory depression in opioid-naive palliative care patients during symptomatic therapy of dyspnea with strong opioids? *J Palliat Med*. 2008;11(2):204-16.
623. Niesters M, Mahajan RP, Aarts L, Dahan A. High-inspired oxygen concentration further impairs opioid-induced respiratory depression. *Br J Anaesth*. 2013;110(5):837-41.
624. Dahan A. Respiratory depression with opioids. *J Pain Palliat Care Pharmacother*. 2007;21(1):63-6.
625. Dahan A, Aarts L, Smith T. Incidence, reversal, and prevention of opioid-induced respiratory depression. *Anesthesiology*. 2010;112(1):226-38.
626. Dahan A, Overdyk F, Smith T, Aarts L, Niesters M. Pharmacovigilance: a review of opioid-induced respiratory depression in chronic pain patients. *Pain Physician*. 2013;16(2):E85-94.
627. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth*. 2006;96(5):627-32.
628. Shapiro A, Zohar E, Zaslansky R, Hoppenstein D, Shabat S, Fredman B. The frequency and timing of respiratory depression in 1524 postoperative patients treated with systemic or neuraxial morphine. *J Clin Anesth*. 2005;17(7):537-42.
629. Taylor S, Kirton OC, Staff I, Kozol RA. Postoperative day one: a high risk period for respiratory events. *Am J Surg*. 2005;190(5):752-6.
630. Sam WJ, MacKey SC, Lotsch J, Drover DR. Morphine and its metabolites after patient-controlled analgesia: considerations for respiratory depression. *J Clin Anesth*. 2011;23(2):102-6.
631. Oertel BG, Felden L, Tran PV, et al. Selective antagonism of opioid-induced ventilatory depression by an ampakine molecule in humans without loss of opioid analgesia. *Clin Pharmacol Ther*. 2010;87(2):204-11.
632. Renaud B, Brichant JF, Clergue F, Chauvin M, Levron JC, Viars P. Ventilatory effects of continuous epidural infusion of fentanyl. *Anesth Analg*. 1988;67(10):971-5.
633. Barletta JF. Clinical and economic burden of opioid use for postsurgical pain: focus on ventilatory impairment and ileus. *Pharmacotherapy*. 2012;32(9 Suppl):12S-8S.
634. Carvalho B. Respiratory depression after neuraxial opioids in the obstetric setting. *Anesth Analg*. 2008;107(3):956-61.
635. Sultan P, Gutierrez MC, Carvalho B. Neuraxial morphine and respiratory depression: finding the right balance. *Drugs*. 2011;71(14):1807-19.
636. Sumida S, Lesley MR, Hanna MN, Murphy JD, Kumar K, Wu CL. Meta-analysis of the effect of extended-release epidural morphine versus intravenous patient-controlled analgesia on respiratory depression. *J Opioid Manag*. 2009;5(5):301-5.
637. Dinis-Oliveira RJ, Carvalho F, Moreira R, et al. Clinical and forensic signs related to opioids abuse. *Curr Drug Abuse Rev*. 2012;5(4):273-90.
638. Etches RC, Sandler AN, Daley MD. Respiratory depression and spinal opioids. *CAN J ANAESTH*. 1989;36(2):165-85.
639. George JA, Lin EE, Hanna MN, et al. The effect of intravenous opioid patient-controlled analgesia with and without background infusion on respiratory depression: a meta-analysis. *J Opioid Manag*. 2010;6(1):47-54.
640. Jarzyna D, Jungquist CR, Pasero C, et al. American Society for Pain Management Nursing guidelines on monitoring for opioid-induced sedation and respiratory depression. *Pain Manag Nurs*. 2011;12(3):118-45 e10.
641. Kato R, Shimamoto H, Terui K, Yokota K, Miyao H. Delayed respiratory depression associated with 0.15 mg intrathecal morphine for cesarean section: a review of 1915 cases. *J Anesth*. 2008;22(2):112-6.
642. Smith LH. Opioid safety: is your patient at risk for respiratory depression? *Clin J Oncol Nurs*. 2007;11(2):293-6.
643. Macintyre PE, Loadsman JA, Scott DA. Opioids, ventilation and acute pain management. *Anaesth Intensive Care*. 2011;39(4):545-58.
644. Mahla ME, White SE, Moneta MD. Delayed respiratory depression after alfentanil. *Anesthesiology*. 1988;69(4):593-5.
645. Pasero C. Opioid-induced sedation and respiratory depression: evidence-based monitoring guidelines. *J Perianesth Nurs*. 2012;27(3):208-11.
646. Berland D, Rodgers P. Rational use of opioids for management of chronic nonterminal pain. *Am Fam Physician*. 2012;86(3):252-8.
647. Burgess F. Methadone analgesia: balancing the risks and benefits. *Pain Medicine News*; 2009.
648. Zacny J. A review of the effects of opioids on psychomotor and cognitive functioning in humans. *Experimental Clinical Psychopharmacology*. 2005;3(4):432-66.
649. Vella-Brincat J, Macleod A. Adverse effects of opioids on the central nervous systems of palliative care patients. *J Pain Palliat Care Pharmacother*. 2007;21(1):15-25.
650. Trescot AM, Helm S, Hansen H, et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines. *Pain Physician*. 2008;11(2 Suppl):S5-S62.

651. Dimsdale J, Norman D, DeJardin D, Wallace M. The effect of opioids on sleep architecture. *J Clin Sleep Med*. 2007;3(1):33-6.
652. Abs R, Abs R, Verhelst J, et al. Endocrine consequences of long-term intrathecal administration of opioids. *J Clin Endocrinol Metab*. 2000;85(6):2215-22.
653. Vuong C, Van Uum S, O'Dell L, Lutfy K, Friedman T. The effects of opioids and opioid analogs on animal and human endocrine systems. *Endocr Rev*. 2010;3198-132.
654. Chaney M. Side effects of intrathecal and epidural opioids. *Can J Anaest*. 1995;42(10):891-903.
655. Chu L, Angst M, Clark D. Opioid-induced hyperalgesia in humans. Molecular mechanisms and clinical considerations. *Clin J Pain*. 2008;24(6):479-96.
656. Lee M, Silverman S, Hansen H, Patel V, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician*. 2011;14(2):145-61.
657. Silverman S. Opioid induced hyperalgesia: clinical implications for the pain practitioner. *Pain Physician*. 2009;12679-84.
658. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology*. 2006;104(3):570-87.
659. Chang G, Chen L, Mao J. Opioid tolerance and hyperalgesia. *Med Clin North Am*. 2007;91(2):199-211.
660. Kidner CL, Mayer TG, Gatchel RJ. Higher opioid doses predict poorer functional outcome in patients with chronic disabling occupational musculoskeletal disorders. *J Bone Joint Surg Am*. 2009;91(4):919-27.
661. Franklin GM, Stover BD, Turner JA, Fulton-Kehoe D, Wickizer TM. Early opioid prescription and subsequent disability among workers with back injuries: the Disability Risk Identification Study Cohort. *SPINE*. 2008;33(2):199-204.
662. Chen SL, Lee SY, Tao PL, et al. Dextromethorphan attenuated inflammation and combined opioid use in humans undergoing methadone maintenance treatment. *J Neuroimmune Pharmacol*. 2012;7(4):1025-33.
663. Braden JB, Russo J, Fan MY, et al. Emergency department visits among recipients of chronic opioid therapy. *Arch Intern Med*. 2010;170(16):1425-32.
664. Ivers N, Dhalla I, Allan G. Opioids for osteoarthritis pain: benefits and risks. *Canadian Family Physician*. 2012;58(12):e708.
665. Portenoy RK, Farrar JT, Backonja MM, et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. *Clin J Pain*. 2007;23(4):287-99.
666. Currow DC, McDonald C, Oaten S, et al. Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. *J Pain Symptom Manage*. 2011;42(3):388-99.
667. Andresen H, Gullans A, Veselinovic M, et al. Fentanyl: toxic or therapeutic? Postmortem and antemortem blood concentrations after transdermal fentanyl application. *J Anal Toxicol*. 2012;36(3):182-94.
668. Modesto-Lowe V, Brooks D, Petry N. Methadone deaths: risk factors in pain and addicted populations. *J Gen Intern Med*. 2010;25(4):305-9.
669. Anchersen K, Clausen T, Gossop M, Hansteen V, Waal H. Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. *Addiction*. 2009;104(6):993-9.
670. Chugh SS, Socoteanu C, Reinier K, Waltz J, Jui J, Gunson K. A community-based evaluation of sudden death associated with therapeutic levels of methadone. *Am J Med*. 2008;121(1):66-71.
671. Manchikanti L, Singh A. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician*. 2008;11(2 Suppl):S63-88.
672. Sadeghian S, Karimi A, Dowlatshahi S, et al. The association of opium dependence and postoperative complications following coronary artery bypass graft surgery: a propensity-matched study. *J Opioid Manag*. 2009;5(6):365-72.
673. Safaii N, Kazemi B. Effect of opium use on short-term outcome in patients undergoing coronary artery bypass surgery. *Gen Thorac Cardiovasc Surg*. 2010;58(2):62-7.
674. Agusti A, Pages E, Cuxart A, et al. Exposure to medicines among patients admitted for hip fracture and the case-fatality rate at 1 year: a longitudinal study. *Eur J Clin Pharmacol*. 2012;68(11):1525-31.
675. Basbaum AI, Julius D. Toward better pain control. *Sci Am*. 2006;294(6):60-7.
676. Mao J, Price DD, Mayer DJ. Thermal hyperalgesia in association with the development of morphine tolerance in rats: roles of excitatory amino acid receptors and protein kinase C. *J Neurosci*. 1994;14(4):2301-12.
677. Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesia and morphine tolerance: a current view of their possible interactions. *Pain*. 1995;62(3):259-74.
678. Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med*. 2003;349(20):1943-53.
679. Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain: a review of the evidence. *Clin J Pain*. 2008;24(6):469-78.
680. Ballantyne J. Chapter 5. Opioid Tolerance, Dependence and Hyperalgesia. In: Mao J, ed. *Opioid-Induced Hyperalgesia*: CRC Press; 2009.
681. Ballantyne JC. "Safe and effective when used as directed": the case of chronic use of opioid analgesics. *J Med Toxicol*. 2012;8(4):417-23.
682. Mitra S. Opioid-induced hyperalgesia: pathophysiology and clinical implications. *J Opioid Manag*. 2008;4(3):123-30.
683. Bannister K, Dickenson AH. Opioid hyperalgesia. *Curr Opin Support Palliat Care*. 2010;4(1):1-5.

684. Daniell HW. Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. *J Pain*. 2008;9(1):28-36.
685. Cicero T, Bell R, Wiest W, Allison J, Polakoski K, Robins E. Function of the male sex organs in heroin and methadone users. *N Engl J Med*. 1975;292(17):882-7.
686. Mendelson J, Meyer R, Ellingboe J, Mirin S, McDougle M. Effects of heroin and methadone on plasma cortisol and testosterone. *J Pharmacology Experimental Therapeutics*. 1975;195(2):296-302.
687. Mendelson JH, Mello NK. Plasma testosterone levels during chronic heroin use and protracted astinence. A study of Hong Kong addicts. *Clin Pharmacol Ther*. 1975;17(5):529-33.
688. Katz N, Mazer NA. The impact of opioids on the endocrine system. *Clin J Pain*. 2009;25(2):170-5.
689. Finch P, Roberts L, Price L, Hadlow N, Pullan P. Hypogonadism in patients treated with intrathecal morphine. *Clin J Pain*. 2000;16(3):251-4.
690. Paice J, Penn R, Ryan W. Altered sexual function and decreased testosterone in patients receiving intraspinal opioids. *J Pain Symptom Manage*. 1994;9(2):126-31.
691. Daniell H. Hypogonadism in men consuming sustained-action oral opioids. *J Pain*. 2002;3(5):377-84.
692. Carman W, Su S, Cook S, Wurzelmann J, McAfee A. Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. *Pharmacoepidemiol Druf Saf*. 2011;20(7):754-62.
693. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. *J Intern Med*. 2013;273(5):511-26.
694. Schuller J, Krantz M. Synthetic opioids and arrhythmia risk: a new paradigm? . *Expert Opin Pharmacother*. 2012;13(13):1825-7.
695. First Databank. Patient Education leaflets. May 2013,.
696. Von Korff M, Kolodny A, Deyo R, Chou R. Long-term opioid therapy reconsidered. *Ann Intern Med*. 2011;155325-8.
697. Thosani S, Jimenez C. Opioid-induced biochemical alterations of the neuroendocrine axis. *Expert Rev Endocrinol Metab*. 2011;6705-13.
698. Daniell HW. DHEAS deficiency during consumption of sustained-action prescribed opioids: evidence for opioid-induced inhibition of adrenal androgen production. *J Pain*. 2006;7(12):901-7.
699. Oltmanns KM, Fehm HL, Peters A. Chronic fentanyl application induces adrenocortical insufficiency. *J Intern Med*. 2005;257(5):478-80.
700. Afsharimani B, Cabot P, Parat MO. Morphine and tumor growth and metastasis. *Cancer Metastasis Rev*. 2011;30(2):225-38.
701. Gach K, Wyrebska A, Fichna J, Janecka A. The role of morphine in regulation of cancer cell growth. *Naunyn Schmiedebergs Arch Pharmacol*. 2011;384(3):221-30.
702. Tavare AN, Perry NJ, Benzonana LL, Takata M, Ma D. Cancer recurrence after surgery: direct and indirect effects of anesthetic agents. *Int J Cancer*. 2012;130(6):1237-50.
703. Upadhyay J, Maleki N, Potter J, et al. Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. *Brain*. 2010;133(Pt 7):2098-114.
704. Greenberg D. How Only the USA Wound Up in this Dire Situation: No Going Back to the Bad Old Days. *California Medical and Pharmacy Boards' Joint Forum to Promote Appropriate Prescribing and Dispensing*. South San Francisco, CA; February 2013.
705. Tassain V, Attal N, Fletcher D, et al. Long term effects of oral sustained release morphine on neuropsychological performance in patients with chronic non-cancer pain. *Pain*. 2003;104(1-2):389-400.
706. King T, Ossipov MH, Vanderah TW, Porreca F, Lai J. Is paradoxical pain induced by sustained opioid exposure an underlying mechanism of opioid antinociceptive tolerance? *Neurosignals*. 2005;14(4):194-205.
707. Mao J. Opioid-induced abnormal pain sensitivity: implications in clinical opioid therapy. *Pain*. 2002;100(3):213-7.
708. Mattioli T. *Opioids and Glia: Investigating the Mechanisms through which Ultra-Low Dose Opioid Antagonists Modulate Opioid Tolerance and Hyperalgesia*. Kingston, ON: Queen's University; 2013.
709. Ossipov MH, Lai J, King T, Vanderah TW, Porreca F. Underlying mechanisms of pronociceptive consequences of prolonged morphine exposure. *Biopolymers*. 2005;80(2-3):319-24.
710. White JM. Pleasure into pain: the consequences of long-term opioid use. *Addict Behav*. 2004;29(7):1311-24.
711. Urban MO, Gebhart GF. Supraspinal contributions to hyperalgesia. *Proc Natl Acad Sci U S A*. 1999;96(14):7687-92.
712. Gutstein H, Akil H. Chapter 18: Opioid analgesics. In: Brunton L, Lazo J, Parker K, eds. *Goodman & Gilman's The Pharmacologic Basis of Therapeutics, 11th Ed*. New York: McGraw-Hill; 2006.
713. Sung HE, Richter L, Vaughan R, Johnson PB, Thom B. Nonmedical use of prescription opioids among teenagers in the United States: trends and correlates. *J Adolesc Health*. 2005;37(1):44-51.
714. Brands B, Paglia-Boak A, Sproule BA, Leslie K, Adlaf EM. Nonmedical use of opioid analgesics among Ontario students. *Can Fam Physician*. 2010;56(3):256-62.
715. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. National Survey on Drug Use and Health, 2010.
716. Jones T, Moore T, Levy J, et al. A comparison of various risk screening methods in predicting discharge from opioid treatment. *Clin J Pain*. 2012;28(2):93-100.

717. Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. *Am J Obstet Gynecol*. 2011;204(4):314 e1-11.
718. Deyo RA, Smith DH, Johnson ES, et al. Prescription opioids for back pain and use of medications for erectile dysfunction. *Spine (Phila Pa 1976)*. 2013;38(11):909-15.
719. Walker JM, Farney RJ, Rhondeau SM, et al. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. *J Clin Sleep Med*. 2007;3(5):455-61.
720. Guilleminault C, Cao M, Yue HJ, Chawla P. Obstructive sleep apnea and chronic opioid use. *Lung*. 2010;188(6):459-68.
721. Dublin S, Walker RL, Jackson ML, et al. Use of opioids or benzodiazepines and risk of pneumonia in older adults: a population-based case-control study. *J Am Geriatr Soc*. 2011;59(10):1899-907.
722. Miller M, Sturmer T, Azrael D, Levin R, Solomon DH. Opioid analgesics and the risk of fractures in older adults with arthritis. *J Am Geriatr Soc*. 2011;59(3):430-8.
723. Saunders KW, Dunn KM, Merrill JO, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. *J Gen Intern Med*. 2010;25(4):310-5.
724. Fields H. Should we be reluctant to prescribe opioids for chronic non-malignant pain? *Pain*. 2007;129(3):233-4.
725. Darnall B, Schatman M, Argoff C, Ballantyne J. Understanding Opioids: Part 1. Accessed www.medscape.com/viewarticle/777126, . 2011.
726. Gomes T, Mamdani M, Dhalla I, Paterson J, Juurlink D. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med*. 2011;171(7):686-91.
727. Maclaren J, Gross R, Sperry J, Boggess J. Impact of opioid use on outcomes of functional restoration. *Clin J Pain*. 2006;22(4):392-8.
728. Hartung D, Middleton L, Haxby D, Koder M, Ketchum K, Chou R. Rates of adverse events of long-acting opioids in a state Medicaid Program. *Ann Pharmacother*. 2007;41(6):921-8.
729. Krebs E, Becker W, Zerzan J, Bair M, McCoy K, Hui S. Comparative mortality among Department of Veterans Affairs patients prescribed methadone or long-acting morphine for chronic pain. *Pain*. 2011;152(8):1789-95.
730. Kahan M, Srivastava A, Wilson L, Gourlay D, Midmer D. Misuse of and dependence on opioids: study of chronic pain patients. *Can Fam Physician*. 2006;52(9):1081-7.
731. Sehgal N, Manchikanti L, Smith H. Prescription opioid abuse in chronic pain: a review of opioid abuse predictors and strategies to curb opioid sbuse. *Pain Physician*. 2012;15(3 Suppl):ES67-92.
732. Wasan AD, Correll DJ, Kissin I, O'Shea S, Jamison RN. Iatrogenic addiction in patients treated for acute or subacute pain: a systematic review. *J Opioid Manag*. 2006;2(1):16-22.
733. Ballantyne JC, LaForge KS. Opioid dependence and addiction during opioid treatment of chronic pain. *Pain*. 2007;129(3):235-55.
734. Ballantyne JC. Opioid analgesia: perspectives on right use and utility. *Pain Physician*. 2007;10(3):479-91.
735. Chou R, Fanciullo GJ, Fine PG, Miaskowski C, Passik SD, Portenoy RK. Opioids for chronic noncancer pain: prediction and identification of aberrant drug-related behaviors: a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain*. 2009;10(2):131-46.
736. Von Korff M, Saunders K, Thomas Ray G, et al. Defacto long-term opioid therapy for non-cancer pain. *Clin J Pain*. 2008;24(6):521-7.
737. Manchikanti L, Giordano J, Boswell M, Fellows B, Manchukonda R, Pampati V. Pyschological factors as predictors of opioid abuse and illicit drug use in chronic pain patients. *J Opioid Manage*. 2007;3(2):89-100.
738. Sullivan M, Von Korff M, Banta-Green C, Merrill J, Saunders K. Problems and concerns of patients receiving chronic opioid therapy for chronic non-cancer pain. *Pain*. 2010;149(2):345-53.
739. Reid M, Engles-Horton L, O'Connor P. Use of opioid medications for chronic noncancer pain syndromes in primary care. *J Gen Intern Med*. 2002;17(3):173-9.
740. Wasan A, Butler S, Budman S, Benoit C, Fernandez K, Jamison R. Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. *Clin J Pain*. 2007;23(4):307-15.
741. Boscarino J, Rukstalis M, Hoffman S, et al. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. *Addiction*. 2010;105(10):1776-82.
742. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain*. 2007;129(3):355-62.
743. Dillie K, Fleming M, Mundt M, French M. Quality of life associated with daily opioid therapy in a primary care chronic pain sample. *J Am Board Family Med*. 2008;21(2):108-17.
744. Emrich H, Vogt P, Herz A. Possible antidepressive effects of opioids: action of buprenorphine. *Annals New York Academy of Sciences*. 1982;398108-12.
745. Sinyor M, Howlett A, Cheung AH, Schaffer A. Substances used in completed suicide by overdose in Toronto: an observational study of coroner's data. *Can J Psychiatry*. 2012;57(3):184-91.
746. Caplehorn JR, Dalton MS, Haldar F, Petrenas AM, Nisbet JG. Methadone maintenance and addicts' risk of fatal heroin overdose. *Subst Use Misuse*. 1996;31(2):177-96.
747. Marsch LA. The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: a meta-analysis. *Addiction*. 1998;93(4):515-32.
748. Sporer KA. Strategies for preventing heroin overdose. *BMJ*. 2003;326(7386):442-4.

749. Strang J, Hall W, Hickman M, Bird SM. Impact of supervision of methadone consumption on deaths related to methadone overdose (1993-2008): analyses using OD4 index in England and Scotland. *BMJ*. 2010;341c4851.
750. Rosca P, Haklai Z, Goldberger N, Zohar P, Margolis A, Ponizovsky AM. Mortality and causes of death among users of methadone maintenance treatment in Israel, 1999-2008. *Drug Alcohol Depend*. 2012;125(1-2):160-3.
751. van Dorp E, Yassen A, Sarton E, et al. Naloxone reversal of buprenorphine-induced respiratory depression. *Anesthesiology*. 2006;105(1):51-7.
752. Hakkinen M, Launiainen T, Vuori E, Ojanpera I. Comparison of fatal poisonings by prescription opioids. *Forensic Sci Int*. 2012;222(1-3):327-31.
753. Pelissier-Alicot AL, Sastre C, Baillif-Couniou V, et al. Buprenorphine-related deaths: unusual forensic situations. *Int J Legal Med*. 2010;124(6):647-51.
754. Lai SH, Teo CE. Buprenorphine-associated deaths in Singapore. *Ann Acad Med Singapore*. 2006;35(7):508-11.
755. Kintz P. A new series of 13 buprenorphine-related deaths. *Clin Biochem*. 2002;35(7):513-6.
756. Romelsjo A, Engdahl B, Stenbacka M, et al. Were the changes to Sweden's maintenance treatment policy 2000-06 related to changes in opiate-related mortality and morbidity? *Addiction*. 2010;105(9):1625-32.
757. Soyka M, Apelt S, Lieb M, Wittchen H. One-year mortality rates of patients receiving methadone and buprenorphine maintenance therapy. A nationally representative cohort study in 2694 patients. *J Clin Psychopharmacol*. 2006;26(6):657-60.
758. Ho RC, Ho EC, Tan CH, Mak A. Pulmonary hypertension in first episode infective endocarditis among intravenous buprenorphine users: case report. *Am J Drug Alcohol Abuse*. 2009;35(3):199-202.
759. Bauer S, Loipl R, Jagsch R, et al. Mortality in opioid-maintained patients after release from an addiction clinic. *Eur Addict Res*. 2008;14:82-91.
760. Kelty E, Hulse G. Examination of mortality rates in a retrospective cohort of patients treated with oral or implant naltrexone for problematic opiate use. *Addiction*. 2012;107(10):1817-24.
761. Webster LR, Choi Y, Desai H, Webster L, Grant BJ. Sleep-disordered breathing and chronic opioid therapy. *Pain Med*. 2008;9(4):425-32.
762. Jamshidi F, Sadighi B, Aghakhani K, Sanaei-Zadeh H, Emamhadi M, Zamani N. Brain computed tomographic scan findings in acute opium overdose patients. *Am J Emerg Med*. 2013;31(1):50-3.
763. Carroll I, Heritier Barras AC, Dirren E, Burkhard PR, Horvath J. Delayed leukoencephalopathy after alprazolam and methadone overdose: a case report and review of the literature. *Clin Neurol Neurosurg*. 2012;114(6):816-9.
764. Foy L, Seeyave DM, Bradin SA. Toxic leukoencephalopathy due to transdermal fentanyl overdose. *Pediatr Emerg Care*. 2011;27(9):854-6.
765. Grigorakos L, Sakagianni K, Tsigou E, Apostolakos G, Nikolopoulos G, Veldekis D. Outcome of acute heroin overdose requiring intensive care unit admission. *J Opioid Manag*. 2010;6(3):227-31.
766. Shprecher DR, Flanigan KM, Smith AG, Smith SM, Schenkenberg T, Steffens J. Clinical and diagnostic features of delayed hypoxic leukoencephalopathy. *J Neuropsychiatry Clin Neurosci*. 2008;20(4):473-7.
767. Molloy S, Soh C, Williams TL. Reversible delayed posthypoxic leukoencephalopathy. *AJNR Am J Neuroradiol*. 2006;27(8):1763-5.
768. Salazar R, Dubow J. Delayed posthypoxic leukoencephalopathy following a morphine overdose. *J Clin Neurosci*. 2012;19(7):1060-2.
769. Morales Odia Y, Jinka M, Ziai W. Severe leukoencephalopathy following acute oxycodone intoxication. *Neurocrit Care*. 2010;13(1):93-7.
770. Cronin AJ, Keifer JC, Davies MF, King TS, Bixler EO. Postoperative sleep disturbance: influences of opioids and pain in humans. *Sleep*. 2001;24(1):39-44.
771. Krenk L, Jennum P, Kehlet H. Sleep disturbances after fast-track hip and knee arthroplasty. *Br J Anaesth*. 2012;109(5):769-75.
772. Franklin GM, Mai J, Turner J, Sullivan M, Wickizer T, Fulton-Kehoe D. Bending the prescription opioid dosing and mortality curves: impact of the Washington State opioid dosing guideline. *Am J Ind Med*. 2012;55(4):325-31.
773. Shaffer T, Simoni-Wastila L, Toler W, Stuart B, Doshi JA. Changing patterns in medication use with increasing probability of death for older Medicare beneficiaries. *J Am Geriatr Soc*. 2010;58(8):1549-55.
774. Sternfeld I, Perras N, Culross PL. Development of a coroner-based surveillance system for drug-related deaths in Los Angeles county. *J Urban Health*. 2010;87(4):656-69.
775. Thompson JG, Vanderwerf S, Seningen J, Carr M, Kloss J, Apple FS. Free oxycodone concentrations in 67 postmortem cases from the Hennepin County medical examiner's office. *J Anal Toxicol*. 2008;32(8):673-9.
776. Schumann H, Erickson T, Thompson TM, Zautcke JL, Denton JS. Fentanyl epidemic in Chicago, Illinois and surrounding Cook County. *Clin Toxicol (Phila)*. 2008;46(6):501-6.
777. Graham NA, Merlo LJ, Goldberger BA, Gold MS. Methadone- and heroin-related deaths in Florida. *Am J Drug Alcohol Abuse*. 2008;34(3):347-53.
778. Porucznik CA, Johnson EM, Rolfs RT, Sauer BC. Specialty of Prescribers Associated with Prescription Opioid Fatalities in Utah, 2002-2010. *Pain Med*. 2013.
779. Baker DD, Jenkins AJ. A comparison of methadone, oxycodone, and hydrocodone related deaths in Northeast Ohio. *J Anal Toxicol*. 2008;32(2):165-71.

780. Giraudon I, Lowitz K, Dargan PI, Wood DM, Dart RC. Prescription opioid abuse in the United Kingdom. *Br J Clin Pharmacol*. 2013.
781. Pilgrim JL, Gerostamoulos D, Drummer OH. Deaths involving serotonergic drugs. *Forensic Sci Int*. 2010;198(1-3):110-7.
782. Pilgrim JL, Gerostamoulos D, Drummer OH. Deaths involving contraindicated and inappropriate combinations of serotonergic drugs. *Int J Legal Med*. 2011;125(6):803-15.
783. Tashakori A, Afshari R. Tramadol overdose as a cause of serotonin syndrome: a case series. *Clin Toxicol (Phila)*. 2010;48(4):337-41.
784. Solarino B, Riesselmann B, Buschmann CT, Tsokos M. Multidrug poisoning involving nicotine and tramadol. *Forensic Sci Int*. 2010;194(1-3):e17-9.
785. Shadnia S, Soltaninejad K, Heydari K, Sasanian G, Abdollahi M. Tramadol intoxication: a review of 114 cases. *Hum Exp Toxicol*. 2008;27(3):201-5.
786. Simonsen KW, Normann PT, Ceder G, et al. Fatal poisoning in drug addicts in the Nordic countries in 2007. *Forensic Sci Int*. 2011;207(1-3):170-6.
787. Hassanian-Moghaddam H, Farajidana H, Sarjami S, Owliaey H. Tramadol-induced apnea. *Am J Emerg Med*. 2013;31(1):26-31.
788. De Backer B, Renardy F, Denooz R, Charlier C. Quantification in postmortem blood and identification in urine of tramadol and its two main metabolites in two cases of lethal tramadol intoxication. *J Anal Toxicol*. 2010;34(9):599-604.
789. Fitzgibbon D, Rathmell J, Michna E, Stephens L, Posner K, Domino K. Malpractice claims associated with medication management for chronic pain. *Pain Med*. 2010;112(4):948-56.
790. Cochella S, Bateman K. Provider detailing: an intervention to decrease prescription opioid deaths in Utah. *Pain Med*. 2011;12(Suppl 2):S73-6.
791. Okie S. A flood of opioids, a rising tide of deaths. *N Engl J Med*. 2010;363(21):1981-5.
792. Webster BS, Cifuentes M, Verma S, Pransky G. Geographic variation in opioid prescribing for acute, work-related, low back pain and associated factors: a multilevel analysis. *Am J Ind Med*. 2009;52(2):162-71.
793. Mailis-Gagnon A, Lakha SF, Ou T, et al. Chronic noncancer pain: characteristics of patients prescribed opioids by community physicians and referred to a tertiary pain clinic. *Can Fam Physician*. 2011;57(3):e97-105.
794. Dhalla IA, Mamdani MM, Gomes T, Juurlink DN. Clustering of opioid prescribing and opioid-related mortality among family physicians in Ontario. *Can Fam Physician*. 2011;57(3):e92-6.
795. Tao XG, Lavin RA, Yuspeh L, Bernacki EJ. Natural history of opioid dosage escalation post-injury: a cohort study of injured workers in the State of Louisiana. *J Occup Environ Med*. 2012;54(4):439-44.
796. White JA, Tao X, Talreja M, Tower J, Bernacki E. The effect of opioid use on workers' compensation claim cost in the state of michigan. *J Occup Environ Med*. 2012;54(8):948-53.
797. Khademi H, Malekzadeh R, Pourshams A, et al. Opium use and mortality in Golestan Cohort Study: prospective cohort study of 50,000 adults in Iran *BMJ*. 2012;344(e2502).
798. Sjogren P, Gronbaek M, Peuckmann V, Ekholm O. A population-based cohort study on chronic pain: the role of opioids. *Clin J Pain*. 2010;26(9):763-9.
799. Inciardi JA, Surratt HL, Cicero TJ, Beard RA. Prescription opioid abuse and diversion in an urban community: the results of an ultrarapid assessment. *Pain Med*. 2009;10(3):537-48.
800. Bjornaas M, Bekken A, Ojlert A, et al. A 20-year prospective study of mortality and causes of death among hospitalized opioid addicts in Oslo. *BMC Psychiatry*. 2008;8(8).
801. Clausen T, Waal H, Thoresen M, Gossop M. Mortality among opiate users: opioid maintenance therapy, age and causes of death. *Addiction*. 2009;104(8):1356-62.
802. Strassels S, Chen C, Carr D. Postoperative analgesia: economics, resource use, and patient satisfaction in an urban teaching hospital. *Anesth Analg*. 2002;94130-7.
803. Kwong W, Diels J, Kavanagh S. Costs of gastrointestinal events after outpatient opioid treatment for non-cancer pain. *Ann Pharmacother*. 2010;44(4):630-40.
804. Masson C, Sorensen J, Batki S, Okin R, Delucchi K, Perlman D. Medical service use and financial charges among opioid users at a public hospital. *Drug Alcohol Depend*. 2002;66(1):45-50.
805. Obradovic M, Ikenberg R, Hertel N, Antonanzas F, Galvez R, Liedgens H. Cost-effectiveness of tapentadol in severe chronic pain in Spain: a cost analysis of data from RCTs. *Clin Ther*. 2012;34(4):926-43.
806. Reme S, Tangen T, Moe T, Eriksen H. Prevalence of psychiatric disorders in sick listed chronic low back pain patients. *Eur J Pain*. 2011;151075-80.
807. Knaster P, Karlsson H, Estlander A, Kalso E. Psychiatric disorders as assessed with SCID in chronic pain patients: the anxiety disorders precede the onset of pain. *Gen Hosp Psychiatry*. 2012;34(1):46-52.
808. Dominick CH, Blyth FM, Nicholas MK. Unpacking the burden: understanding the relationships between chronic pain and comorbidity in the general population. *Pain*. 2012;153(2):293-304.
809. Gerhardt A, Hartmann M, Schuller-Roma B, et al. The prevalence and type of Axis-I and Axis-II mental disorders in subjects with non-specific chronic back pain: results from a population-based study *Pain Med*. 2011;12(8):1231-40.
810. Gerrits M, Vogelzangs N, van Oppen P, van Marwijk H, van der Horst H, Penninx B. Impact of pain on the course of depressive and anxiety disorders. *Pain*. 2012;153(2):429-36.
811. Ho P, Li C, Ng Y, Tsui S, Ng K. Prevalence of and factors associated with psychiatric morbidity in chronic pain patients. *J Psychosom Res*. 2011;70(6):541-7.

812. Wesseling J, Welsing P, Bierma-Zeinstra S, et al. Impact of self-reported comorbidity on physical and mental health status in early symptomatic osteoarthritis: the CHECK (Cohort Hip and Cohort Knee) study. *Rheumatology*. 2013;52(1):180-8.
813. Paras ML, Murad MH, Chen LP, et al. Sexual abuse and lifetime diagnosis of somatic disorders: a systematic review and meta-analysis. *Jama*. 2009;302(5):550-61.
814. Brands B, Blake J, Sproule B, Gourlay D, Busto U. Prescription opioid abuse in patients presenting for methadone maintenance treatment. *Drug Alcohol Depend*. 2004;73(2):199-207.
815. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med*. 2005;6(6):432-42.
816. Springs FE, Friedrich WN. Health risk behaviors and medical sequelae of childhood sexual abuse. *Mayo Clin Proc*. 1992;67(6):527-32.
817. Tang N, Goodchild C, Sanborn A, Howard J, Salkovskis P. Deciphering the temporal link between pain and sleep in a heterogeneous chronic pain patient sample: a multilevel daily process study. *Sleep*. 2012;35(5):675-87.
818. Ohayon M, Stingl J. Prevalence and comorbidity of chronic pain in the German general population. *J Psychiatr Res*. 2012;46(4):444-50.
819. Wong W, Fielding R. The co-morbidity of chronic pain, insomnia, and fatigue in the general adult population of Hong Kong: Prevalence and associated factors. *J Psychosomatic Res*. 2012;73(1):28-34.
820. Gudin J. Risk Evaluation and Mitigation Strategies (REMS) for extended-release and long-acting opioid analgesics: considerations for palliative care practice. *J Pain Palliative Care Pharmacotherapy*. 2012;26(2):136-43.
821. Centers for Disease Control and Prevention. Press Release: Opioids Drive Continued Increase in Drug Overdose Deaths. Available at: http://www.cdc.gov/media/releases/2013/p0220_drug_overdose_deaths.html. February 20, 2013.
822. U.S. Department of Health and Human Services: Office of Inspector General. FDA Lacks Comprehensive Data to Determine Whether Risk Evaluation and Mitigation Strategies Improve Drug Safety. Retrieved from https://oig.hhs.gov/oei/reports/oei-04-11-00510.pdf. 2013.
823. U.S. Department of Health and Human Services: U.S. Food and Drug Administration. Risk Evaluation and Mitigation Strategy (REMS) for Extended-release and Long-acting Opioids. Available at: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm. 2013.
824. U.S. Department of Health and Human Services: U.S. Food and Drug Administration. Questions and answers: FDA Requires a Risk Evaluation and Mitigation Strategy (REMS) for Long-acting and Extended-release Opioids. Available at: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm251752.htm. 2013.
825. U.S. Department of Health and Human Services: U.S. Food and Drug Administration. Post-approval REMS notification. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM251595.pdf.
826. Slevin KA, Ashburn MA. Primary care physician opinion survey on FDA opioid risk evaluation and mitigation strategies. *J Opioid Manag*. 2011;7(2):109-15.
827. Dal Pan G. A short tutorial on REMS: The FDA perspective. Retrieved from http://www.medscape.com/viewarticle/762240. 2012.
828. Katz N, Fanciullo G. Role of urine toxicology testing in the management of chronic opioid therapy. *Clin J Pain*. 2002;18(4 Suppl):S76-82.
829. Phillips K, Ch'ien AP, Norwood BR, Smith C. Chronic low back pain management in primary care. *Nurse Pract*. 2003;28(8):26-31.
830. Hammett-Stabler C, Webster L. *A Clinical Guide to Urine Drug Testing: Augmenting Pain Management & Enhancing Patient Care*; 2008.
831. U.S. Department of Transportation. Part 40 DOT 5-Panel Notice. Available at: http://www.dot.gov/odapc/part-40-dot-5-panel-notice. 2010.
832. Swotinsky R, Smith D. *The Medical Review Officer's Manual - MROCC's Guide to Drug Testing, Fourth Edition*. Beverly Farms, MA: OEM Press; 2010.
833. Rengarajan A, Mullins ME. How often do false-positive phencyclidine urine screens occur with use of common medications? *Clin Toxicol (Phila)*. 2013;51(6):493-6.
834. Birch MA, Couchman L, Pietromartire S, et al. False-positive buprenorphine by CEDIA in patients prescribed amisulpride or sulpiride. *J Anal Toxicol*. 2013;37(4):233-6.
835. Tenore PL. False-positive buprenorphine EIA urine toxicology results due to high dose morphine: a case report. *J Addict Dis*. 2012;31(4):329-31.
836. King AM, Pugh JL, Menke NB, Krasowski MD, Lynch MJ, Pizon AF. Nonfatal tramadol overdose may cause false-positive phencyclidine on Emit-II assay. *Am J Emerg Med*. 2013;31(2):444 e5-9.
837. Collins AA, Merritt AP, Bourland JA. Cross-reactivity of tapentadol specimens with DRI methadone enzyme immunoassay. *J Anal Toxicol*. 2012;36(8):582-7.
838. Mikel C, Pesce AJ, Rosenthal M, West C. Therapeutic monitoring of benzodiazepines in the management of pain: current limitations of point of care immunoassays suggest testing by mass spectrometry to assure accuracy and improve patient safety. *Clin Chim Acta*. 2012;413(15-16):1199-202.
839. Melanson SE, Snyder ML, Jarolim P, Flood JG. A new highly specific buprenorphine immunoassay for monitoring buprenorphine compliance and abuse. *J Anal Toxicol*. 2012;36(3):201-6.
840. Ly BT, Thornton SL, Buono C, Stone JA, Wu AH. False-positive urine phencyclidine immunoassay screen result caused by interference by tramadol and its metabolites. *Ann Emerg Med*. 2012;59(6):545-7.

841. Lippi G, Romero A, Cervellin G, Mercadanti M. Unusual false-positive case of urinary screening for buprenorphine. *J Clin Lab Anal*. 2011;25(4):244-5.
842. Manchikanti L, Malla Y, Wargo BW, Fellows B. Comparative evaluation of the accuracy of immunoassay with liquid chromatography tandem mass spectrometry (LC/MS/MS) of urine drug testing (UDT) opioids and illicit drugs in chronic pain patients. *Pain Physician*. 2011;14(2):175-87.
843. Tenore PL. Advanced urine toxicology testing. *J Addict Dis*. 2010;29(4):436-48.
844. Rogers SC, Pruitt CW, Crouch DJ, Caravati EM. Rapid urine drug screens: diphenhydramine and methadone cross-reactivity. *Pediatr Emerg Care*. 2010;26(9):665-6.
845. Straseski JA, Stolbach A, Clarke W. Opiate-positive immunoassay screen in a pediatric patient. *Clin Chem*. 2010;56(8):1220-3.
846. Melanson SE, Baskin L, Magnani B, Kwong TC, Dizon A, Wu AH. Interpretation and utility of drug of abuse immunoassays: lessons from laboratory drug testing surveys. *Arch Pathol Lab Med*. 2010;134(5):735-9.
847. Crooks CR, Brown S. Roche DAT immunoassay: sensitivity and specificity testing for amphetamines, cocaine, and opiates in oral fluid. *J Anal Toxicol*. 2010;34(2):103-9.
848. Gingras M, Laberge MH, Lefebvre M. Evaluation of the usefulness of an oxycodone immunoassay in combination with a traditional opiate immunoassay for the screening of opiates in urine. *J Anal Toxicol*. 2010;34(2):78-83.
849. Taylor K, Elliott S. A validated hybrid quadrupole linear ion-trap LC-MS method for the analysis of morphine and morphine glucuronides applied to opiate deaths. *Forensic Sci Int*. 2009;187(1-3):34-41.
850. Fugelstad A, Ahlner J, Brandt L, et al. Use of morphine and 6-monoacetylmorphine in blood for the evaluation of possible risk factors for sudden death in 192 heroin users. *Addiction*. 2003;98(4):463-70.
851. Burt MJ, Kloss J, Apple FS. Postmortem blood free and total morphine concentrations in medical examiner cases. *J Forensic Sci*. 2001;46(5):1138-42.
852. Meissner W, Ullrich K, Zwacka S, Schreiber T, Reinhart K. Quality management in postoperative pain therapy. *Anaesthesist*. 2001;50(9):661-70.
853. Spiehler V, Brown R. Unconjugated morphine in blood by radioimmunoassay and gas chromatography/mass spectrometry. *J Forensic Sci*. 1987;32(4):906-16.
854. Manchikanti L, Pampati V, Damron KS, Fellows B, Barnhill RC, Beyer CD. Prevalence of opioid abuse in interventional pain medicine practice settings: a randomized clinical evaluation. *Pain Physician*. 2001;4(4):358-65.
855. Manchikanti L, Manchukonda R, Pampati V, et al. Does random urine drug testing reduce illicit drug use in chronic pain patients receiving opioids? *Pain Physician*. 2006;9(2):123-9.
856. Fishbain DA, Cutler RB, Rosomoff HL, Rosomoff RS. Validity of self-reported drug use in chronic pain patients. *Clin J Pain*. 1999;15(3):184-91.
857. Moore TM, Jones T, Browder JH, Daffron S, Passik SD. A comparison of common screening methods for predicting aberrant drug-related behavior among patients receiving opioids for chronic pain management. *Pain Med*. 2009;10(8):1426-33.
858. Jones T, Moore T. Preliminary data on a new opioid risk assessment measure: the Brief Risk Interview. *J Opioid Manag*. 2013;9(1):19-27.
859. Adams L, Gatchel R, Robinson R, et al. Development of a self-report screening instrument for assessing potential opioid medication misuse in chronic pain patients. *J Pain Symptom Manage*. 2004;27(5):440.
860. Akbik H, Butler S, Budman S, Fernandez K, Katz N, Jamison R. Validation and clinical application of the Screener and Opioid Assessment for Patients with Pain (SOAPP). *J Pain Symptom Manage*. 2006;32(3):287-93.
861. Turk D. Predicting opioid misuse by chronic pain patients. A systematic review and literature synthesis. *Clin J Pain*. 2008;24(6):497-508.
862. Manchikanti L, Atluri S, Trescot AM, Giordano J. Monitoring opioid adherence in chronic pain patients: tools, techniques, and utility. *Pain Physician*. 2008;11(2 Suppl):S155-80.
863. Passik S, Kirsh K, Casper D. Addiction-related assessment tools and pain management: instruments for screening, treatment planning, and monitoring compliance. *Pain Med*. 2008;9(S2):S145-66.
864. Smith HS, Kirsh KL, Passik SD. Chronic opioid therapy issues associated with opioid abuse potential. *J Opioid Manag*. 2009;5(5):287-300.
865. Wu S, Compton P, Bolus R, et al. The Addiction Behaviors Checklist: validation of a new clinician-based measure of inappropriate opioid use in chronic pain. *J Pain Symptom Manage*. 2006;32(4):342-51.
866. Compton P, Darakjian J, Miotto K. Screening for addiction in patients with chronic pain and “problematic” substance use: evaluation of a pilot assessment tool. *J Pain Symptom Manage*. 1998;16(6):355-63.
867. Coombs R, Coombs C. Drug testing attitudes of mandatory participants. *Journal of Substance Misuse for Nursing Health and Social Care*. 1996;1(2):85-90.
868. Friedman R, Li V, Mehrotra D. Treating pain patients at risk: evaluation of a screening tool in opioid-treated pain patients with and without addiction. *Pain Med*. 2003;4(2):182-5.
869. Belgrade MJ, Schamber CD, Lindgren BR. The DIRE score: predicting outcomes of opioid prescribing for chronic pain. *J Pain*. 2006;7(9):671-81.
870. Jamison RN, Serraillier J, Michna E. Assessment and treatment of abuse risk in opioid prescribing for chronic pain. *Pain Res Treat*. 2011;2011941808.
871. Paice JA, Cohen FL. Validity of a verbally administered numeric rating scale to measure cancer pain intensity. *Cancer Nurs*. 1997;20(2):88-93.
872. Pollard CA. Preliminary validity study of the pain disability index. *Percept Mot Skills*. 1984;59(3):974.

873. Butler S, Budman S, Fernandez K, Jamison R. Validation of a screener and opioid assessment measure for patients with chronic pain. *Pain*. 2004;112(1-2):65-75.
874. Butler S, Budman S, Fernandez K, Fanciullo G, Jamison R. Cross-validation of a Screener to Predict Opioid Misuse in Chronic Pain Patients (SOAPP-R). *J Addict Med*. 2009;3(2):66-73.
875. Butler S, Budman S, Fernandez K, et al. Development and validation of the current opioid misuse measure. *Pain*. 2007;130(1-2):144-56
876. Martel MO, Wasan AD, Jamison RN, Edwards RR. Catastrophic thinking and increased risk for prescription opioid misuse in patients with chronic pain. *Drug Alcohol Depend*. 2013;132(1-2):335-41.
877. Jamison RN, Ross EL, Michna E, Chen LQ, Holcomb C, Wasan AD. Substance misuse treatment for high-risk chronic pain patients on opioid therapy: a randomized trial. *Pain*. 2010;150(3):390-400.
878. Butler S, Budman S, Fanciullo G, Jamison R. Cross validation of the Current Opioid Misuse Measure (COMM) to monitor chronic pain patients on opioid therapy. *Clin J Pain*. 2010;26(9):770-6.
879. Meltzer EC, Rybin D, Saitz R, et al. Identifying prescription opioid use disorder in primary care: diagnostic characteristics of the Current Opioid Misuse Measure (COMM). *Pain*. 2011;152(2):397-402.
880. Parhami I, Hyman M, Siani A, et al. Screening for addictive disorders within a workers' compensation clinic: an exploratory study. *Subst Use Misuse*. 2012;47(1):99-107.
881. Dowling LS, Gatchel RJ, Adams LL, Stowell AW, Bernstein D. An evaluation of the predictive validity of the Pain Medication Questionnaire with a heterogeneous group of patients with chronic pain. *J Opioid Manag*. 2007;3(5):257-66.
882. Holmes C, Gatchel R, Adams L, et al. An opioid screening instrument: long-term evaluation of the utility of the Pain Medication Questionnaire. *Pain Prac*. 2006;6(2):74-88.
883. Hojsted J, Nielsen PR, Kendall S, Frich L, Sjogren P. Validation and usefulness of the Danish version of the Pain Medication Questionnaire in opioid-treated chronic pain patients. *Acta Anaesthesiol Scand*. 2011;55(10):1231-8.
884. Park J, Lavin R. Risk factors associated with opioid medication misuse in community-dwelling older adults with chronic pain. *Clin J Pain*. 2010;26(8):647-55.
885. Passik S, Kirsh K, Whitcomb L, et al. Monitoring outcomes during long-term opioid therapy for noncancer pain: results with the Pain Assessment and Documentation Tool. *J Opioid Management*. 2005;1(5):257-66.
886. Bunten H, Liang WJ, Pounder DJ, Seneviratne C, Osselton D. OPRM1 and CYP2B6 gene variants as risk factors in methadone-related deaths. *Clin Pharmacol Ther*. 2010;88(3):383-9.
887. Buchard A, Linnet K, Johansen SS, Munkholm J, Fregerslev M, Morling N. Postmortem blood concentrations of R- and S-enantiomers of methadone and EDDP in drug users: influence of co-medication and p-glycoprotein genotype. *J Forensic Sci*. 2010;55(2):457-63.
888. Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. *N Engl J Med*. 2009;361(8):827-8.
889. Fishbain D, Lewis J, Gao J. Allegations of medical malpractice in chronic opioid analgesic therapy possibly related to collaborative/split treatment and the P-450 enzyme system: forensic case report. *Pain Med*. 2010;11:1419-25.
890. Musshoff F, Stamer UM, Madea B. Pharmacogenetics and forensic toxicology. *Forensic Sci Int*. 2010;203(1-3):53-62.
891. Haddad A, Davis M, Lagman R. The pharmacological importance of cytochrome CYP3A4 in the palliation of symptoms: review and recommendations for avoiding adverse drug interactions. *Support Care Cancer*. 2007;15(3):251-7.
892. Argoff CE. Clinical implications of opioid pharmacogenetics. *Clin J Pain*. 2010;26 Suppl 10S16-20.
893. Stingl JC, Brockmoller J, Viviani R. Genetic variability of drug-metabolizing enzymes: the dual impact on psychiatric therapy and regulation of brain function. *Mol Psychiatry*. 2013;18(3):273-87.
894. Samer CF, Lorenzini KI, Rollason V, Daali Y, Desmeules JA. Applications of CYP450 testing in the clinical setting. *Mol Diagn Ther*. 2013;17(3):165-84.
895. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype. *Clin Pharmacol Ther*. 2012;91(2):321-6.
896. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet*. 2006;368(9536):704.
897. Poulsen L, Brosen K, Arendt-Nielsen L, Gram LF, Elbaek K, Sindrup SH. Codeine and morphine in extensive and poor metabolizers of sparteine: pharmacokinetics, analgesic effect and side effects. *Eur J Clin Pharmacol*. 1996;51(3-4):289-95.
898. Eckhardt K, Li S, Ammon S, Schanzle G, Mikus G, Eichelbaum M. Same incidence of adverse drug events after codeine administration irrespective of the genetically determined differences in morphine formation. *Pain*. 1998;76(1-2):27-33.
899. Stamer UM, Lehnen K, Hothker F, et al. Impact of CYP2D6 genotype on postoperative tramadol analgesia. *Pain*. 2003;105(1-2):231-8.
900. Stamer UM, Stuber F. Codeine and tramadol analgesic efficacy and respiratory effects are influenced by CYP2D6 genotype. *Anaesthesia*. 2007;62(12):1294-5; author reply 5-6.
901. Stamer UM, Stuber F, Muders T, Musshoff F. Respiratory depression with tramadol in a patient with renal impairment and CYP2D6 gene duplication. *Anesth Analg*. 2008;107(3):926-9.

902. Stamer UM, Zhang L, Stuber F. Personalized therapy in pain management: where do we stand? *Pharmacogenomics*. 2010;11(6):843-64.
903. Zwisler ST, Enggaard TP, Mikkelsen S, Brosen K, Sindrup SH. Impact of the CYP2D6 genotype on post-operative intravenous oxycodone analgesia. *Acta Anaesthesiol Scand*. 2009;54(2):232-40.
904. Zwisler ST, Enggaard TP, Noehr-Jensen L, et al. The antinociceptive effect and adverse drug reactions of oxycodone in human experimental pain in relation to genetic variations in the OPRM1 and ABCB1 genes. *Fundam Clin Pharmacol*. 2010;24(4):517-24.
905. Zwisler ST, Enggaard TP, Noehr-Jensen L, et al. The hypoalgesic effect of oxycodone in human experimental pain models in relation to the CYP2D6 oxidation polymorphism. *Basic Clin Pharmacol Toxicol*. 2009;104(4):335-44.
906. Jannetto PJ, Wong SH, Gock SB, Laleli-Sahin E, Schur BC, Jentzen JM. Pharmacogenomics as molecular autopsy for postmortem forensic toxicology: genotyping cytochrome P450 2D6 for oxycodone cases. *J Anal Toxicol*. 2002;26(7):438-47.
907. Herbild L, Andersen SE, Werge T, Rasmussen HB, Jurgens G. Does pharmacogenetic testing for CYP450 2D6 and 2C19 among patients with diagnoses within the schizophrenic spectrum reduce treatment costs? *Basic Clin Pharmacol Toxicol*. 2013;113(4):266-72.
908. Crettol S, Deglon JJ, Besson J, et al. ABCB1 and cytochrome P450 genotypes and phenotypes: influence on methadone plasma levels and response to treatment. *Clin Pharmacol Ther*. 2006;80(6):668-81.
909. Crettol S, Deglon JJ, Besson J, et al. Methadone enantiomer plasma levels, CYP2B6, CYP2C19, and CYP2C9 genotypes, and response to treatment. *Clin Pharmacol Ther*. 2005;78(6):593-604.
910. Eap CB, Crettol S, Rougier JS, et al. Stereoselective block of hERG channel by (S)-methadone and QT interval prolongation in CYP2B6 slow metabolizers. *Clin Pharmacol Ther*. 2007;81(5):719-28.
911. Pedersen RS, Damkier P, Brosen K. Enantioselective pharmacokinetics of tramadol in CYP2D6 extensive and poor metabolizers. *Eur J Clin Pharmacol*. 2006;62(7):513-21.
912. Wang Y, Al-Gazzar A, Seibert C, Sharif A, Lane C, Griffiths WJ. Proteomic analysis of cytochromes P450: a mass spectrometry approach. *Biochem Soc Trans*. 2006;34(Pt 6):1246-51.
913. Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte--an update of guidelines. *Clin Pharmacol Ther*. 2011;89(5):662-73.
914. Otton SV, Schadel M, Cheung SW, Kaplan HL, Busto UE, Sellers EM. CYP2D6 phenotype determines the metabolic conversion of hydrocodone to hydromorphone. *Clin Pharmacol Ther*. 1993;54(5):463-72.
915. Kirchheiner J, Keulen JT, Bauer S, Roots I, Brockmoller J. Effects of the CYP2D6 gene duplication on the pharmacokinetics and pharmacodynamics of tramadol. *J Clin Psychopharmacol*. 2008;28(1):78-83.
916. Witkin LR, Diskina D, Fernandes S, Farrar JT, Ashburn MA. Usefulness of the opioid risk tool to predict aberrant drug-related behavior in patients receiving opioids for the treatment of chronic pain. *J Opioid Manag*. 2013;9(3):177-87.
917. Manchikanti L, Pampati V, Damron K, McManus C. Evaluation of variables in illicit drug use: does a controlled substance abuse screening tool identify illicit drug use? *Pain Physician*. 2004;7(1):71-5.
918. McCance-Katz EF, Rainey PM, Jatlow P, Friedland G. Methadone effects on zidovudine disposition (AIDS Clinical Trials Group 262). *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;18(5):435-43.
919. McCance-Katz EF, Rainey PM, Friedland G, Kosten TR, Jatlow P. Effect of opioid dependence pharmacotherapies on zidovudine disposition. *Am J Addict*. 2001;10(4):296-307.
920. Rainey PM, Friedland G, McCance-Katz EF, et al. Interaction of methadone with didanosine and stavudine. *J Acquir Immune Defic Syndr*. 2000;24(3):241-8.
921. McCance-Katz EF, Rainey PM, Smith P, et al. Drug interactions between opioids and antiretroviral medications: interaction between methadone, LAAM, and delavirdine. *Am J Addict*. 2006;15(1):23-34.
922. Atazanavir (Reyataz) Product Label. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021567s007lbl.pdf.
923. Freimuth WW. Delavirdine mesylate, a potent non-nucleoside HIV-1 reverse transcriptase inhibitor. *Adv Exp Med Biol*. 1996;394279-89.
924. Darunavir (Prezista) Product Label.
925. McCance-Katz EF, Gourevitch MN, Arnsten J, Sarlo J, Rainey P, Jatlow P. Modified directly observed therapy (MDOT) for injection drug users with HIV disease. *Am J Addict*. 2002;11(4):271-8.
926. McCance-Katz EF, Rainey PM, Friedland G, Jatlow P. The protease inhibitor lopinavir-ritonavir may produce opiate withdrawal in methadone-maintained patients. *Clin Infect Dis*. 2003;37(4):476-82.
927. McCance-Katz EF. Treatment of opioid dependence and coinfection with HIV and hepatitis C virus in opioid-dependent patients: the importance of drug interactions between opioids and antiretroviral agents. *Clin Infect Dis*. 2005;41 Suppl 1S89-95.
928. Boffito M, Rossati A, Reynolds HE, Hoggard PG, Back DJ, Di Perri G. Undefined duration of opiate withdrawal induced by efavirenz in drug users with HIV infection and undergoing chronic methadone treatment. *AIDS Res Hum Retroviruses*. 2002;18(5):341-2.
929. Back D, Gibbons S, Khoo S. Pharmacokinetic drug interactions with nevirapine. *J Acquir Immune Defic Syndr*. 2003;34 Suppl 1S8-14.
930. McCance-Katz EF, Moody DE, Morse GD, et al. Interactions between buprenorphine and antiretrovirals. I. The nonnucleoside reverse-transcriptase inhibitors efavirenz and delavirdine. *Clin Infect Dis*. 2006;43 Suppl 4S224-34.

931. McCance-Katz EF, Moody DE, Smith PF, et al. Interactions between buprenorphine and antiretrovirals. II. The protease inhibitors nelfinavir, lopinavir/ritonavir, and ritonavir. *Clin Infect Dis*. 2006;43 Suppl 4S235-46.
932. McCance-Katz EF, et al. Interaction of buprenorphine and nevirapine. In press.
933. Fosamprenavir (Lexiva) Product Label.
934. Nelfinavir (Viracept) Product Label.
935. McCance-Katz EF. Drug Interactions between Opioids and Infectious Disease Therapeutics: Why Should We Care? *American Society of Addiction Medicine Annual Meeting NIDA Symposium*. April 2009;New Orleans, LA.
936. Brown LS, Sawyer RC, Li R, Cobb MN, Colborn DC, Narang PK. Lack of a pharmacologic interaction between rifabutin and methadone in HIV-infected former injecting drug users. *Drug Alcohol Depend*. 1996;43(1-2):71-7.
937. Berk SI, Litwin AH, Arnsten JH, Du E, Soloway I, Gourevitch MN. Effects of pegylated interferon alfa-2b on the pharmacokinetic and pharmacodynamic properties of methadone: a prospective, nonrandomized, crossover study in patients coinfected with hepatitis C and HIV receiving methadone maintenance treatment. *Clin Ther*. 2007;29(1):131-8.
938. Gupta SK, Sellers E, Somoza E, Angles L, Kolz K, Cutler DL. The effect of multiple doses of peginterferon alfa-2b on the steady-state pharmacokinetics of methadone in patients with chronic hepatitis C undergoing methadone maintenance therapy. *J Clin Pharmacol*. 2007;47(5):604-12.
939. *Physician's Desk Reference. 63rd.* Montvale, NJ: Thomson; 2009.
940. Karin H, Segerdahi M, Gustafsson L, Kalso E. Methadone, ciprofloxacin and adverse drug reactions. *Lancet*. 2000;356;2069-70.
941. Bertschy G, Eap C, Powell K, Baumann P. Fluoxetine addition to methadone in addicts: pharmacokinetic aspects. *Ther Drug Monit*. 1996;18570-2.
942. Bertschy G, Baumann P, Eap CB, Baettig D. Probable metabolic interaction between methadone and fluvoxamine in addict patients. *Ther Drug Monit*. 1994;16(1):42-5.
943. Hamilton SP, Nunes EV, Janal M, Weber L. The effect of sertraline on methadone plasma levels in methadone-maintenance patients. *Am J Addict*. 2000;9(1):63-9.
944. Dvir Y, Smallwood P. Serotonin syndrome: a complex but easily avoidable condition. *Gen Hosp Psychiatry*. 2008;30(3):284-7.
945. Gore M, Sadosky A, Leslie D, Sheehan AH. Selecting an appropriate medication for treating neuropathic pain in patients with diabetes: a study using the U.K. and Germany Mediplus databases. *Pain Pract*. 2008;8(4):253-62.
946. Bomsien S, Skopp G. An in vitro approach to potential methadone metabolic-inhibition interactions. *Eur J Clin Pharmacol*. 2007;63(9):821-7.
947. Di Y, Li C, Xue C, Zhou S. Clinical drugs that interact with St. John's wort and implication in drug development. *Curr Pharm Des*. 2008;141723-42.
948. Maany I, Dhopesh V, Arndt IO, Burke W, Woody G, O'Brien CP. Increase in desipramine serum levels associated with methadone treatment. *Am J Psychiatry*. 1989;146(12):1611-3.
949. Lotrich FE, Rosen J, Pollock BG. Dextromethorphan-induced delirium and possible methadone interaction. *Am J Geriatr Pharmacother*. 2005;3(1):17-20.
950. Uehlinger C, Crettol S, Chassot P, et al. Increased (R)-methadone plasma concentrations by quetiapine in cytochrome P450s and ABCB1 genotyped patients. *J Clin Psychopharmacol*. 2007;27(3):273-8.
951. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. *Br J Clin Pharmacol*. 2006;61(3):246-55.
952. Sharma A, Hamelin BA. Classic histamine H1 receptor antagonists: a critical review of their metabolic and pharmacokinetic fate from a bird's eye view. *Curr Drug Metab*. 2003;4(2):105-29.
953. McCance-Katz EF, Jatlow P, Rainey PM. Effect of cocaine use on methadone pharmacokinetics in humans. *Am J Addict*. 2010;19(1):47-52.
954. McCance-Katz EF, Rainey PM, Moody DE. Effect of cocaine use on buprenorphine pharmacokinetics in humans. *Am J Addict*. 2010;19(1):38-46.
955. Pellinen P, Stenback F, Kojo A, Honkakoski P, Gelboin HV, Pasanen M. Regenerative changes in hepatic morphology and enhanced expression of CYP2B10 and CYP3A during daily administration of cocaine. *Hepatology*. 1996;23(3):515-23.
956. Lopez P, Velez R, Rivera V. Characteristics of P-glycoprotein (Pgp) upregulated in chronic cocaine users and HIV infected persons. *Retrovirology*. 2005;2(Suppl 1):142.
957. Madden JA, Konkol RJ, Keller PA, Alvarez TA. Cocaine and benzoylecgonine constrict cerebral arteries by different mechanisms. *Life Sci*. 1995;56(9):679-86.
958. Kreek MJ. Opioid interactions with alcohol. *Adv Alcohol Subst Abuse*. 1984;3(4):35-46.
959. Kreek MJ. Metabolic interactions between opiates and alcohol. *Ann N Y Acad Sci*. 1981;36236-49.
960. Mercadante S, Arcuri E, Tirelli W, Casuccio A. Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, crossover, double-dose study. *J Pain Symptom Manage*. 2000;20(4):246-52.

961. Centers for Disease Control and Prevention, *Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008.* MMWR, 2011. **60**(43): p. 1487-92.
962. Centers for Disease Control and Prevention (CDC), *Vital signs: risk of overdose from methadone used for pain relief-United States, 1999-2010.* MMWR, 2012. **61:**: p. 493-7.
963. Harris, J.S., et al., *Methodology to update the practice recommendations in the American College of Occupational and Environmental Medicine's Occupational Medicine Practice Guidelines, second edition.* J Occup Environ Med, 2008. **50**(3): p. 282-95.
964. Talmage, J., J. Melhorn, and M. Hyman, *Chapter 9. Medications, Driving, and Work*, in *AMA Guides (TM) to the Evaluation of Work Ability and Return to Work. Second Edition.*, J. Talmage, J. Melhorn, and M. Hyman, Editors. 2011, American Medical Association: Chicago, IL.
965. Hoffmann, D. and A. Tarzian, *Achieving the right balance in oversight of physician opioid prescribing for pain: the role of State Medical Boards.* J Law Med Ethics, 2003. **31**: p. 21-40.
966. Goodman, A., *Addiction: Definition and implications.* British Journal of Addiction, 1990. **85**(11): p. 1403-1408.
967. Caudill-Slosberg, M.A., L.M. Schwartz, and S. Woloshin, *Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 vs. 2000.* Pain, 2004. **109**(3): p. 514-9.
968. Berecki-Gisolf, J., A. Collie, and R.J. McClure, *Prescription opioids for occupational injury: results from workers' compensation claims records.* Pain Medicine, 2014. **15**(9): p. 1549-1557.
969. Hayes S, S.A., *Pain Management and the Use of Opioids in the Treatment of Back Conditions in the California Workers Compensation System.* 2016.
970. Park, T.W., et al., *Understanding risk factors for opioid overdose in clinical populations to inform treatment and policy.* Journal of addiction medicine, 2016. **10**(6): p. 369-381.
971. Heins, S.E., et al., *Early opioid prescription and risk of long-term opioid use among US workers with back and shoulder injuries: a retrospective cohort study.* Injury prevention, 2016. **22**(3): p. 211-215.
972. Beaudoin, F.L., G.N. Banerjee, and M.J. Mello, *State-level and system-level opioid prescribing policies: the impact on provider practices and overdose deaths, a systematic review.* Journal of opioid management, 2016. **12**(2): p. 109-118.
973. Delorme, J., et al., *Incidence of high dosage buprenorphine and methadone shopping behavior in a retrospective cohort of opioid-maintained patients in France.* Drug and alcohol dependence, 2016. **162**: p. 99-106.
974. Dilokthornsakul, P., et al., *Risk Factors of Prescription Opioid Overdose Among Colorado Medicaid Beneficiaries.* The Journal of Pain, 2016. **17**(4): p. 436-443.
975. Weiner, S.G., et al., *Characteristics of emergency department "doctor shoppers".* The Journal of emergency medicine, 2015. **48**(4): p. 424-431. e1.
976. Cheng, M., et al., *Comparison of opioid-related deaths by work-related injury.* Am J Industrial Med, 2013. **56**: p. 308-16.
977. Franklin, G.M., et al., *Opioid dosing trends and mortality in Washington State workers' compensation, 1996-2002.* Am J Ind Med, 2005. **48**(2): p. 91-9.
978. Volkow, N. and T. McLellan, *Curtailing diversion and abuse of opioid analgesics without jeopardizing pain treatment* JAMA, 2011. **305**(13): p. 1346-7.
979. Parsells Kelly, J., et al., *Prevalence and characteristics of opioid use in the US adult population.* Pain, 2008. **138**(3): p. 507-13.
980. Substance Abuse and Mental Health Services Administration, *Federal Guidelines for Opioid Treatment.* 2013.
981. Centers for Disease Control and Prevention, *Adult Use of Prescription Opioid Pain Medications - Utah, 2008.* MMWR, 2010. **59**(6): p. 153-7.
982. Centers for Disease Control and Prevention, *Emergency department visits involving nonmedical use of selected prescription drugs - United States, 2004-2008.* MMWR, 2010. **59**(23): p. 705-9.
983. Coben, J.H., et al., *Hospitalizations for poisoning by prescription opioids, sedatives, and tranquilizers.* Am J Prev Med, 2010. **38**(5): p. 517-24.
984. Kress, H.G. and B. Kraft, *Opioid medication and driving ability.* Eur J Pain, 2005. **9**(2): p. 141-4.
985. Gomes, T., et al., *Opioid dose and risk of road trauma in Canada: a population-based study.* JAMA Intern Med, 2013. **173**(3): p. 196-201.
986. Gibson, J.E., et al., *Use of self-controlled analytical techniques to assess the association between use of prescription medications and the risk of motor vehicle crashes.* Am J Epidemiol, 2009. **169**(6): p. 761-8.
987. Engeland, A., S. Skurtveit, and J. Morland, *Risk of road traffic accidents associated with the prescription of drugs: a registry-based cohort study.* Ann Epidemiol, 2007. **17**(8): p. 597-602.
988. Dubois, S., M. Bedard, and B. Weaver, *The association between opioid analgesics and unsafe driving actions preceding fatal crashes.* Accid Anal Prev, 2010. **42**(1): p. 30-7.
989. Moore, R.A. and H.J. McQuay, *Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids.* Arthritis Res Ther, 2005. **7**(5): p. R1046-51.
990. Howard, M.E., et al., *Sleepiness, sleep-disordered breathing, and accident risk factors in commercial vehicle drivers.* Am J Respir Crit Care Med, 2004. **170**(9): p. 1014-21.

991. Isiordia-Espinoza, M.A., et al., *Pre-emptive analgesic effectiveness of meloxicam versus tramadol after mandibular third molar surgery: a pilot study.* J Oral Maxillofac Surg, 2012. **70**(1): p. 31-6.
992. Hansen, M., et al., *Intranasal fentanyl in the treatment of acute pain – a systematic review.* Acta Anaesthesiol Scand, 2012. **56**(4): p. 407-19.
993. Warner, M., et al., *Drug poisoning deaths in the United States, 1980-2008.* NCHS Data Brief, 2011. **No. 81**.
994. Rosenblatt, R.A. and M. Catlin, *Opioids for chronic pain: first do no harm.* Ann Fam Med, 2012. **10**(4): p. 300-1.
995. Campbell, C.I., et al., *Age and gender trends in long-term opioid analgesic use for noncancer pain.* Am J Public Health, 2010. **100**(12): p. 2541-7.
996. Kuehn, B., *Safety plan for opioids meets resistance opioid-linked deaths continue to soar.* JAMA, 2010. **303**(6): p. 495-7.
997. Piercefield, E., et al., *Increase in unintentional medication overdose deaths: Oklahoma, 1994-2006.* Am J Prev Med, 2010. **39**(4): p. 357-63.
998. Al-Asmari, A.I. and R.A. Anderson, *The role of dihydrocodeine (DHC) metabolites in dihydrocodeine-related deaths.* J Anal Toxicol, 2010. **34**(8): p. 476-90.
999. Al-Asmari, A.I., R.A. Anderson, and G.A. Cooper, *Oxycodone-related fatalities in the west of Scotland.* J Anal Toxicol, 2009. **33**(8): p. 423-32.
1000. Dhalla, I.A., et al., *Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone.* CMAJ, 2009. **181**(12): p. 891-6.
1001. Porucznik, C.A., et al., *Studying adverse events related to prescription opioids: the Utah experience.* Pain Med, 2011. **12 Suppl 2**: p. S16-25.
1002. Tanne, J.H., *Deaths from prescription opioids soar in New York.* BMJ, 2013. **346**: p. f921.
1003. Centers for Disease Control and Prevention, *Alcohol and Other Drug Use Among Victims of Motor-Vehicle Crashes–West Virginia, 2004-2005.* MMWR, 2006. **55**(48): p. 1293-6.
1004. Hall, A., et al., *Patterns of abuse among unintentional pharmaceutical overdose fatalities.* JAMA, 2008. **300**(22): p. 2613-20.
1005. Warner, M., L. Chen, and D. Makuc, *Increase in Fatal Poisonings Involving Opioid Analgesics in the United States, 1999–2006.* NCHS Data Brief, 2009. **22**.
1006. Kuehn, B.M., *Methadone overdose deaths rise with increased prescribing for pain.* JAMA, 2012. **308**(8): p. 749-50.
1007. Mack, K., C. Jones, and L. Paulozzi, *Vital Signs: Overdoses of Prescription Opioid Pain Relievers and Other Drugs Among Women - United States, 1999-2010.* MMWR, 2013. **62**(26): p. 537-42.
1008. Wunsch, M., et al., *Opioid deaths in rural Virginia: a description of the high prevalence of accidental fatalities involving prescribed medications.* Am J Addict, 2009. **18**(1).
1009. Green, T.C., et al., *Epidemiologic trends and geographic patterns of fatal opioid intoxications in Connecticut, USA: 1997-2007.* Drug Alcohol Depend, 2011. **115**(3): p. 221-8.
1010. Ekman, E.F., et al., *The COX-2 specific inhibitor valdecoxib versus tramadol in acute ankle sprain: a multicenter randomized, controlled trial.* Am J Sports Med, 2006. **34**(6): p. 945-55.
1011. Clark, E., et al., *A randomized, controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma.* Pediatrics, 2007. **119**(3): p. 460-7.
1012. Lovell, S.J., et al., *Comparison of valdecoxib and an oxycodone-acetaminophen combination for acute musculoskeletal pain in the emergency department: a randomized controlled trial.* Acad Emerg Med, 2004. **11**(12): p. 1278-82.
1013. Veenema, K., Leahey N, and S. S., *Ketorolac versus meperidine: ED treatment of severe musculoskeletal low back pain.* Am J Emerg Med, 2000. **18**(4): p. 404-7.
1014. Innes, G.D., et al., *Ketorolac versus acetaminophen-codeine in the emergency department treatment of acute low back pain.* J Emerg Med, 1998. **16**(4): p. 549-56.
1015. Brown, F.L., Jr., et al., *Comparison of diflunisal and acetaminophen with codeine in the treatment of initial or recurrent acute low back strain.* Clin Ther, 1986. **9** (Suppl C): p. 52-8.
1016. Muncie, H.L., Jr., D.E. King, and B. DeForge, *Treatment of mild to moderate pain of acute soft tissue injury: diflunisal vs acetaminophen with codeine.* J Fam Pract, 1986. **23**(2): p. 125-7.
1017. Chang, D.J., et al., *The analgesic efficacy of etoricoxib compared with oxycodone/acetaminophen in an acute postoperative pain model: a randomized, double-blind clinical trial.* Anesth Analg, 2004. **99**(3): p. 807-15, table of contents.
1018. Eriksen, J., et al., *Critical issues on opioids in chronic non-cancer pain: An epidemiological study.* Pain, 2006. **125**(1-2): p. 172-9.
1019. Atluri, S. and G. Sudarshan, *Development of a screening tool to detect the risk of inappropriate prescription opioid use in patients with chronic pain.* Pain Physician, 2004. **7**(3): p. 333-8.
1020. Shah, N.G., et al., *Unintentional drug overdose death trends in New Mexico, USA, 1990-2005: combinations of heroin, cocaine, prescription opioids and alcohol.* Addiction, 2008. **103**(1): p. 126-36.
1021. Webster, L., et al., *An analysis of the root causes for opioid-related overdose deaths in the United States.* Pain Med, 2011. **12**(Suppl 2): p. S26-35.
1022. Dunn, K.M., et al., *Opioid prescriptions for chronic pain and overdose: a cohort study.* Ann Intern Med, 2010. **152**(2): p. 85-92.

1023. Paulozzi, L.J., et al., *A comparison of drug overdose deaths involving methadone and other opioid analgesics in West Virginia.* Addiction, 2009. **104**(9): p. 1541-8.
1024. Paulozzi, L., et al., *CDC Grand Rounds: Prescription Drug Overdoses-a U.S. Epidemic.* MMWR, 2012. **61**(1): p. 10-3.
1025. Grattan, A., et al., *Depression and prescription opioid misuse among chronic opioid therapy recipients with no history of substance abuse.* Annals Fam Med, 2012. **10**(4): p. 304-11.
1026. Manchikanti, L., et al., *Evaluation of variables in illicit drug use: does a controlled substance abuse screening tool identify illicit drug use?* Pain Physician, 2004. **7**(1): p. 71-5.
1027. Nyhlen, A., et al., *Substance abuse and psychiatric co-morbidity as predictors of premature mortality in Swedish drug abusers: a prospective longitudinal study 1970-2006.* BMC Psychiatry, 2011. **11**: p. 122.
1028. Hadidi, M.S., et al., *Current trends in drug abuse associated fatalities - Jordan, 2000-2004.* Forensic Sci Int, 2009. **186**(1-3): p. 44-7.
1029. Wysowski, D.K., L.A. Governale, and J. Swann, *Trends in outpatient prescription drug use and related costs in the US: 1998-2003.* Pharmacoeconomics, 2006. **24**(3): p. 233-6.
1030. Wysowski, D.K., *Surveillance of prescription drug-related mortality using death certificate data.* Drug Saf, 2007. **30**(6): p. 533-40.
1031. Toblin, R.L., et al., *Mental illness and psychotropic drug use among prescription drug overdose deaths: a medical examiner chart review.* J Clin Psychiatry, 2010. **71**(4): p. 491-6.
1032. Centers for Disease Control and Prevention, *Unintentional deaths from drug poisoning by urbanization of area — New Mexico, 1994–2003.* MMWR, 2005. **54**(35): p. 870-3.
1033. Fareed, A., et al., *High dose versus moderate dose methadone maintenance: is there a better outcome?* J Addict Dis, 2009. **28**(4): p. 399-405.
1034. Deyo, R.A., et al., *Opioids for back pain patients: primary care prescribing patterns and use of services.* J Am Board Fam Med, 2011. **24**(6): p. 717-27.
1035. Goodridge, D., et al., *Factors associated with opioid dispensation for patients with COPD and lung cancer in the last year of life: A retrospective analysis.* Int J Chron Obstruct Pulmon Dis, 2010. **5**: p. 99-105.
1036. Dean, M., *Opioids in renal failure and dialysis patients.* J Pain Symptom Manage, 2004. **28**(5): p. 497-504.
1037. Seal, K.H., et al., *Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan.* JAMA, 2012. **307**(9): p. 940-7.
1038. Mills, K., et al., *The costs and outcomes of treatment for opioid dependence associated with posttraumatic stress disorder.* Psychiatr Serv, 2005. **56**(8): p. 940-5.
1039. Walter, S.R., et al., *Trends in mortality after diagnosis of hepatitis B or C infection: 1992-2006.* J Hepatol, 2011. **54**(5): p. 879-86.
1040. Cifuentes, M., et al., *The course of opioid prescribing for a new episode of disabling low back pain: opioid features and dose escalation.* Pain, 2010. **151**(1): p. 22-9.
1041. Volinn, E., J.D. Fargo, and P.G. Fine, *Opioid therapy for nonspecific low back pain and the outcome of chronic work loss.* Pain, 2009. **142**(3): p. 194-201.
1042. Dersh, J., et al., *Prescription opioid dependence is associated with poorer outcomes in disabling spinal disorders.* Spine, 2008. **33**(20): p. 2219-27.
1043. Von Korff, M., et al., *Long-term opioid therapy reconsidered.* Ann Intern Med, 2011. **155**: p. 325-8.
1044. Hartrick, C., R. Gatchel, and S. Conroy, *Identification and management of pain medication abuse and misuse: current state and future directions.* Expert Rev Neurother, 2012. **12**(5).
1045. Kidner, C.L., R.J. Gatchel, and T.G. Mayer, *MMPI disability profile is associated with degree of opioid use in chronic work-related musculoskeletal disorders.* Clin J Pain, 2010. **26**(1): p. 9-15.
1046. Bohnert, A.S., et al., *Association between opioid prescribing patterns and opioid overdose-related deaths.* JAMA, 2011. **305**(13): p. 1315-21.
1047. Naliboff, B.D., et al., *A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain.* J Pain, 2011. **12**(2): p. 288-96.
1048. Lees, R., et al., *Comparison of ethyl glucuronide in hair with self-reported alcohol consumption.* Alcohol Alcohol, 2012. **47**(3): p. 267-72.
1049. Politi, L., et al., *Markers of chronic alcohol use in hair: comparison of ethyl glucuronide and cocaethylene in cocaine users.* Forensic Sci Int, 2007. **172**(1): p. 23-7.
1050. Lamoureux, F., et al., *Determination of ethyl-glucuronide in hair for heavy drinking detection using liquid chromatography-tandem mass spectrometry following solid-phase extraction.* Anal Bioanal Chem, 2009. **394**(7): p. 1895-901.
1051. Cooper, G.A., R. Kronstrand, and P. Kintz, *Society of Hair Testing guidelines for drug testing in hair.* Forensic Sci Int, 2012. **218**(1-3): p. 20-4.
1052. Kulaga, V., et al., *The effect of hair pigment on the incorporation of fatty acid ethyl esters (FAEE).* Alcohol Alcohol, 2009. **44**(3): p. 287-92.
1053. Krebs, E., et al., *Comparative mortality among Department of Veterans Affairs patients prescribed methadone or long-acting morphine for chronic pain.* Pain, 2011. **152**(8): p. 1789-95.
1054. Appenzeller, B.M., et al., *Segmental determination of ethyl glucuronide in hair: a pilot study.* Forensic Sci Int, 2007. **173**(2-3): p. 87-92.
1055. Federal Drug Administration, *Introduction for the FDA blueprint for prescriber education for extended-release and long-acting opioid analgesics.*

http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf. *(Accessed July 14, 2012).* July 9, 2012.
1056. Commissions, I.A.o.I.A.B.a. *Reducing Inappropriate Opioid Use in Treatment of Injured Workers:A Policy Guide*. 2013; Available from: http://www.iaiabc.org/files/OpioidPolicies_05-29-13.pdf.
1057. Thomsen, A.B., N. Becker, and J. Eriksen, *Opioid rotation in chronic non-malignant pain patients. A retrospective study.* Acta Anaesthesiol Scand, 1999. **43**(9): p. 918-23.
1058. Eap, C.B., et al., *Stereoselective block of hERG channel by (S)-methadone and QT interval prolongation in CYP2B6 slow metabolizers.* Clin Pharmacol Ther, 2007. **81**(5): p. 719-28.
1059. Gatti, A., et al., *Controlled-release oxycodone and pregabalin in the treatment of neuropathic pain: results of a multicenter Italian study.* Eur Neurol, 2009. **61**(3): p. 129-37.
1060. Quang-Cantagrel, N.D., M.S. Wallace, and S.K. Magnuson, *Opioid substitution to improve the effectiveness of chronic noncancer pain control: a chart review.* Anesth Analg, 2000. **90**(4): p. 933-7.
1061. Kalso, E., et al., *Opioids in chronic non-cancer pain: systematic review of efficacy and safety.* Pain, 2004. **112**(3): p. 372-80.
1062. Webster, L.R., et al., *Oxytrex minimizes physical dependence while providing effective analgesia: a randomized controlled trial in low back pain.* J Pain, 2006. **7**(12): p. 937-46.
1063. Hale, M.E., C. Dvergsten, and J. Gimbel, *Efficacy and safety of oxymorphone extended release in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study.* J Pain, 2005. **6**(1): p. 21-8.
1064. Hale, M., et al., *Once-daily OROS hydromorphone ER compared with placebo in opioid-tolerant patients with chronic low back pain.* Curr Med Res Opin, 2010. **26**(6): p. 1505-18.
1065. Peloso, P.M., et al., *Analgesic efficacy and safety of tramadol/ acetaminophen combination tablets (Ultracet) in treatment of chronic low back pain: a multicenter, outpatient, randomized, double blind, placebo controlled trial.* J Rheumatol, 2004. **31**(12): p. 2454-63.
1066. Ruoff, G.E., et al., *Tramadol/acetaminophen combination tablets for the treatment of chronic lower back pain: a multicenter, randomized, double-blind, placebo-controlled outpatient study.* Clin Ther, 2003. **25**(4): p. 1123-41.
1067. Schnitzer, T.J., et al., *Efficacy of tramadol in treatment of chronic low back pain.* J Rheumatol, 2000. **27**(3): p. 772-8.
1068. Simpson, D., et al., *Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a multicenter, randomized, double-blind, placebo-controlled study.* Clin Ther, 2007. **29**(4): p. 588-601.
1069. Breckenridge, J. and J. Clark, *Patient characteristics associated with opioid versus nonsteroidal anti-inflammatory drug management of chronic low back pain. .* J Pain, 2003. **4**(6): p. 344-50.
1070. Buvanendran, A., et al., *Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial.* Anesth Analg, 2010. **110**(1): p. 199-207.
1071. Nader, A., et al., *A randomized trial of epidural analgesia followed by continuous femoral analgesia compared with oral opioid analgesia on short- and long-term functional recovery after total knee replacement.* Pain Med, 2012. **13**(7): p. 937-47.
1072. Pavelka, K., et al., *Intraindividual differences in pain relief and functional improvement in osteoarthritis with diclofenac or tramadol.* Clin Drug Investig, 1998. **16**(6): p. 421-9.
1073. Matsumoto, A., N. Babul, and H. Ahdieh, *Oxymorphone extended-release tablets relieve moderate to severe pain and improve physical function in osteoarthritis: results of a randomized, double-blind, placebo- and active-controlled phase III trial.* Pain Med, 2005. **6**(5): p. 357-66.
1074. Rosenthal, N.R., et al., *Tramadol/acetaminophen combination tablets for the treatment of pain associated with osteoarthritis flare in an elderly patient population.* J Am Geriatr Soc, 2004. **52**(3): p. 374-80.
1075. Freeman, R., et al., *Randomized study of tramadol/acetaminophen versus placebo in painful diabetic peripheral neuropathy.* Curr Med Res Opin, 2007. **23**(1): p. 147-61.
1076. Gammaitoni, A.R., et al., *Effectiveness and safety of new oxycodone/acetaminophen formulations with reduced acetaminophen for the treatment of low back pain.* Pain Med, 2003. **4**(1): p. 21-30.
1077. Martell, B.A., et al., *Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction.* Ann Intern Med, 2007. **146**(2): p. 116-27.
1078. Maruta, T., D.W. Swanson, and R.E. Finlayson, *Drug abuse and dependency in patients with chronic pain.* Mayo Clin Proc, 1979. **54**(4): p. 241-4.
1079. Chabal, C., et al., *Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors.* Clin J Pain, 1997. **13**(2): p. 150-5.
1080. Butler, S., et al., *Validation of the revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R).* J Pain 2008. **9**(4): p. 360-72.
1081. Michna, E., et al., *Predicting aberrant drug behavior in patients treated for chronic pain: importance of abuse history.* J Pain Symptom Manage, 2004. **28**(3): p. 250-8.
1082. Baratta, R., *A double-blind comparative study of carisoprodol, propoxyphene, and placebo in the management of low back syndrome.* Curr Ther Res Clin Exp, 1976. **20**(3): p. 233-40.
1083. Chang, A.K., et al., *Safety and efficacy of hydromorphone as an analgesic alternative to morphine in acute pain: a randomized clinical trial.* Ann Emerg Med, 2006. **48**(2): p. 164-72.

1084. Webster, B., S. Verma, and R. Gatchel, *Relationship between early opioid prescribing for acute occupational low back pain and disability duration, medical costs, subsequent surgery and late opioid use.* Spine, 2007. **32**(19): p. 2127-32.
1085. Gora-Harper, M., et al., *Opioid analgesics versus ketorolac in spine and joint procedures: impact on healthcare resources.* Ann Pharmacother, 2001. **35**(11): p. 1320-6.
1086. Khoromi, S., et al., *Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. .* Pain, 2007. **130**(1-2): p. 66-75.
1087. Siddall, P.J., et al., *The efficacy of intrathecal morphine and clonidine in the treatment of pain after spinal cord injury.* Anesth Analg, 2000. **91**(6): p. 1493-8.
1088. Li, C., et al., *Analgesic efficacy and tolerability of flupirtine vs. tramadol in patients with subacute low back pain: a double-blind multicentre trial*.* Curr Med Res Opin, 2008. **24**(12): p. 3523-30.
1089. Moulin, D., et al., *Randomised trial of oral morphine for chronic non-cancer pain.* Lancet, 1996. **347**(8995): p. 143-7.
1090. Wu, C.L., et al., *Morphine versus mexiletine for treatment of postamputation pain: a randomized, placebo-controlled, crossover trial.* Anesthesiology, 2008. **109**(2): p. 289-96.
1091. Parr, G., et al., *Joint pain and quality of life; results of a randomised trial.* Br J Clin Pharmacol, 1989. **27**(2): p. 235-42.
1092. Jamison, R.N., et al., *Opioid therapy for chronic noncancer back pain. A randomized prospective study.* Spine 1998. **23**(23): p. 2591-600.
1093. Edwards, R.R., et al., *Elevated pain sensitivity in chronic pain patients at risk for opioid misuse.* J Pain, 2011. **12**(9): p. 953-63.
1094. Vaglienti, R.M., et al., *Misuse of prescribed controlled substances defined by urinalysis.* W V Med J, 2003. **99**(2): p. 67-70.
1095. Noble, M., et al., *Long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and safety.* J Pain Symptom Manage, 2008. **35**(2): p. 214-28.
1096. Furlan, A., et al., *Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects.* CMAJ, 2006. **174**(11): p. 1589-94.
1097. Wiedemer, N., et al., *The opioid renewal clinic: a primary care, managed approach to opioid therapy in chronic pain patients at risk for substance abuse.* Pain Med, 2007. **8**(7): p. 573-84.
1098. Michna, E., R. Jamison, and L. Pham, et al. , *Urine toxicology screening among chronic pain patients on opioid therapy: frequency and predictability of abnormal findings.* Clin J Pain, 2007. **23**(2): p. 173-9.
1099. Chou, R., et al., *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.* J Pain, 2009. **10**(2): p. 147-59.
1100. Freye, E., et al., *Opioid rotation from high-dose morphine to transdermal buprenorphine (Transtec) in chronic pain patients.* Pain Pract, 2007. **7**(2): p. 123-9.
1101. McNicol, E., et al., *Nonsteroidal anti-inflammatory drugs, alone or combined with opioids, for cancer pain: a systematic review.* J Clin Oncol, 2004. **22**(10): p. 1975-92.
1102. Davies, E., et al., *Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes.* PLoS ONE, 2009. **4**(2): p. e4439.
1103. Oderda, G., et al., *Opioid-related adverse drug events in surgical hospitalizations: impact on costs and length of stay.* Ann Pharmacother, 2007. **41**(3): p. 400-6.
1104. Choiniere, M., *Efficacy and Costs of Patient-controlled Analgesia versus Regularly Administered Intramuscular Opioid Therapy.* Anesthesiology 1998. **89**.
1105. Rittenhouse, B. and M. Choiniere, *An economic evaluation of pain therapy after hysterectomy. Patient-controlled analgesia versus regular intramuscular opioid therapy.* Intl J Technology Assessment Health Care, 1999. **15**(3): p. 548-62.
1106. Vojtassak, J., et al., *A Phase IIIb, Multicentre, Randomised, Parallel-Group, Placebo-Controlled, Double-Blind Study to Investigate the Efficacy and Safety of OROS Hydromorphone in Subjects with Moderate-to-Severe Chronic Pain Induced by Osteoarthritis of the Hip or the Knee.* Pain Res Treat, 2011: p. 1-9.
1107. Friedmann, N., V. Klutzaritz, and L. Webster, *Long-term safety of Remoxy(R) (extended-release oxycodone) in patients with moderate to severe chronic osteoarthritis or low back pain.* Pain Med, 2011. **12**(5): p. 755-60.
1108. Martin, B.C., et al., *Long-term chronic opioid therapy discontinuation rates from the TROUP study.* J Gen Intern Med, 2011. **26**(12): p. 1450-7.
1109. Nilsen, H.K., et al., *Patients with problematic opioid use can be weaned from codeine without pain escalation.* Acta Anaesthesiol Scand, 2010. **54**(5): p. 571-9.
1110. Murphy, J.L., M.E. Clark, and E. Banou, *Opioid cessation and multidimensional outcomes after interdisciplinary chronic pain treatment.* Clin J Pain, 2013. **29**(2): p. 109-17.
1111. Dreifuss, J.A., et al., *Patient characteristics associated with buprenorphine/naloxone treatment outcome for prescription opioid dependence: Results from a multisite study.* Drug Alcohol Depend, 2013. **131**(1-2): p. 112-8.
1112. Orman, J.S. and G.M. Keating, *Buprenorphine/naloxone: a review of its use in the treatment of opioid dependence.* Drugs, 2009. **69**(5): p. 577-607.

1113. Weiss, R.D., et al., *Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial.* Arch Gen Psychiatry, 2011. **68**(12): p. 1238-46.
1114. Dunn, K.E., et al., *The association between outpatient buprenorphine detoxification duration and clinical treatment outcomes: a review.* Drug Alcohol Depend, 2011. **119**(1-2): p. 1-9.
1115. Westermeyer, J. and E.F. McCance-Katz, *Course and treatment of buprenorphine/naloxone withdrawal: an analysis of case reports.* Am J Addict, 2012. **21**(5): p. 401-3.
1116. Jones, J.D., et al., *The subjective, reinforcing, and analgesic effects of oxycodone in patients with chronic, non-malignant pain who are maintained on sublingual buprenorphine/naloxone.* Neuropsychopharmacology, 2011. **36**(2): p. 411-22.
1117. Ling, W., et al., *Comparisons of analgesic potency and side effects of buprenorphine and buprenorphine with ultra-low-dose naloxone.* J Addict Med, 2012. **6**(2): p. 118-23.
1118. Farahmand, S., et al., *Does adding low doses of oral naltrexone to morphine alter the subsequent opioid requirements and side effects in trauma patients?* Am J Emerg Med, 2012. **30**(1): p. 75-8.
1119. Webster, L.R., et al., *Randomized, double-blind, placebo-controlled study of the abuse potential of different formulations of oral oxycodone.* Pain Med, 2012. **13**(6): p. 790-801.
1120. Fiellin, D.A., et al., *Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence.* N Engl J Med, 2006. **355**(4): p. 365-74.
1121. Fiellin, D.A., et al., *A randomized trial of cognitive behavioral therapy in primary care-based buprenorphine.* Am J Med, 2013. **126**(1): p. 74 e11-7.
1122. Fudala, P.J., et al., *Effects of buprenorphine and naloxone in morphine-stabilized opioid addicts.* Drug Alcohol Depend, 1998. **50**(1): p. 1-8.
1123. Krupitsky, E., et al., *Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial.* Lancet, 2011. **377**(9776): p. 1506-13.
1124. Krupitsky, E., et al., *Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence.* Arch Gen Psychiatry, 2012. **69**(9): p. 973-81.
1125. Mannelli, P., et al., *The combination very low-dose naltrexone-clonidine in the management of opioid withdrawal.* Am J Drug Alcohol Abuse, 2012. **38**(3): p. 200-5.
1126. Majdzadeh, R., et al., *Opium consumption and the risk of traffic injuries in regular users: a case-crossover study in an emergency department.* Traffic Inj Prev, 2009. **10**(4): p. 325-9.
1127. Bachs, L.C., et al., *The risk of motor vehicle accidents involving drivers with prescriptions for codeine or tramadol.* Clin Pharmacol Ther, 2009. **85**(6): p. 596-9.
1128. Corsenac, P., et al., *Road traffic crashes and prescribed methadone and buprenorphine: a French registry-based case-control study.* Drug Alcohol Depend, 2012. **123**(1-3): p. 91-7.
1129. Bramness, J.G., et al., *An increased risk of motor vehicle accidents after prescription of methadone.* Addiction, 2012. **107**(5): p. 967-72.
1130. Movig, K.L., et al., *Psychoactive substance use and the risk of motor vehicle accidents.* Accid Anal Prev, 2004. **36**(4): p. 631-6.
1131. Burgess, F., *Methadone analgesia: balancing the risks and benefits*, in *Pain Medicine News*. 2009.
1132. Webster, L.R., et al., *Impact of intravenous naltrexone on intravenous morphine-induced high, drug liking, and euphoric effects in experienced, nondependent male opioid users.* Drugs R D, 2011. **11**(3): p. 259-75.
1133. Modesto-Lowe, V., D. Brooks, and N. Petry, *Methadone deaths: risk factors in pain and addicted populations.* J Gen Intern Med, 2010. **25**(4): p. 305-9.
1134. Chugh, S.S., et al., *A community-based evaluation of sudden death associated with therapeutic levels of methadone.* Am J Med, 2008. **121**(1): p. 66-71.
1135. Berland, D. and P. Rodgers, *Rational use of opioids for management of chronic nonterminal pain.* Am Fam Physician, 2012. **86**(3): p. 252-8.
1136. Chou, R., et al., *Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain.* J Pain, 2009. **10**(2): p. 113-30.
1137. Rosca, P., et al., *Mortality and causes of death among users of methadone maintenance treatment in Israel, 1999-2008.* Drug Alcohol Depend, 2012. **125**(1-2): p. 160-3.
1138. Kelty, E. and G. Hulse, *Examination of mortality rates in a retrospective cohort of patients treated with oral or implant naltrexone for problematic opiate use.* Addiction, 2012. **107**(10): p. 1817-24.
1139. Smith, H., *A comprehensive review of rapid-onset opioids for breakthrough pain.* CNS Drugs, 2012. **26**(6): p. 509-35.
1140. Zeppetella, G., C. O'Doherty, and S. Collins, *Prevalence and characteristics of breakthrough pain in cancer patients admitted to a hospice.* J Pain Symptom Manage, 2000. **20**(2): p. 87-92.
1141. Simmonds, M., *Management of breakthrough pain due to cancer.* Oncology, 1999. **13**(8): p. 1103-8.
1142. Zeppetella, G. and M. Ribeiro, *Opioids for the management of breakthrough (episodic) pain in cancer patients.* Cochrane Database Syst Rev, 2006(1): p. CD004311.
1143. Coffey, R.J., et al., *Mortality associated with implantation and management of intrathecal opioid drug infusion systems to treat noncancer pain.* Anesthesiology, 2009. **111**(4): p. 881-91.
1144. Lemming, D., et al., *Managing chronic whiplash associated pain with a combination of low-dose opioid (remifentanil) and NMDA-antagonist (ketamine).* Eur J Pain, 2007. **11**(7): p. 719-32.

1145. Lemming, D., et al., *The responses to pharmacological challenges and experimental pain in patients with chronic whiplash-associated pain.* Clin J Pain, 2005. **21**(5): p. 412-21.
1146. Miele, V.J., et al., *A review of intrathecal morphine therapy related granulomas.* Eur J Pain, 2006. **10**(3): p. 251-61.
1147. Rauck, R.L., et al., *A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain.* J Pain Symptom Manage, 2006. **31**(5): p. 393-406.
1148. Raffaeli, W., et al., *Opioid-related side-effects after intrathecal morphine: a prospective, randomized, double-blind dose-response study.* Eur J Anaesthesiol, 2006. **23**(7): p. 605-10.
1149. Hay, J.L., et al., *Hyperalgesia in opioid-managed chronic pain and opioid-dependent patients.* J Pain, 2009. **10**(3): p. 316-22.
1150. Ram, K.C., et al., *Oral opioid use alters DNIC but not cold pain perception in patients with chronic pain - new perspective of opioid-induced hyperalgesia.* Pain, 2008. **139**(2): p. 431-8.
1151. Carman, W., et al., *Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort.* Pharmacoepidemiol Druf Saf, 2011. **20**(7): p. 754-62.
1152. Li, L., et al., *Opioid use for noncancer pain and risk of myocardial infarction amongst adults.* J Intern Med, 2013. **273**(5): p. 511-26.
1153. Solomon, D.H., et al., *The comparative safety of opioids for nonmalignant pain in older adults.* Arch Intern Med, 2010. **170**(22): p. 1979-86.
1154. Broussard, C.S., et al., *Maternal treatment with opioid analgesics and risk for birth defects.* Am J Obstet Gynecol, 2011. **204**(4): p. 314 e1-11.
1155. Kidner, C.L., T.G. Mayer, and R.J. Gatchel, *Higher opioid doses predict poorer functional outcome in patients with chronic disabling occupational musculoskeletal disorders.* J Bone Joint Surg Am, 2009. **91**(4): p. 919-27.
1156. Franklin, G.M., et al., *Early opioid prescription and subsequent disability among workers with back injuries: the Disability Risk Identification Study Cohort.* Spine, 2008. **33**(2): p. 199-204.
1157. Chen, S.-L., *Dextromethorphan Attenuated Inflammation and Combined Opioid Use in Humans Undergoing Methadone Maintenance Treatment.* Neuroimmune Pharmacology, 2012. **7**(4): p. 1025-1033.
1158. Braden, J.B., et al., *Emergency department visits among recipients of chronic opioid therapy.* Arch Intern Med, 2010. **170**(16): p. 1425-32.
1159. Portenoy, R.K., et al., *Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study.* Clin J Pain, 2007. **23**(4): p. 287-99.
1160. Currow, D.C., et al., *Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study.* J Pain Symptom Manage, 2011. **42**(3): p. 388-99.
1161. Andresen, H., et al., *Fentanyl: toxic or therapeutic? Postmortem and antemortem blood concentrations after transdermal fentanyl application.* J Anal Toxicol, 2012. **36**(3): p. 182-94.
1162. Manchikanti, L. and A. Singh, *Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids.* Pain Physician, 2008. **11**(2 Suppl): p. S63-88.
1163. Trescot, A.M., et al., *Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines.* Pain Physician, 2008. **11**(2 Suppl): p. S5-S62.
1164. Dimsdale, J., et al., *The effect of opioids on sleep architecture.* J Clin Sleep Med, 2007. **3**(1): p. 33-6.
1165. Sadeghian, S., et al., *The association of opium dependence and postoperative complications following coronary artery bypass graft surgery: a propensity-matched study.* J Opioid Manag, 2009. **5**(6): p. 365-72.
1166. Safaii, N. and B. Kazemi, *Effect of opium use on short-term outcome in patients undergoing coronary artery bypass surgery.* Gen Thorac Cardiovasc Surg, 2010. **58**(2): p. 62-7.
1167. Agusti, A., et al., *Exposure to medicines among patients admitted for hip fracture and the case-fatality rate at 1 year: a longitudinal study.* Eur J Clin Pharmacol, 2012. **68**(11): p. 1525-31.
1168. Silverman, S., *Opioid induced hyperalgesia: clinical implications for the pain practitioner.* Pain Physician, 2009. **12**: p. 679-84.
1169. Daniell, H.W., *Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain.* J Pain, 2008. **9**(1): p. 28-36.
1170. Katz, N. and N.A. Mazer, *The impact of opioids on the endocrine system.* Clin J Pain, 2009. **25**(2): p. 170-5.
1171. Finch, P., et al., *Hypogonadism in patients treated with intrathecal morphine.* Clin J Pain, 2000. **16**(3): p. 251-4.
1172. Paice, J., R. Penn, and W. Ryan, *Altered sexual function and decreased testosterone in patients receiving intraspinal opioids.* J Pain Symptom Manage, 1994. **9**(2): p. 126-31.
1173. Daniell, H., *Hypogonadism in men consuming sustained-action oral opioids.* J Pain, 2002. **3**(5): p. 377-84.
1174. Gach, K., et al., *The role of morphine in regulation of cancer cell growth.* Naunyn Schmiedebergs Arch Pharmacol, 2011. **384**(3): p. 221-30.
1175. Tavare, A.N., et al., *Cancer recurrence after surgery: direct and indirect effects of anesthetic agents.* Int J Cancer, 2012. **130**(6): p. 1237-50.
1176. Afsharimani, B., P. Cabot, and M.O. Parat, *Morphine and tumor growth and metastasis.* Cancer Metastasis Rev, 2011. **30**(2): p. 225-38.
1177. von Korff, M., et al., *Defacto long-term opioid therapy for non-cancer pain.* Clin J Pain, 2008. **24**(6): p. 521-7.

1178. Manchikanti, L., et al., *Pyschological factors as predictors of opioid abuse and illicit drug use in chronic pain patients.* J Opioid Manage, 2007. **3**(2): p. 89-100.
1179. Emrich, H., P. Vogt, and A. Herz, *Possible antidepressive effects of opioids: action of buprenorphine.* Annals New York Academy of Sciences, 1982. **398**: p. 108-12.
1180. Sinyor, M., et al., *Substances used in completed suicide by overdose in Toronto: an observational study of coroner's data.* Can J Psychiatry, 2012. **57**(3): p. 184-91.
1181. Dahan, A., et al., *Buprenorphine induces ceiling in respiratory depression but not in analgesia.* Br J Anaesth, 2006. **96**(5): p. 627-32.
1182. Clemens, K.E., I. Quednau, and E. Klaschik, *Is there a higher risk of respiratory depression in opioid-naive palliative care patients during symptomatic therapy of dyspnea with strong opioids?* J Palliat Med, 2008. **11**(2): p. 204-16.
1183. Caspi, J., et al., *Delayed respiratory depression following fentanyl anesthesia for cardiac surgery.* Crit Care Med, 1988. **16**(3): p. 238-40.
1184. van Dorp, E., et al., *Naloxone reversal of buprenorphine-induced respiratory depression.* Anesthesiology, 2006. **105**(1): p. 51-7.
1185. Cronin, A.J., et al., *Postoperative sleep disturbance: influences of opioids and pain in humans.* Sleep, 2001. **24**(1): p. 39-44.
1186. Webster, L.R., et al., *Sleep-disordered breathing and chronic opioid therapy.* Pain Med, 2008. **9**(4): p. 425-32.
1187. Krenk, L., P. Jennum, and H. Kehlet, *Sleep disturbances after fast-track hip and knee arthroplasty.* Br J Anaesth, 2012. **109**(5): p. 769-75.
1188. Franklin, G.M., et al., *Bending the prescription opioid dosing and mortality curves: impact of the Washington State opioid dosing guideline.* Am J Ind Med, 2012. **55**(4): p. 325-31.
1189. Fitzgibbon, D., et al., *Malpractice claims associated with medication management for chronic pain.* Pain Med, 2010. **112**(4): p. 948-56.
1190. Cochella, S. and K. Bateman, *Provider detailing: an intervention to decrease prescription opioid deaths in Utah.* Pain Med, 2011. **12**(Suppl 2): p. S73-6.
1191. Okie, S., *A flood of opioids, a rising tide of deaths.* N Engl J Med, 2010. **363**(21): p. 1981-5.

