GUIDELINE FOR THE

Use of Chronic Opioid Therapy in Chronic Noncancer Pain

Evidence Review

The American Pain Society in Conjunction with
The American Academy of Pain Medicine

American Pain Society

RESEARCH
EDUCATION
TREATMENT
ADVOCACY

CLINICAL GUIDELINE FOR THE USE OF CHRONIC OPIOID THERAPY IN CHRONIC NONCANCER PAIN

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INTRODUCTION

Purpose of evidence review

This review evaluates evidence on use of opioids in adults with chronic noncancer pain. The American Pain Society (APS), which commissioned this report, used this review in partnership with the American Academy of Pain Medicine (AAPM) to develop evidence-based clinical practice guidelines for use of chronic opioid therapy (see glossary) in adults with chronic noncancer pain. The guidelines are available in the February 10, 2009 issue of the Journal of Pain.

BACKGROUND

Opioids are drugs that exert their activity on opioid receptors. They are considered the most potent analgesics. Epidemiologic studies indicate that use of opioids for chronic noncancer pain has increased substantially over the last two decades. In one large U.S. survey, the proportion of office visits for chronic musculoskeletal pain in which any opioids were prescribed doubled from 8% in 1980 to 16% in 2000[1]. Use of more potent opioids (such as morphine, hydromorphone, oxycodone, and fentanyl) has also increased. Over the same two decades, the proportion of office visits in which prescriptions for potent opioids were given increased from 2% to 9%.

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"[2]. Chronic pain is defined by the IASP as "pain that persists beyond normal tissue healing time, which is assumed to be three months[3]." Although the term *chronic noncancer pain* encompasses pain associated with a wide diversity of conditions, common treatment goals regardless of the underlying cause are pain relief and/or improvement in physical and psychological functioning.

Chronic pain is a common problem in the U.S.A. and other countries, though estimates of prevalence vary widely depending on the population evaluated and definitions used for chronic pain. One systematic review of epidemiologic studies published through 1996 estimated prevalence of chronic pain in adults ranging from 2% to 40% in developed countries[4]. In a survey of primary care settings in 15 developed and developing countries, an average of 22% of patients reported persistent pain (range 6% to 33%)[5]. One-quarter of U.S. adults surveyed in 1999 to 2002 reported pain lasting at least 24 hours in the last month[6]. In adults 65 years and older, over one-half of those with pain reported persistent symptoms for over one year. One large survey of nursing home residents older aged 65 and older found that nearly half reported persistent pain[7].

In addition to being common, chronic noncancer pain is also very costly. In 1998, total health care expenditures incurred by individuals with back pain, the most common cause of pain, were $90.7 billion in the U.S., with incremental costs attributed to back pain $26.3 billion[8]. Medical

treatment for chronic low back pain is estimated to cost $9,000 to $19,000 per patient annually, and interventional treatments cost a minimum of $13 billion in 1990[9]. In addition to direct medical costs, chronic pain results in substantial indirect costs due to days lost from work. Low back pain is the most common cause for chronic or permanent impairment in U.S. adults under the age of 65, and the most common cause of activity limitations in persons under the age of 45[10]. Among all persons with disabilities, arthritis and low back pain are the most commonly reported pain conditions[11]. Chronic pain is also frequently associated with depression and anxiety[5, 12, 13].

Although chronic noncancer pain is one of the most common reasons patients consult healthcare providers, it is frequently inadequately treated[14]. One large survey of nursing home residents found that one-quarter of those with persistent pain received no analgesics[7]. As part of efforts to address shortcomings in the treatment of pain, the U.S. Congress declared the 10-year period beginning in 2001 the "Decade of Pain Control and Research". In addition, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) published pain management standards in 2000 that recognize the right of individuals to appropriate assessment and management of pain[15].

Several published guidelines and consensus statements recommend judicious use of opioids in appropriately selected patients with chronic noncancer pain who have not responded to other treatments and analgesic medications[14, 16-20]. Nonetheless, there remains uncertainty about the optimal use of opioids for chronic noncancer pain. Some patients do not experience significant improvements in pain or function even on high doses of opioids[21]. In addition, opioids are associated with a variety of potentially serious adverse events, as well as aberrant drug-related behaviors (see glossary), including abuse (see glossary), addiction, and diversion (see glossary)[22, 23]. In 2005, for example, about 5% of U.S. persons over the age of 12 reported non-medical use of pain relievers (defined as any use other than prescribed or recommended) in the past year[24]. Non-medical use of pain relievers was highest among those aged 18 to 25 years (12%). Efforts to decrease abuse and diversion of opioids have been widely publicized. However, fear of governmental and other regulatory action may also discourage legitimate use of opioids[25]. Complicating matters, until recently there have been few controlled trials assessing benefits and harms of opioids for chronic noncancer pain to inform clinical decision-making[26].

The American Pain Society, in partnership with the American Academy of Pain Medicine, initiated this project to systematically review the current state of evidence and develop recommendations for use of opioids in patients with chronic noncancer pain using an explicit, evidence-based, balanced, and multidisciplinary approach.

Previous guidelines

Several guidelines on use of opioids for noncancer pain sponsored by different organizations have been published, including the following:

The American Society of Interventional Pain Physicians (2006)[20]

The British Pain Society (2005)[16]

Janssen Pharmaceutica (Europe) (2003)[19]

U.S. Department of Veterans Affairs/Department of Defense (2003)[27]

The Canadian Pain Society (2002)[18]

The Australian Pain Society (1997)[28]

Each of these guidelines is similar in recommending use of opioids in patients with chronic noncancer pain who have failed other interventions, including non-opioid analgesics. They also all recommend that clinicians assess risk for aberrant drug-related behaviors prior to starting opioid therapy; use of medication agreements; preferential use of sustained-release or long-acting opioids prescribed around-the-clock over immediate-release or short-acting opioids used as-needed; regular monitoring to assess treatment response, adverse events, and signs of aberrant drug-related behaviors; and referral of patients who do not improve or who are at high risk for aberrant drug-related behaviors to clinicians with expertise in diagnosing and treating chronic pain or addiction (see glossary). However, all of the guidelines except one were developed using a consensus process, and did not perform (or report) a systematic evidence review or attempt to grade the strength of recommendations or the quality of the evidence supporting the recommendations. The exception was the VA/DoD guidelines[27], which adapted methods developed by the U.S. Preventive Services Task Force[29] to grade strength of recommendations (Appendix 1). However, the VA/DoD guidelines do not clearly describe how the quality of evidence was determined or how assessments of quality or estimates of net benefit were used to assign the strength of recommendation grades. They also do not describe how the number of available studies, magnitude of effects, and consistency and directness of evidence were used to determine the quality of evidence.

The VA/DoD guidelines include 81 unique recommendations. Of these, 12 received an A grade, 12 a B grade, 6 a C grade, and 50 an I grade. The A and B recommendations are summarized in Appendix 2.

SCOPE OF EVIDENCE REVIEW

List of Key Questions

A multidisciplinary expert panel convened by the American Pain Society and the American Academy of Pain Medicine developed 37 Key Questions used to guide this evidence review. The panel believed it was critical to systematically address the evidence for each of these questions in order to develop evidence-based recommendations.

Risk-benefit assessment

1. In patients being considered for opioids for chronic noncancer pain, how accurate are patient features or characteristics for predicting:

   a. Benefits of chronic opioid therapy?
   b. Opioid-related harms?
   c. Aberrant drug-related behaviors?
2. In patients being considered for opioids for chronic noncancer pain, how accurate are formal screening instruments for predicting benefits of opioid therapy, harms, or aberrant drug-related behaviors?
3. In patients being considered for opioids for chronic noncancer pain, how effective is risk assessment for:
   a. Improving clinical outcomes?
   b. Reducing risk of aberrant drug behaviors?

Benefits and harms of chronic opioid therapy (including high risk patients)

4. What are the benefits (including long-term benefits) of opioids for chronic noncancer pain?
5. What are the harms (including long-term harms) of opioids for chronic noncancer pain? In patients at higher risk for abuse or addiction?
6. What are the benefits and harms of opioids for noncancer pain in patients with a history of substance abuse or addiction that are undergoing treatment for addiction?
7. What are the comparative benefits and harms of different opioids and different formulations of opioids for chronic noncancer pain?
8. Do the comparative benefits and harms of opioids vary in subpopulations defined by demographics (e.g. age, gender, and race), specific underlying pain conditions, or co-morbidities (e.g. liver disease, renal disease, respiratory disease, heart disease, HIV, drug misuse, cancer survivors)?

Prevention and treatment of opioid-related adverse effects

9. How effective are different strategies for minimizing or treating opioid-related adverse events?

Driving and work safety

10. How does initial or chronic use of opioids impact driving or work safety?

Initiation and titration of chronic opioid therapy

11. What are the benefits and harms of different methods for initiating and titrating opioids for chronic noncancer pain?

Selection of opioids and dosing methods

12. What are the benefits and harms of round-the-clock versus as needed dosing of opioids, or round-the-clock with as needed dosing versus as needed dosing alone for chronic noncancer pain?

13. What are the benefits and harms of regular intramuscular, subcutaneous, intranasal, buccal, or rectal versus oral or transdermal administration of opioids for chronic noncancer pain?

Breakthrough pain (see glossary)

14. What are the comparative benefits of different strategies for treating acute exacerbations of pain or a new acute pain problem in patients on chronic opioids for chronic noncancer pain?

Opioid rotation

15. What are the benefits and harms of opioid rotation versus continued treatment or dose escalation with the same opioid in patients with chronic noncancer pain?
16. What are the benefits and harms of different methods for switching patients on opioids for chronic noncancer pain from one opioid to another?

Dose escalations and high-dose opioid therapy

17. How accurate are patient characteristics or features for predicting lack of response to high doses of opioids for chronic noncancer pain?
18. How do dose-related responses for opioids change at different dose ranges or with long-term use?
19. What are the benefits and harms of high (>200 mg/day of morphine or equivalent) versus lower doses of opioids for chronic noncancer pain?
20. Are high doses of opioids associated with different or unique harms compared to lower doses?

Use of non-opioid therapies

21. How effective are patient education methods or clinician advice for improving outcomes associated with chronic opioid therapy?
22. How effective is co-prescription with other pain-attenuating medications or combining opioids for improving pain control or decreasing adverse events associated with opioid analgesics?
23. What is the effect of concomitant use of drugs with central nervous system (CNS) effects on adverse events associated with opioids for chronic noncancer pain?
24. What are the benefits associated with behavioral therapy, multidisciplinary rehabilitation, and/or functional restoration/work hardening in addition to or instead of opioids for chronic noncancer pain?

Informed consent and opiooid management plans

25. How effective are opioid agreements/contracts for improving clinical benefits and reducing harms, including abuse, addiction, or other aberrant drug-related behaviors associated with opioids for chronic noncancer pain?

Methods for monitoring opioid use and detecting aberrant drug-related behaviors

26. In patients receiving opioids for chronic noncancer pain, how accurate are formal screening instruments for identifying aberrant drug-related behaviors?
27. In patients receiving opioids for chronic noncancer pain, what is the diagnostic accuracy of urine drug screening and different urine drug screening methods for:
    a. Detecting illicit drug use?
    b. Identifying the presence or absence of prescribed and non-prescribed opioids and estimating doses of opioids?
28. In patients receiving opioids for chronic noncancer pain, how effective is urine drug screening and different urine drug screening methods for reducing abuse, addiction, and other aberrant drug-related behaviors, or increasing adherence to taking opioids as prescribed?
29. In patients receiving opioids for chronic noncancer pain, how effective are other methods (pill counts, limited prescriptions, monitoring blood levels) for detecting or reducing abuse, addiction, other aberrant drug-related behaviors, or whether patients are taking opioids as prescribed?
30. Is re-evaluation of patients on chronic opioid therapy at different intervals associated with different outcomes?
31. What are the benefits and harms associated with different methods for evaluating outcomes in patients receiving opioids for chronic noncancer pain?
32. In patients receiving opioids for chronic noncancer pain, what is the accuracy of tools for differentiating drug-related behaviors due to inadequate symptom relief from true aberrant drug-related behaviors?
33. In patients receiving opioids for chronic noncancer pain, what is the effect of diagnosing drug-related behaviors due to inadequate symptom relief on clinical outcomes?

Discontinuing opioids

34. What patient features or characteristics predict improved outcomes with discontinuation of long-term opioids versus continued treatment?
35. What are the benefits and harms of different methods for discontinuing opioids?

Pregnancy

36. What are the benefits and harms of continuing opioids versus switching to alternative analgesics in women with chronic noncancer pain who become pregnant or are planning to become pregnant?

Opioid prescribing policies

37. What are the benefits and harms of opioid prescribing policies on clinical outcomes?

Populations

Target populations and conditions for this review:

- Adults (≥18 years old)
- Chronic noncancer (defined as pain lasting 1 month longer than healing of lesion, pain that recurs after healing of lesion, pain associated with a non-healing lesion, or pain persistent for longer than 3 months) pain
- Pregnant women (not including management of pain during labor)
- Persons with chronic pain and a history of substance abuse

Populations and conditions excluded from this review:

- Children and adolescents (<18 years old)
- Persons with active cancer pain
- Persons requiring end-of-life care
- Persons with acute pain (including post-surgical pain, acute pregnancy/labor pain, and acute sickle cell pain)

Studies that included a mixed population of patients with chronic noncancer pain and cancer pain were included if >75% of patients had noncancer pain or if results for noncancer pain patients were reported separately. Children and adolescents were excluded because therapeutic considerations may differ from those in adults[30, 31].

Interventions

Target interventions for this review:

- Any opioid (including agonist-antagonists) administered as monotherapy or as part of multimodal therapy, administered via oral, transdermal, buccal, or rectal routes, or via regular intramuscular or subcutaneous injections
- Tramadol

We excluded opioids administered via intravenous and intrathecal or intraspinal routes from this review.

Outcomes

For studies evaluating efficacy and safety of opioids, we selected patient-centered target outcomes suggested in recent recommendations for studies evaluating patients with pain[32-36]:

- Pain relief or pain intensity
- Physical functioning
- Emotional functioning
- Participant ratings of global improvement and satisfaction with treatment
- Adverse events
- Participant disposition (including withdrawals and patients lost to follow-up)
- Work measures

Studies of chronic pain vary widely in how outcomes are assessed and reported. Most studies measure pain intensity with either visual analogue or categorical pain scales (using either numbers or a list of adjectives describing different levels of pain intensity)[37]. Visual analogue scales (VAS) usually consist of a line on a piece of paper labeled 0 at one end, indicating no pain, and a maximum number (commonly 10 or 100) at the other, indicating excruciating pain. Patients designate their current pain level on the line. Categorical pain scales, on the other hand, consist of several pain category options from which a patient must choose (e.g., no pain, mild, moderate, or severe for a verbal rating scale, or 0 to 10 for a numerical rating scale such as the Brief Pain Inventory). Many studies also report the proportion of patients with a clinically significant improvement in pain, such as at least a 2-point (or 30%) improvement on a 0 to10 numerical rating scale[38]. The Medical Outcomes Study Short Form-36 (SF-36) bodily pain scale has been recommended as a preferred method for reporting pain outcomes for low back pain because it measures both pain intensity and interference with activities[32]. In addition to assessments of pain intensity using VAS or categorical rating scales, measurement of rescue analgesic medication use is a recommended supplementary measure[34].

Studies often evaluate the effect of pain on functioning using the Multidimensional Pain Inventory or the interference items of the Brief Pain Inventory. These questionnaires measure the effect of pain on physical, social, and cognitive function. Scales that assess functional

status for specific pain conditions are also available. For example, the two most commonly used measures to assess back-specific function are the Roland Morris Disability Questionnaire (RDQ) and the Oswestry Disability Index (ODI)[39]. The RDQ is reported on a 0 to 24 scale and the ODI on a 0 to 100 scale. Improvements of 2-5 points on the RDQ and 10 points on the ODI, or improvements of 30% compared to baseline scores, have been proposed as minimal clinically important differences[40, 41]. The Western Ontario McMaster Osteoarthritis Index (WOMAC) is the most widely used instrument to measure function for osteoarthritis[42]. It consists of a 24-item scale divided into three dimensions: pain (five items), stiffness (two items), and physical function (17 items)[43]. The score for each domain is calculated by summing the scores for the relevant items. A composite score is calculated by summing the scores for all 24 items. The WOMAC is scored using either a 5-point Likert scale (maximum composite score 120) or 0 to 100 visual analogue scales (maximum composite score: 2400).

In contrast to pain- or condition-specific measures of function, generic measures provide the advantage of permitting comparisons of functional status across different diseases. A disadvantage is that they may not assess distinct issues associated with specific conditions and may be less responsive to effects of treatment compared to disease-specific measures. The most commonly used instrument for measuring generic health status is the Medical Outcomes Study Short Form-36 (SF-36). It measures 8 dimensions, each on a 0 to 100 scale[44]. The individual dimensions can also be combined into several commonly reported subscales (such as the Physical Component Summary and Mental Component Summary). The SF-36 bodily pain scale has been recommended as a preferred method for reporting pain outcomes because it measures both pain intensity and interference with activities[45].

Work status is often measured by employment status, days off work, or length of time before returning to work. Patient satisfaction is usually assessed using a generic global scale, though more formal methods have been developed. Some studies also report effects of interventions on mood (using scales such as the Beck Depression Inventory or Profile of Mood States) or the preference for one medication over another.

We reviewed evidence on adverse events and disposition of patients enrolled in trials, including the overall number who withdrew as well as those who withdrew due to lack of efficacy or adverse events. Adverse events of particular importance identified by the panel included the following:

- Nausea/vomiting
- Sedation/lethargy/dizziness/CNS adverse events (including risk of falls)
- Constipation and urinary retention
- Dermatological adverse events
- Cardiac adverse events
- Overdose/mortality

- Abuse/addiction/aberrant drug-related behaviors
- Endocrinologic adverse events
- Psychiatric adverse events
- Dysimmune effects
- Hyperalgesia (see glossary)

When available, we also evaluated data on cost-effectiveness. We converted cost data using other currencies to U.S. dollars using conversion rates as of May 2007.

We excluded studies that only evaluated intermediate or surrogate outcomes such as results of psychomotor testing or opioid dispensing rates. Although driving tests or simulators may also be considered intermediate outcomes, we included studies reporting such outcomes because prospective studies of actual driving events in patients with chronic noncancer pain are sparse.

CONFLICT OF INTEREST

The evidence review was conducted at the Oregon Evidence-based Practice Center with funding from APS. None of the investigators conducting this review (RC, LHH and TD) have any conflicts of interest to disclose.

METHODS

Literature search and strategy

We searched the topics of opioids and chronic pain on the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic reviews, MEDLINE®, and EMBASE through October 2008 using broad terms for opioids or narcotics combined with chronic pain. We also conducted searches for the following specific topics related to use of opioids (detailed search strategies are shown in Appendix 3):

1. Opioid abuse, misuse (see glossary), and diversion
2. Urine drug screening
3. Driving safety
4. Pseudoaddiction
5. Prognosis
6. Drug monitoring

Reviews of reference lists and expert suggestions supplemented the electronic searches. Studies only published as conference abstracts were not included in systematic searches. Reviews, policy statements, and other papers with contextual value were also obtained.

Inclusion and exclusion criteria

All identified citations were imported into an electronic database (EndNote® X1) and considered for inclusion. We included studies that met all of the following criteria:

1. Evaluated adults (≥18 years old) with chronic noncancer pain
2. Were relevant to one of the Key Questions
3. Evaluated a risk assessment or monitoring instrument for use of opioids (including tramadol), a relevant diagnostic test, or benefits or harms of at least one opioid
4. Either reported diagnostic accuracy (for risk assessment instruments, monitoring instruments, and studies of diagnostic tests) or clinical outcomes (pain relief or pain intensity, physical functioning, emotional functioning, participant ratings of global improvement and satisfaction with treatment, adverse events, participant disposition[including withdrawals and patients lost to follow-up], or work measures)

We defined systematic reviews as studies that at a minimum described systematic methods for identifying and selecting studies and synthesizing evidence. We included systematic reviews on efficacy of opioids for chronic noncancer pain if they were relevant to one of the Key Questions and included studies that met our inclusion criteria.

Criteria for inclusion of observational studies varied for different Key Questions, depending on the clinical issue addressed. For Key Questions on risk prediction (1, 2, 3, 17, and 34), we included prospective observational studies that reported the association between baseline characteristics and the outcome of interest. For Key Questions on diagnostic test accuracy (26, 27, 32), we included studies that reported sensitivity, specificity, positive predictive value, negative predictive value or other measures of diagnostic accuracy against a reference standard. For Key Questions that evaluated efficacy or harms of opioids or different treatment or monitoring strategies (4-16,18-25,28-31,33,35-37), we included cohort and case-control studies on long-term outcomes and adverse events, or adverse events not adequately covered by the trials. Other observational study designs that did not include control subjects (such as case series and pre-post studies) or may not adequately assess causality (such as cross-sectional studies of efficacy or harms) were excluded, unless no other evidence was available. Such studies provide a very low level of evidence, ranking just above expert opinion[29, 46].

We included cost studies that were conducted alongside a randomized trial or were a full economic analysis (cost-effectiveness, cost-minimization, or cost-utility study)[47]. We only included non-English language trials if they were already included in English-language systematic reviews. Studies of non-human subjects and those without original data were excluded. We excluded studies of patients with cancer pain or end-of-life conditions. We also excluded uncontrolled observational studies (e.g., case series, case reports, pre-post studies), retrospective studies of risk prediction instruments, studies only published as conference abstracts, and other unpublished studies.

Data extraction and synthesis

Systematic reviews

We classified each systematic review as quantitative (performed a meta-analysis) or qualitative (no meta-analysis). For each systematic review, we abstracted the following information:

1. Purpose of the review
2. Databases searched
3. Dates of the searches
4. Language restrictions, if any
5. Number of studies included
6. Criteria used to include studies
7. Limitations of the included studies
8. Methods for rating the quality of included studies
9. Methods for synthesizing the evidence
10. Interventions evaluated
11. Main efficacy outcomes (including number and quality of studies for each comparison and outcome)
12. Adverse events

The reliability of systematic reviews depends on how well they are conducted. We used predefined criteria to assess the internal validity (quality) of included systematic reviews on efficacy of opioids for chronic noncancer pain based on the methods developed by Oxman and Guyatt (Appendix 4)[48]. Each study was scored between 1 and 7 based on the following criteria: comprehensiveness of search strategy; application of pre-defined inclusion criteria to select studies, appropriate assessment of validity, and use of appropriate methods to synthesize the evidence. The Oxman and Guyatt method does not assign a final score based on the total number of criteria that are met. Rather, a final score is assigned based on an overall assessment of the seriousness of methodological shortcomings. Using the Oxman and Guyatt system, systematic reviews with a score of four or less are considered to have potential major flaws; we classified these as 'lower quality'. Systematic reviews with major flaws are more likely to produce positive conclusions about the effectiveness of interventions[49, 50]. We classified systematic reviews with scores of five or more 'higher quality'.

Randomized trials on benefits and harms of interventions

We did not abstract results of individual trials (randomized or non-randomized controlled clinical trials) if they were included in a higher-quality systematic review. Instead, we determined the number and quality of trials, individual trial results, and magnitude of effects for each comparison and outcome of interest, based on the results of the systematic reviews. Although

methods for rating internal validity varied across systematic reviews, we considered studies that received more than half of the maximum possible quality score to be of 'higher-quality' for any quality rating system used[51, 52]. If a higher-quality systematic review did not use a point scoring system to assign quality scores to randomized trials (for instance, using a qualitative system to rate studies as good, fair, or poor[53]), we independently rated trial quality.

For each clinical trial not included in a higher-quality systematic review, we abstracted the following information:

1. Study design
2. Purpose of study
3. Inclusion and exclusion criteria
4. Number of patients approached, eligible, and randomized
5. Demographics and baseline characteristics
6. Setting
7. Funding source
8. Interventions evaluated
9. Main efficacy results
10. Adverse events (including withdrawal due to adverse events)
11. Duration of follow-up
12. Loss to follow-up
13. Compliance to treatment

We assessed internal validity of randomized clinical trials using the eleven predefined criteria developed by the Cochrane Back Review Group (see Appendix 5 for details on how we operationalized the criteria)[54]. We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; the use of co-interventions; compliance to allocated therapy; adequate reporting of dropouts; loss to follow-up; non-differential timing of outcome assessment; and the use of intention-to-treat analysis. Trials were scored between zero and eleven, according to the number of criteria met. We considered trials receiving scores of six or more 'higher-quality' and those receiving five or less 'lower-quality'[51, 52]. We also assessed internal validity using the Jadad criteria[55]. This instrument assigns a score of zero to five based on adequacy of randomization (up to 2 points), adequacy of blinding (up to 2 points), and adequacy of reporting of withdrawals (1 point). We rated trials scoring 3 or higher using the Jadad criteria 'higher-quality' (see Appendix 5 for details on how we operationalized the criteria). When discrepancies were present between classification of trials according to Jadad and Cochrane Back Review Group criteria, we evaluated whether these discrepancies would lead to any differences in

assessments of the quality of a body of evidence (a following section describes how we assessed the quality of bodies of evidence).

Observational studies on benefits and harms of interventions

For each observational study that met inclusion criteria, we abstracted the following information:

1. Study design
2. Purpose of study
3. Inclusion and exclusion criteria
4. Number of patients approached, eligible, and randomized
5. Demographics and baseline characteristics
6. Setting
7. Funding source
8. Interventions evaluated
9. Main efficacy results
10. Adverse events (including withdrawal due to adverse events)
11. Duration of follow-up
12. Loss to follow-up
13. Compliance to treatment

To assess the internal validity of observational studies on benefits and harms of opioids or opioid-related interventions, we evaluated whether they used nonbiased selection methods; whether rates of loss to follow-up were acceptable; whether pre-defined outcomes were specified; whether they used appropriate methods for ascertaining exposures, potential confounders, and outcomes; and whether they performed appropriate statistical analyses of potential confounders. Although many tools exist for quality assessment of nonrandomized trials, there is no consensus on optimal quality rating methods[56] and little empiric data on how methodological shortcomings affect estimates of benefits or harms. We therefore did not use a formal scoring system to rate the quality of the observational studies included in this review, but noted important methodological deficiencies in any of the above areas when present.

Studies of risk prediction and diagnostic test accuracy

For each risk prediction or diagnostic test accuracy study that met inclusion criteria, we abstracted the following information:

1. Study design
2. Purpose of study
3. Inclusion and exclusion criteria

4. Number of patients approached, eligible, and randomized
5. Demographics and baseline characteristics
6. Setting
7. Funding source
8. Prognostic factor, diagnostic test, or risk assessment instrument evaluated
9. Outcomes or diagnoses evaluated
10. Reference standard for outcomes of diagnoses evaluated
11. Main diagnostic accuracy results
12. Clinical outcomes data, if reported
13. Duration of follow-up
14. Loss to follow-up
15. Compliance to treatment

If diagnostic accuracy measures were not available but data were available from the studies, we used the *diagti* procedure (confidence intervals based on the exact method) in Stata (Stata version 10, StataCorp, College Station, TX) to calculate sensitivities and specificities and the *cci* procedure (confidence intervals based on the normal approximation) to calculate positive likelihood ratios (PLRs), negative likelihood ratios (NLRs), and diagnostic odds ratios (DORs). If a cell of a 2 x 2 table had zero events, we added 0.5 to all cells to calculate likelihood and diagnostic odds ratios.

We assessed the quality of studies of risk prediction and diagnostic test accuracy using nine criteria adapted from methods developed by the U.S. Preventive Services Task Force[29] or evaluated in empiric studies[57, 58] of sources of variation and bias in studies of diagnostic tests. For each study, we determined if it:

1. Evaluated diagnostic test performance in a population other than the one used to derive the instrument
2. Evaluated a consecutive series of patients or a random subset
3. Adequately described symptom severity, underlying condition, and duration and doses of opioid use in enrolled patients
4. Adequately described the risk assessment instruments or diagnostic tests evaluated
5. Included appropriate criteria in the instrument (to meet this criterion, the instrument must have included prior history of history of addiction or substance abuse and at least one other psychosocial item)
6. Adequately described the methods used to identify aberrant drug-related behaviors

7. Used appropriate criterion to identify aberrant drug-related behaviors (used either a validated questionnaire or urine drug screen plus other corroborating data)
8. Evaluated outcomes or the reference standard in all patients enrolled (up to 10% loss considered acceptable)
9. Evaluated outcomes blinded to results of the screening instrument.

We considered studies that met at least five of the nine criteria to be of higher-quality.

Dual review

Two reviewers independently rated the quality of each systematic review and primary study. Discrepancies were resolved using a consensus process.

Assessing research applicability and clinical relevance (including magnitude of benefits and harms)

Factors we considered when assessing the applicability of trials included whether the publication adequately described the study population and interventions, whether the setting or population was so different from typical U.S. settings that results might not be applicable, whether the differences were clinically (as well as statistically) significant, and whether the treatment received by the control group was reasonably representative of standard practice[59, 60]. We also recorded funding source and role of the sponsor.

Although trials varied widely in how outcomes were assessed and reported, we used pre-specified criteria to categorize magnitude of effects for the most commonly reported outcomes. For pain relief and functional status, we considered mean differences in effects of 5 to 10 points on a 100 point VAS scale (or equivalent) as small/slight, 10 to 20 points as moderate, and >20 points as large. For studies of opioids for low back pain, for example, we considered mean improvements in the RDQ of 2 to 5 points or 10 to 20 points on the ODI as moderate[40].

In order to compare and combine results across trials using different measures for the same outcome (such as pain relief or functional status), some systematic reviews report standardized mean differences (SMD). The SMD permits consistent interpretation across studies because mean differences are adjusted by within-group standard deviations. When SMD's were reported, we considered values from 0.2 to 0.5 small/modest, 0.5 to 0.8 moderate, and >0.8 large/substantial[61]. Though interpretation of the SMD can vary across different interventions and outcomes, there is some evidence that our classifications for SMD's and changes on pain scores and functional status are roughly concordant. In trials of bed rest for low back pain, for example, an SMD between 0.2 and 0.3 was equivalent to 5 to 7.5 points on a 100 point VAS pain scale, and 1.2 to 1.8 points on the RDQ (all classified as small/slight)[62, 63]. A Cochrane review of spinal manipulation for low back pain estimated an SMD of 0.2 as equivalent to 5 mm on a 100 point VAS pain scale (both classified as small/slight using our system)[64, 65] and two different systematic reviews of acupuncture calculated an SMD of 0.54[66] and weighted mean difference of 17.8 on a 100 point pain scale[67, 68] for the same treatment comparison (both

classified as moderate). Because few trials reported the proportion of patients meeting specific thresholds (such as >30% reduction in pain score) for target outcomes, it was often not possible to report numbers needed to treat or harm. However, when such data were provided, we defined (a priori) a relative risk (RR) of 1.25 to 2.00 for the proportion of patients reporting >30% (or greater) pain relief a moderate benefit, and a RR >2.00 a large or substantial benefit.

Small/slight size of effect: Pain or functional status: Mean 5-10 mm improvement on a 100 mm visual analogue scale (VAS), or equivalent. All outcomes: Standardized mean difference (SMD) 0.2 to 0.5.

Moderate size of effect: Pain or functional status: Mean 10-20 mm improvement on a 100 mm VAS, or equivalent. All outcomes: SMD 0.5 to 0.8.

Large/substantial size of effect: Pain or functional status: Mean >20 mm improvement on a 100 mm VAS, or equivalent. All outcomes: SMD >0.8s.

For studies of risk prediction or diagnostic accuracy, we classified PLRs >10 and NLRs ≤0.1 as "large," PLRs >5 and ≤10 and NLRs >0.1 and ≤ 0.2 as "moderate," and PLRs >2 and ≤5 and NLRs >0.2 and ≤0.5 as "small"[69].

Rating a body of evidence

We assessed the overall strength of evidence for the body of literature, addressing each comparison and outcome evaluated for the Key Questions, using methods adapted from the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group[46, 70]. To assign an overall strength of evidence (good, fair, or poor) for each comparison and outcome, we examined the type, number, size and quality of studies; the strength of association; and the consistency of results between studies. Using this system, each body of evidence was graded high-quality, moderate-quality, or low-quality. We operationalized GRADE methods for each of these categories as follows:

High-quality: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (at least two consistent, higher-quality randomized controlled trials*, or multiple, consistent observational studies with no significant methodological flaws showing large effects).

Moderate-quality: Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (at least one higher-quality trial* with >100 subjects; two or more higher-quality trials* with some inconsistency; at least two consistent, lower-quality trials*, or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects).

Low-quality: Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between

higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

*Or prospective studies on risk prediction or studies of diagnostic accuracy when appropriate.

Consistent results from higher-quality studies across a broad range of populations suggest a high degree of certainty that the results of the studies are true (that is, the entire body of evidence would be considered "high-quality"). Large effect sizes on important, patient-centered outcomes increases confidence in study findings, particularly when they are reported by large, higher-quality studies. For a moderate-quality body of evidence, consistent results could be due to true effects, or be due to biases operating across some or all of the studies. Inconsistent results between studies can lower confidence that the results of any particular study are true, or reflect diversity between studies in the populations or interventions evaluated. For a low-quality body of evidence, reliable conclusions are not possible because of insufficient evidence, so there is low certainty that the results are not due to bias or other methodologic shortcomings in the studies.

When more than one relevant systematic review for a topic was available, we focused on results from higher-quality and more comprehensive systematic reviews[71]. We also compared results across higher-quality systematic reviews and trials to evaluate consistency of findings and conclusions. To evaluate consistency, we classified conclusions of trials and systematic reviews as positive (the opioid [or opioid-related intervention] is beneficial), negative (the opioids [or opioid-related intervention] is harmful or not beneficial), or uncertain (estimates are imprecise, evidence is unclear, or results are inconsistent across the primary studies)[49]. We defined "inconsistency" as >25% of higher-quality trials reaching discordant conclusions (positive versus negative), two or more higher-quality systematic reviews reaching discordant conclusions, or unexplained heterogeneity (for pooled data). When results were inconsistent, we investigated potential sources of discrepancy between reviews including the methods used for identifying, including, rating and synthesizing evidence and differences in the populations, interventions, or outcomes addressed in the reviews.

Sparse data lowers confidence in conclusions from a body of evidence because of imprecise estimates, lack of statistical power, and a higher likelihood that conclusions will be affected by new evidence. We defined "sparse data" as ≤2 studies (any sample size), or ≤3 studies with no study having >100 subjects. If the body of evidence for an intervention consisted of a single, small (N<100) study, we rated it low-quality, even if the trial itself was rated higher-quality. We also downgraded studies that used unvalidated methods for evaluating outcomes because it is difficult to know how accurately or reliably they estimate true magnitudes of benefits or harms. A heavy reliance on indirect comparisons (effect of intervention A versus intervention C estimated from evidence comparing intervention A to intervention B and evidence comparing intervention B to intervention C) could also lower the quality rating for an overall body of evidence[72, 73].

RESULTS

Size of literature reviewed

Investigators reviewed 10,933 potentially relevant citations. Of these, 193 full-text articles were retrieved to review for inclusion. After review of full-text articles, we judged 98 studies to be relevant to one or more key questions and to meet inclusion criteria. The most common reasons for study exclusion were: evaluation of acute or postoperative pain, evaluation of cancer pain or pain associated with end of life, evaluation of parenteral opioids, evaluation of children, non-controlled observational study design, and lack of original data (e.g., review article or editorial).

Of the 98 studies judged to meet inclusion criteria, 17 were systematic reviews. A list of the 13 systematic reviews on efficacy of opioids for chronic noncancer pain, along with our quality rating assignments, is shown in Appendix 6[53, 74-85]. Two other systematic reviews evaluated driving safety associated with opioids[86, 87] one systematic review evaluated instruments to predict aberrant drug-related behaviors[88], and one systematic review evaluated risk of hip fractures based on observational studies[89]. A list of excluded systematic reviews is shown in Appendix 8, along with reasons for exclusion. We also identified 81 primary studies (including 43 randomized trials) that were relevant for at least one key question and met inclusion criteria. A list of included randomized trials, along with our quality rating assignments, is shown in Appendix 9. The number of studies that met inclusion criteria for each key question is summarized in Appendix 16.

Quality of included systematic reviews evaluating efficacy of opioids for chronic noncancer pain and randomized trials

Out of 13 systematic reviews[53, 74-85] that evaluated efficacy or harms of opioids for chronic noncancer pain, 9 (69%) were rated higher-quality[53, 74, 76, 78-82, 84] using the Oxman criteria[48, 49]. All of the higher-quality systematic reviews used a point scoring system to rate the quality of included trials, with the exception of one systematic review that used a qualitative system[53]. Out of 43 randomized trials not included in existing systematic reviews, 28 (65%)[90-117] were rated higher-quality using the Cochrane Back Review Group method[54] and 34 (79%)[90-123] using the Jadad method[55]. Differences between ratings using the Cochrane Back Review Group and Jadad methods did not affect conclusions or assessments of overall quality for any body of evidence.

Research applicability

None of the trials of opioids reviewed for this report met all criteria for effectiveness studies[59], as they all utilized numerous inclusion and exclusion criteria to evaluate highly selected populations and were usually conducted in specialty and academic centers. In addition, many trials used run-in periods to exclude patients at higher risk for not responding to therapy or for developing adverse events. Over 90% of the trials were short-term, or less than 12 weeks in duration.

KEY QUESTIONS

Key Question 1a

In patients being considered for opioids for chronic noncancer pain, how accurate are patient features or characteristics for predicting benefits of chronic opioid therapy?

Up to 50% of opioid-naïve patients placed on potent opioids report no change or worsening of their chronic pain[124]. About 10% of patients randomized to opioids in primarily short-term clinical trials withdraw due to lack of efficacy[81, 83]. Evidence on patient features or clinical characteristics helpful for predicting benefits of chronic opioid therapy or opioid responsiveness (analgesia or symptom relief achievable with tolerable adverse effects) in patients with noncancer pain could help guide decisions to initiate and manage use of long-term opioids.

Results of search: systematic reviews

We identified three systematic reviews that evaluated whether the type of chronic noncancer pain is associated with differential benefits from opioid therapy[79, 81, 83]. One of the systematic reviews[81] also assessed the usefulness of intravenous opioid test infusions for predicting subsequent response to oral opioids.

Results of search: primary studies

We identified two secondary analyses of randomized trials that evaluated the association between baseline characteristics and response to opioids[125, 126] and one randomized trial that performed a subgroup analysis to determine whether basal heat pain thresholds predicted opioid analgesia in patients with postherpetic neuralgia[127]. We identified no other randomized trials or prospective observational studies that directly evaluated usefulness of patient features or characteristics for predicting effectiveness of chronic opioid therapy in patients with chronic noncancer pain. Five studies evaluated different procedures for categorizing responsiveness to opioids, but were excluded because they did not evaluate how well the categorizations predicted effectiveness of therapy[128-132]. One randomized trial evaluated whether gender predicted responsiveness to opioids, but was excluded because it was performed in a short-term, acute pain (emergency room) setting[133]. Two studies that evaluated formal screening instruments for predicting outcomes of opioid prescribing are reviewed for Key Question 2[134, 135].

Findings

One secondary analysis of a randomized trial (N=680) found no differences between responders (patients achieving at least 30% pain relief) and non-responders in age, sex, type of pain, or duration of pain[125]. A secondary analysis of another, smaller trial (N=49) also identified no baseline predictors of opioid response (patients achieving at least 50% pain relief or a score of ≤5 on a 0 to 10 scale, tolerable pain, and tolerable adverse effects), but did not report the variables analyzed[126].

Three higher-quality systematic reviews that included 53 unique trials found no clear differences in estimates of opioid benefits versus placebo after trials were stratified according to underlying pain condition (Table 1)[79, 81, 83]. In the two systematic reviews in which formal statistical analyses were reported, estimates for pain relief[79] and rates of withdrawal due to lack of efficacy[83] were similar across different types of pain conditions, or had overlapping confidence intervals.

Table 1. Systematic reviews reporting benefits of opioids, stratified by underlying pain condition

Author, year	Underlying condition (number of trials)	Main results versus placebo	Quality*
Furlan, 2006[79]	Neuropathic (10)	**Pain relief** SMD -0.59 (95% CI -0.77 to -0.40)	7/7
	Nociceptive (17)	SMD -0.62 (95% CI -0.75 to -0.50)	
	Fibromyalgia (2)	SMD -0.41 (95% CI -0.61 to -0.21)	
	Mixed neuropathic and nociceptive (1)	SMD -0.33 (95% CI -0.92 to 0.26)	
Kalso, 2004[81]	Neuropathic (6), Musculoskeletal (4) Mixed (1)	**Mean pain relief** About 30% for both neuropathic and nociceptive pain (data not reported)	5/7
Moore, 2005[83]	Arthritis (16)	**Withdrawal due to lack of efficacy (rate difference, as a proportion)** 7.8 (95% CI 6.4 to 9.2)	6/7
	Musculoskeletal pain (7)	5.7 (95% CI 3.9 to 7.5)	
	Neuropathic pain (2)	7.8 (95% CI 2.9 to 13)	
	Pain of mixed origin (5)	3.9 (95% CI 2.3 to 5.6)	

*Oxman/Guyatt scale, maximum score: 7
SMD=standardized mean difference, CI=confidence interval

One of the systematic reviews included three small studies (N=48, 15, and 13) that found inconclusive evidence on the usefulness of intravenous opioid test infusions for predicting longer-term effectiveness of opioid therapy[81]. Although two[136, 137] studies found that a positive response to an intravenous opioid test infusion predicted subsequent response to oral opioids through one to three months, the third[138] found no association. In one of the studies that reported a positive association, only 20% of patients remained on oral morphine after one year[136].

One small (N=64), higher-quality randomized trial that compared oral opioids to tricyclic antidepressants for postherpetic neuralgia included a subgroup analysis on the usefulness of basal heat pain thresholds for predicting response to opioids in a subgroup of patients[127]. It found that higher heat pain threshold scores on the unaffected side were associated with larger reductions in pain and higher pain relief ratings with opioids, accounting for 10% of the variance in pain reduction and 18% of the variance in pain relief in a hierarchical regression model.

Higher scores were also associated with a greater likelihood of 30% or more reduction in pain (p=0.04, relative risks or odds ratios not reported).

Summary of evidence

- Two secondary analyses of randomized trials identified no baseline characteristics that predicted response to opioids (level of evidence: low).
- In indirect comparisons from multiple trials, there was insufficient evidence to determine whether differences in the type of chronic noncancer pain predict effectiveness of opioids for chronic noncancer pain (level of evidence: low).
- There is insufficient evidence from three small studies with inconsistent results to determine the usefulness of an intravenous opioid test infusion for predicting effectiveness of chronic opioids (level of evidence: low).
- One subgroup analysis (N=64) from a higher-quality randomized trial found basal heat pain threshold scores predictive of response to opioids in patients with post-herpetic neuralgia (level of evidence: low).

Key Question 1b

In patients being considered for opioids for chronic noncancer pain, how accurate are patient features or characteristics for predicting opioid-related harms?

Adverse events are frequent in patients prescribed opioids for chronic noncancer pain. About half of patients randomized to opioids in randomized trials report adverse events, and nearly one-quarter withdraw from the trials due to adverse events[83]. Information on patient features or characteristics useful for predicting opioid-related harms could be helpful for assessing potential risks associated with initiation of opioid therapy.

Results of search: systematic reviews

We identified one systematic review that evaluated whether the type of chronic noncancer pain is associated with differential harms from opioid therapy[83]. No other systematic review evaluated the usefulness of other patient or clinical features for predicting the occurrence of adverse events.

Results of search: primary studies

We identified no randomized trials or prospective observational studies that evaluated the usefulness of patient or clinical features for predicting opioid-related harms.

Findings

One higher-quality systematic review (35 trials) reported estimates of common, primarily short-term adverse events in patients stratified according to the type of underlying pain condition (Table 2)[83]. For some outcomes, adverse event rates appeared to differ across conditions. For

example, rates of any adverse event were lower in trials of patients with pain of mixed origin (24%, 95% CI 20 to 28%) compared to patients with arthritis (54%, 95% CI 51 to 57%), musculoskeletal pain (57%, 95% CI 55 to 61%), or neuropathic pain 62% (95% CI 48 to 76%), with non-overlapping confidence intervals. However, these results should be interpreted cautiously, as such comparisons are indirect[72, 73]. For indirect comparisons to be valid, assumptions about similarity of treatment effects across different sets of trials must be met. These assumptions can be violated by methodological shortcomings in the trials or differences in patient populations, interventions, settings, or measurement of outcomes. Further, these comparisons and are based on absolute event rates (rather than relative risks or odds ratios). In this case, apparent differences in rates of adverse events could be due to differences across trials in baseline pain severity, doses of opioids evaluated, presence of comorbid conditions, trial settings, or methods used to assess and report adverse events. Use of run-in periods by some trials could also affect estimates of adverse events by systematically excluding patients more likely to experience adverse events.

Table 2. Systematic review evaluating harms associated with opioids, stratified by underlying pain condition

Author, year	Outcome	Arthritis	Musculoskeletal pain	Neuropathic pain	Pain of mixed origin
Moore, 2005[83]	Any adverse event (%)	54 (95% CI 51 to 57), 15 trials	57 (95% CI 55 to 61), 12 trials	62 (95% CI 48 to 76), 1 trial	24% (95% CI 20 to 28), 3 trials
	Withdrawal due to adverse events (%)	26 (95% CI 25 to 28), 24 trials	16 (95% CI 14 to 18), 14 trials	13 (95% CI 8 to 18), 3 trials	22 (95% CI 19 to 26), 5 trials
	Dry mouth (%)	25 (95% CI 21 to 29), 8 trials	Not reported	Not reported	Not reported
	Nausea (%)	24 (95% CI 22 to 29), 20 trials	21 (95% CI 19 to 23), 16 trials	19 (95% CI 13 to 25), 3 trials	18 (95% CI 15 to 24), 6 trials
	Constipation (%)	18 (95% CI 16 to 20), 21 trials	13 (95% CI 11 to 15), 15 trials	18 (95% CI 12 to 24), 2 trials	9 (95% CI 6 to 11), 6 trials
	Dizziness (%)	14 (95% CI 13 to 16), 18 trials	17 (95% CI 15 to 19), 15 trials	16 (95% CI 10 to 23), 2 trials	3 (95% CI 2 to 4), 6 trials
	Drowsiness or somnolence (%)	13 (95% CI 11 to 15), 13 trials	18 (95% CI 16 to 20), 11 trials	19 (95% CI 13 to 25), 3 trials	5 (95% CI 4 to 7), 6 trials
	Pruritus (%)	15 (95% CI 11 to 18), 5 trials	26 (95% CI 19 to 32), 4 trials	6 (95% CI 0.3 to 12), 1 trial	5 (95% CI 2 to 7), 4 trials
	Vomiting (%)	13 (95% CI 11 to 15), 17 trials	10 (95% CI 8 to 11), 13 trials	0, 1 trial	6 (95% CI 4 to 8), 5 trials

No study evaluated factors predictive of long-term or serious harms, including abuse, addiction, or overdose. In general, patients at higher risk for such adverse events were excluded from

trials. One systematic review found that all 25 trials that referred to abuse or addiction history in inclusion or exclusion criteria excluded patients reporting prior or current substance abuse[79]. Most trials also excluded patients with medical co-morbidities such as significant cardiovascular, respiratory, gastrointestinal, or neurologic disease.

Summary of evidence

- There is insufficient evidence from indirect comparisons to conclude that different types of chronic noncancer pain are associated with different risks for short-term, common adverse events (level of evidence: low).
- There is no evidence to judge the usefulness of patient features or characteristics for predicting risk of long-term harms, including risks of abuse, addiction, overdose, or other aberrant drug-related behaviors.

Key Question 1c

In patients being considered for opioids for chronic noncancer pain, how accurate are patient features or characteristics for predicting aberrant drug-related behaviors?

Estimates of aberrant drug-related behaviors, drug abuse, or misuse in patients with chronic pain range from 0% to 50%, depending in part on the population evaluated and methods used to define and identify these outcomes[139]. Most studies have evaluated factors associated with aberrant drug-related behaviors in patients already prescribed chronic opioids. The factor that has been most frequently evaluated is previous history of substance abuse, with somewhat mixed results. Although most studies report an association between history of substance abuse and aberrant drug-related behaviors[140-145], others found no association[146, 147]. Younger age[142, 145, 148] and psychiatric disorders[140, 141] were also associated with aberrant drug-related behaviors in patients prescribed opioids in some studies.

Identification of patient features or characteristics that are accurate for predicting future aberrant drug-related behaviors could be very helpful for assessing potential harms associated with initiating opioids.

Results of search: systematic reviews

We identified one systematic review that evaluated the accuracy of patient features or characteristics for predicting aberrant drug-related behaviors[88]. However, all of the studies included in this review were either retrospective or evaluated formal screening instruments (discussed in Key Question 2).

Results of search: primary studies

We identified no study that prospectively evaluated the accuracy of individual patient factors or characteristics for predicting aberrant drug-related behaviors in patients being started on opioids for chronic noncancer pain. Four studies that prospectively evaluated formal screening

instruments for predicting aberrant drug-related behaviors are reviewed for Key Question 2[149-152]. We excluded eight studies that were retrospective or evaluated risk factors associated with aberrant drug-related behaviors including illicit drug use or presence or unprescribed opioids on urine toxicology, in patients already prescribed chronic opioids[140-143, 145, 147, 148, 153-157].

Findings

We found no prospective studies that evaluated individual patient features or characteristics associated with development of future aberrant drug-related behaviors.

Summary of evidence

- There is no evidence from prospective studies on accuracy of individual patient features or characteristics for predicting risk of aberrant drug-related behaviors. Accuracy of formal screening instruments is addressed in Key Question 2.

Key Question 2

In patients being considered for opioids for chronic noncancer pain, how accurate are formal screening instruments for predicting benefits of opioid therapy, harms, or aberrant drug-related behaviors?

A number of screening instruments have been proposed for evaluating the risk of aberrant drug-related behaviors in patients with noncancer pain who are being considered for chronic opioid therapy[158]. However, only a few have been assessed in prospective studies.

Results of search: systematic review

One systematic review evaluated instruments for prediction of future aberrant drug-related behaviors and identification of current aberrant drug-related behaviors[88]. We independently abstracted and analyzed the two studies on risk prediction instruments that were included in this review[150, 152]. No systematic review evaluated accuracy of screening instruments for predicting benefits or other harms of opioid therapy.

Results of search: primary studies

We identified four prospective studies that assessed accuracy of two different screening instruments for predicting aberrant drug-related behaviors in patients initiating opioids for chronic noncancer pain[149-152]. Studies that evaluated screening instruments for identification of aberrant drug-related behaviors in patients already prescribed opioid therapy are reviewed separately (see Key Question 26). We identified one study that evaluated an instrument for predicting effectiveness of opioid therapy but excluded it because it enrolled patients already prescribed opioids[134]

Findings

Four prospective studies (658 patients completed follow-up) evaluated the ability of three different self-administered instruments to predict aberrant drug-related behaviors (Table 3)[149-152]. The number of risk assessment items in these instruments ranged from 10 to 24. Although the

specific items varied, they included a personal or family history of drug or alcohol abuse, previous aberrant drug-related behaviors, dysfunctional coping strategies, co-morbid psychiatric conditions, cigarette smoking, age, and childhood sexual abuse, based on findings from previously published studies. Three of the four studies met our threshold for a higher-quality study[149-151], but none met all quality criteria. Two studies evaluated diagnostic test performance in the same population used to derive the instrument[150, 151]. It was not clear in any study if outcome assessors were blinded to the results of the screening instrument. In addition, definitions for aberrant drug-related behaviors and abnormal urine toxicology results were not well standardized and did not distinguish relatively mild from more serious behaviors. In one study[152], aberrant behaviors were not clearly pre-defined. Attrition bias was also a concern. In three studies, 20% to more than 40% of patients who completed the screening instrument were not assessed for main outcomes[149-151]. In the fourth study, the number of patients lost to follow-up was unclear[152]. One study only enrolled patients on chronic opioids[151], two appeared to enroll patients starting on opioids[149, 152], and the fourth enrolled a mixed population[150]. Only one study described baseline severity of pain (average pain 6 on a 0 to 10 scale)[151], and none attempted to control or adjust for demographic or treatment factors (such as dose or type or opioid prescribed).

Table 3. Prospective studies of screening instruments for predicting risk of aberrant drug-related behaviors

Author, year Instrument evaluated	Number of patients Duration of follow-up Opioid use at enrollment	Definition of aberrant drug-related behaviors	Quality*
Akbik, 2006[149] Screener and Opioid Assessment for Patients with Pain (SOAPP) Version 1 Self-administered, 14 items	N=397 (155 had urine toxicology results) Duration unclear Patients not on opioids	Urine toxicology screen showing illicit substances and/or unprescribed opioids	5/9
Butler, 2004[150] Screener and Opioid Assessment for Patients with Pain (SOAPP) Version 1 Self-administered, 14 items	N=175 (95 completed 6 month follow-up) 6 months Mixed population	Prescription Drug Use Questionnaire score ≥11 (out of 42) and/or staff assessment of serious drug behavior by 2 or 3 staff members and/or urine toxicology sample with unexpected medications, absence of prescribed medications, and/or illicit substances	5/9
Butler, 2008[151] Revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R) Self-administered, 24 items	N=283 (223 completed 5 month follow-up) 5 months All patients on opioids	Positive result on the Aberrant Drug Behavior Index: Score on the 42-item Prescription Drug Use Questionnaire of >11, or 2 or more positive results on the 11-item Prescription Opioid Therapy Questionnaire plus an abnormal urine toxicology result (illicit drug or non-prescribed opioid)	6/9
Webster, 2005[152] Opioid Risk Tool (ORT) Self-administered, 10 items	N=185 12 months All patients on opioids	Not defined; 23 different aberrant behaviors reported. Methods for identifying behaviors also not reported.	4/9

*Using nine criteria described in Methods (maximum score 9)

Two higher-quality studies evaluated the Screener and Opioid Assessment for Patients with Pain (SOAPP) Version 1 instrument (Table 4)[149, 150]. The first study derived the 14-item, self-administered SOAPP Version 1 (each scored on a 0 to 4 categorical scale, maximum score 56) from 24 original items and evaluated the diagnostic test characteristics of the final instrument in a mixed population of patients on chronic opioids or being considered for therapy (proportion on chronic opioids not reported)[150]. It found a cut-off score of ≥7 to be optimal, with a sensitivity of 0.91 (95% CI 0.78 to 0.98) and specificity of 0.69 (95% CI 0.54 to 0.81) for identifying aberrant drug-related behaviors after six months based on a questionnaire, staff assessment, and urine toxicology results (PLR 2.90 [95% CI 1.91 to 4.39], NLR 0.13 [95% CI 0.05 to 0.34], and DOR 21.9 [95% CI 6.89 to 68.5])[150]. In a second study, a score ≥8 on the previously derived SOAPP Version 1 instrument was associated with a sensitivity and specificity of 0.68 (95% CI 0.52 to 0.81) and 0.38 (95% CI 0.29 to 0.49), respectively (PLR 1.11 [95% CI 0.86 to 1.43], NLR 0.83 [95% CI 0.50 to 1.36], and DOR 1.34 [95% CI 0.64 to 2.84])[149]. However, these results are difficult to interpret because aberrant drug-related behaviors were identified solely on the basis

of urine drug screen results; urine drug screens were not obtained in most patients, and duration of follow-up was unclear.

A third study derived the 24-item, self-administered revised SOAPP (SOAPP-R) from 97 original items and evaluated the diagnostic test characteristics of the final instrument in patients already prescribed chronic opioid therapy (average duration six years)[151]. The SOAPP-R was designed in part to include less transparent items on drug abuse compared to the SOAPP Version 1, in order to potentially reduce the likelihood of overt patient deception. At a cutoff score of ≥18 (each item scored from 0 to 4, maximum score 96), sensitivity was 0.80 (95% CI 0.70 to 0.89) and specificity was 0.68 (95% CI 0.60 to 0.75) for identification of any aberrant drug-related behavior based on results of two questionnaires and a urine drug screen (PLR 2.50 [95% CI 1.93 to 3.24], NLR 0.29 [95% CI 0.18 to 0.46], and DOR 8.71 [95% CI 4.51 to 16.8]). The area under-the-receiver operating curve (0.81, 95% CI 0.75 to 0.87) was similar to results for the SOAPP Version 1 (0.88, 95% CI 0.81 to 0.95)[150], but may not be directly comparable due to use of different criteria to define aberrant drug-related behaviors and differences in the proportion of patients on chronic opioid therapy at enrollment.

A fourth, lower-quality study evaluated the self-administered Opioid Risk Tool (ORT), which consists of 10 items (maximum score 26)[152]. Items in this instrument were chosen and weighted prior to evaluation of diagnostic test characteristics, and cut-off scores for different risk categories appeared to be selected on an a priori basis. Aberrant drug-related behaviors were identified in 6% (1/18) of patients categorized as low risk (score 0 to 3), compared to 28% (35/123) of patients categorized as moderate risk (score 4 to 7) and 91% (41/44) of those categorized as high risk (score ≥8) after 12 months. A high-risk score strongly increased the likelihood of subsequent aberrant drug-related behaviors (PLR 14.3 [95% CI 5.35 to 38.4]), a moderate risk score had little effect (PLR 0.57 [95% CI 0.44 to 0.74]), and a low risk score strongly decreased the likelihood (PLR 0.08 [159]). An important shortcoming of this study is that it did not use standardized methods (e.g., questionnaires or urine drug screening) to identify aberrant drug-related behaviors, and aberrant behaviors were not clearly pre-defined.

Table 4. Results, prospective studies of screening instruments for predicting risk of aberrant drug-related behaviors

Author, year Instrument evaluated Method of administration	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio
Akbik, 2006[149] Screener and Opioid Assessment for Patients with Pain (SOAPP) Version 1 Self-administered, 14 items	0.68 (95% CI 0.52 to 0.81) for SOAPP Version 1 score ≥8	0.39 (95% CI 0.29 to 0.49) for SOAPP Version 1 score ≥8	1.11 (95% CI 0.86 to 1.43) for SOAPP Version 1 score ≥8	0.83 (95% CI 0.50 to 1.36) for SOAPP Version 1 score ≥8
Butler, 2004[150] Screener and Opioid Assessment for Patients with Pain (SOAPP) Version 1 Self-administered, 14 items	0.91 (95% CI 0.78 to 0.98) for SOAPP Version 1 score ≥7 0.86 (95% CI 0.73 to 0.95) for SOAPP Version 1 score ≥8	0.69 (95% CI 0.54 to 0.81) for SOAPP Version 1 score ≥7 0.72 (95% CI 0.58 to 0.84) for SOAPP Version 1 score ≥8	2.90 (95% CI 1.91 to 4.39) for SOAPP Version 1 score ≥7 3.15 (95% CI 1.98 to 4.99) for SOAPP Version 1 score ≥8	0.13 (95% CI 0.05 to 0.34) for SOAPP Version 1 score ≥7 0.19 (95% CI 0.09 to 0.40) for SOAPP Version 1 score ≥8
Butler, 2008[151] Revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R) Self-administered, 24 items	0.80 (95% CI 0.70 to 0.89) for SOAPP-R score ≥17	0.68 (95% CI 0.60 to 0.75) for SOAPP-R score ≥17	2.50 (95% CI 1.93 to 3.24) for SOAPP-R score ≥17	0.29 (95% CI 0.18 to 0.46) for SOAPP-R score ≥17
Webster, 2005[152] Opioid Risk Tool (ORT) Self-administered, 10 items	Not applicable (not dichotomous)	Not applicable (not dichotomous)	High risk (score ≥8): 14.3 (95% CI 5.35 to 38.4) Moderate risk (score 4 to 7): 0.57 (95% CI 0.44 to 0.74) Low risk (score 0 to 3): 0.08 (95% CI 0.01 to 0.62)	Not applicable (not dichotomous)

No study evaluated the utility of formal risk stratification instruments compared to informal clinical assessments alone, or compared one screening instrument to another.

The only study to evaluate a formal screening instrument to predict efficacy of analgesia and patient compliance with long-term opioids did not meet inclusion criteria because it only evaluated patients already on opioids[134]. The Diagnosis, Intractability, Risk, Efficacy (DIRE) instrument consists of seven items, each scored between 1 and 3 (maximum score 21). For each 1 point increase in the DIRE score, patients on opioids were 1.45 times more likely to be in a higher efficacy category (good, fair, or poor), and 0.65 times less likely to be taken off of opioids. Important methodological shortcomings in this study include ambiguous definitions for

categorizing outcomes, inclusion of items in the instrument that measure efficacy, and lack of blinding of outcomes assessors to results of the DIRE score.

Summary of evidence

- Four prospective studies found that the SOAPP Version 1, SOAPP-R, and ORT may be useful for predicting future aberrant drug-related behaviors in patients started on opioids for chronic noncancer pain, but evidence is sparse and primarily based on derivation studies, is limited by methodological shortcomings, and in some cases (the SOAPP Version 1 and SOAPP-R) the instruments appear to be relatively weak predictors (level of evidence: low).
- There is no evidence from prospective studies on accuracy of formal screening instruments for predicting benefits or other harms associated with initiation of opioids.

Key Question 3

In patients being considered for opioids for chronic noncancer pain, how effective is risk assessment for:

a. Improving clinical outcomes?

b. Reducing risk of aberrant drug behaviors?

Markers of diagnostic accuracy such as sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios are intermediate outcomes because they do not measure the patient outcomes that could be affected by correct or incorrect diagnoses of the conditions of interest. Risk assessment tools that affect clinician behavior and improve patient outcomes are considered to be supported by the highest level of evidence[160]. For example, studies showing that use of a risk assessment instrument to guide decisions to start patients on opioids improves patient outcomes compared to usual care without using the risk assessment instrument would be viewed as strong evidence supporting its use.

Results of search: systematic reviews and primary studies

We identified no systematic reviews, randomized trials, or controlled observational studies that evaluated effectiveness of risk assessment methods for improving clinical outcomes or reducing risk of aberrant drug-related behaviors, abuse, or addiction.

Summary of evidence

- There are no studies on effectiveness of risk assessment methods for improving clinical outcomes or reducing risk of aberrant drug-related behaviors, abuse, or addiction in patients with chronic noncancer pain being considered for opioids.

Key Question 4

What are the benefits (including long-term benefits) of opioids for chronic noncancer pain?

Results of search: systematic reviews

We identified twelve systematic reviews that evaluated primarily short-term benefits of opioids for chronic noncancer pain[74-85]. One of these systematic reviews focused on long-term benefits of opioids[84]. We excluded 19 systematic reviews that did not meet inclusion criteria (see Appendix 8).

Results of search: primary studies

We identified thirteen placebo-controlled randomized trials of opioids for chronic noncancer pain not included in the systematic reviews[91, 95, 97, 102-106, 114, 117, 120, 123, 161].

Findings

A total of 70 unique randomized trials on efficacy of opioids for chronic noncancer pain were included in twelve systematic reviews (Table 5). Most trials included in the systematic reviews were short-term. In the systematic review with the largest number of trials (39), duration of follow-up ranged from 1 to 16 weeks[79]. In the two largest systematic reviews (35 and 39 trials), 87 to 97 percent of trials were rated higher-quality (defined as receiving greater than half of the maximum possible quality rating score)[79, 83]. The most commonly evaluated opioids were codeine, morphine, oxycodone and tramadol. Osteoarthritis, low back pain and neuropathic pain were the most common underlying conditions.

Table 5. Characteristics of systematic reviews evaluating efficacy of opioids for chronic noncancer pain

Author, year Type of review	Number of randomized trials included (number rated higher-quality)	Total number of patients enrolled Sample sizes for individual trials	Underlying conditions	Interventions evaluated (number of trials)	Quality rating*
Cepeda, 2006[74] Quantitative	11 (11)	1823 20 to 308 (median=129)	Osteoarthritis (11)	Tramadol (9), tramadol + acetaminophen (2)	7/7
Clark, 2004[75] Quantitative	3 (quality not rated) (trials of noncancer pain patients)	980 302 to 683	Mixed (1), back pain (1)	Transdermal fentanyl (3), morphine (2)	2/7
Deshpande, 2007[76] Quantitative and qualitative	4 (3)	944 36 to 380	Low back pain (4)	Tramadol, alone or in combination with acetaminophen (3), oxycodone and morphine (1)	7/7
Devulder, 2005[77] Qualitative	6 (6)	1284 26 to 683 (median=129)	Osteoarthritis (1), low back pain (1), neuropathic pain (2), mixed (2)	Transdermal fentanyl (2), morphine (3), tramadol (3)	2/7
Eisenberg, 2005[78] Qualitative	8 (8) (trials of opioids for >24 hours)	447 12 to 159 (median=42)	Neuropathic pain (8)	Levorphanol (1), methadone (2), morphine (3), oxycodone (3)	7/7
Furlan, 2006[79] Quantitative	39 (34)	5856 8 to 846 (median=76)	Neuropathic pain (10), osteoarthritis (15), low back pain (4), rheumatoid arthritis (3), fibromyalgia (2), mixed or other (5)	Codeine (7), dextropropoxyphene (1), methadone (1), morphine (9), oxycodone (6), propoxyphene (1), tramadol (17)	7/7
Hollingshead, 2006[80] Quantitative	6 (3)	269 21 to 131 (median=42)	Neuropathic pain (6)	Tramadol (6)	6/7
Kalso, 2004[81] Qualitative	11 (11) (excluding trials of intravenous opioids)	1030 12 to 295 (median=61)	Neuropathic pain (6), osteoarthritis (3), mixed or other (2)	Methadone (1), morphine (6), oxycodone (5)	5/7

Table 5. Characteristics of systematic reviews evaluating efficacy of opioids for chronic noncancer pain

Author, year Type of review	Number of randomized trials included (number rated higher-quality)	Total number of patients enrolled Sample sizes for individual trials	Underlying conditions	Interventions evaluated (number of trials)	Quality rating*
Martell, 2007[82] Quantitative	8 (8) (trials of oral or transdermal opioids)	856 36 to 330 (median=82)	Low back pain (8)	Codeine (3), dextropropoxyphene (2), morphine (1), oxycodone (5), oxymorphone (1), tramadol (1)	7/7
Moore, 2005[83] Quantitative	35 (34)	5546	Arthritis (16), musculoskeletal (10), neuropathic (5), mixed (3)	Codeine (10), dextropropoxyphene (6), dihydrocodeine (2), meptazinol morphine (5), meptazinol (1), oxycodone (4), pentazocine (1), tramadol (14)	6/7
Noble, 2008[84] Quantitative	1 (0) (also 9 uncontrolled observational studies)	4583 (oral or intrathecal opioids) 12 to 532 (median=317)	Low back pain (3), osteoarthritis (3), diabetic neuropathy (1), neuropathic or back pain (1), unspecified (2)	Transdermal fentanyl (3), methadone (1), morphine (2), oxycodone (1), oxymorphone (1), tramadol (1), mixed (1)	7/7
Sandoval, 2005[85] Qualitative	1 (1)	19	Neuropathic pain (1)	Methadone (1)	2/7

*Using Oxman criteria, maximum score 7

Two higher-quality systematic reviews that evaluated efficacy of opioids for chronic noncancer pain conditions in general each found oral opioids moderately effective for pain relief compared to placebo, though benefits were only small for functional outcomes (Table 6)[79, 81]. Compared to placebo, opioids were associated with an SMD=-0.60 for pain relief (28 trials, 95% CI -0.69 to -0.50) and an SMD=-0.31 for functional outcomes (20 trials, 95% CI -0.42 to -0.22)[79], or a mean decrease in pain intensity of at least 30%[81]. A third higher-quality systematic review found that 6.5% (95% CI 5.6 to 7.4%) of patients randomized to oral opioids withdrew due to lack of efficacy, compared to 20% (95% CI 17 to 23%) of patients randomized to placebo[83]. In all three systematic reviews, results were similar in patients with neuropathic or nociceptive pain (see Key Question 1a). Compared to other medications (NSAIDs and tricyclic antidepressants), one higher-quality systematic review found strong (oxycodone and morphine, 2 trials, SMD=-0.34, 95% CI -0.67 to -0.01) but not weak (propoxyphene, codeine, tramadol, 6 trials) opioids slightly more effective for pain relief, but not for functional outcomes[79].

Five other higher-quality systematic reviews focused on specific populations (neuropathic pain[78], low back pain[76, 82]) or medications (tramadol[74, 80]). One systematic review on efficacy of opioids for neuropathic pain reported results consistent with the first two systematic reviews[78]. It found opioids associated with an average decrease in pain intensity of about 14 units (6 trials, 95% CI -18 to -10) on a 100 point pain scale. A second systematic review found tramadol slightly superior to placebo for short-term pain relief (3 trials, SMD=-8.5 on a 100 point scale, 95% CI -12.0 to -5.0) in patients with osteoarthritis[74]. There were no differences between tramadol and other active treatments (2 trials).

Two systematic reviews came to somewhat conflicting conclusions regarding efficacy of opioids for low back pain. One systematic review found insufficient evidence to conclude that opioids are effective compared to placebo for chronic low back pain[82]. However, two of the four trials categorized as 'placebo-controlled' evaluated comparator treatments that included acetaminophen/caffeine or naproxen. In addition, this systematic review did not include two higher-quality trials published in 2007 that both found opioids more effective than placebo for chronic low back pain (see Table 7)[97, 102], and it did not include trials of tramadol. The other systematic review found tramadol (with or without acetaminophen) moderately more effective than placebo for pain relief (SMD=-0.71, 95% CI -1.02 to -0.39) and statistically superior to placebo for improving function, though the difference did not reach our threshold for a small clinical effect (SMD=-0.17, 95% CI -0.3 to -0.04)[76].

Three lower-quality systematic reviews focused on specific outcomes (quality of life) or opioids (transdermal fentanyl and methadone)[75, 77, 85]. One lower-quality systematic review found opioids effective for improving long-term quality of life, but based its conclusions primarily on assessments of before-after improvements in patients receiving opioids, rather than on improvements versus placebo or another comparator[77]. Two other systematic reviews of methadone[85] and transdermal fentanyl versus sustained-release oral morphine[75] included small numbers of randomized trials (one to three trials of noncancer pain patients), did not assess quality of trials, and included observational data.

Table 6. Main findings of systematic reviews on efficacy of opioids for chronic noncancer pain

Author, year	Number of randomized trials included (number rated higher-quality)	Main findings (efficacy)	Quality rating*
Cepeda, 2006[74]	11 (11)	Tramadol vs. placebo for osteoarthritis Pain relief: WMD=-8.5 on a 0 to 100 scale (95% CI -12.0 to -5.0) NNT for moderate improvement=6 (95% CI 4 to 9)	7/7
Clark, 2004[75]	3 (quality not rated) (trials of noncancer pain patients)	Sustained-release morphine versus transdermal fentanyl for noncancer pain Average pain (0 to 100 scale): -17.7 + 26.2 (N=121) vs. -21.0 + 24.4 (N=271) NS Pain 'right now' (0 to 100 scale): -16.5 + 28.9 (N=121) vs -24.1 + 28.7 (N=272) p=0.017	2/7
Deshpande, 2007[76]	4 (3)	Tramadol (with or without acetaminophen) vs. placebo Pain relief (SMD): -0.71 (95% CI -1.02 to -0.39), 3 trials Roland Disability Questionnaire (SMD): -0.17 (95% CI -0.3 to -0.04), 3 trials	7/7
Devulder, 2005[77]	6 (6)	Of four RCTs (noncancer pain) in which baseline QoL was reported, three showed an improvement in QoL in patients randomized to opioids	2/7
Eisenberg, 2005[78]	8 (8) (trials of opioids for >24 hours)	Opioid vs. placebo for neuropathic pain Pain intensity: WMD=-14 points on a 0 to 100 scale (95% CI, -18 to -10, 8 trials)	7/7
Furlan, 2006[79]	39 (34)	Opioids vs. placebo for noncancer pain Pain: SMD=-0.60, 95% CI -0.69 to -0.50 (28 trials) Function: SMD=-0.31, 95% CI -0.41 to -0.22 (20 trials)	7/7
Hollingshead, 2006[80]	6 (3)	Tramadol vs. placebo for neuropathic pain Proportion of subjects with 40% or 50% pain relief: RR=1.8, 95% CI 1.4 to 2.3 (4 trials). NNT for 50% pain relief=3.8 (95% CI 2.8 to 6.3)	6/7
Kalso, 2004[81]	11 (11) (excluding trials of intravenous opioids)	Oral opioid vs. placebo for noncancer pain Pain relief: > 30% improvement with opioids in both neuropathic and nociceptive pain ($p<0.05$ to $p<0.0001$ in 7 trials)	5/7
Martell, 2007[82]	8 (8) (trials of oral or transdermal opioids)	Opioid vs. placebo or nonopioid for low back pain Pain relief: SMD=-0.199, 95% CI -0.49-0.11 (4 trials)	7/7
Moore, 2005[83]	35 (34)	Opioid vs. placebo for noncancer pain Withdrawal due to lack of efficacy: 6.5% (95% CI 6 to 7%) vs. 20% (95% CI 17-23%)	6/7
Noble, 2008[84]	1 (0) (also 9 uncontrolled observational studies)	Improvement in pain scores among patients able to remain on oral opioids for at least six months: SMD=1.99 (95% CI 1.17 to 2.80)	7/7
Sandoval, 2005[85]	1 (1)	Methadone associated with 'meaningful' improvement in 1 RCT and in 59% of patients in uncontrolled studies	2/7

*Using Oxman criteria, maximum score 7

Data from clinical trials on long-term (>6 months) efficacy is very sparse. One higher-quality systematic review included one head-to-head trial of transdermal fentanyl and sustained-release oral morphine[124] and nine open-label, observational studies[84]. It found oral opioids associated with a large reduction in pain scores in patients who remained on therapy for at least six months, but this estimate is based on weak evidence (SMD 1.99, 95% CI 1.17 to 2.80). Only 51% of the 680 patients enrolled in the randomized trial completed the 13 month course[124]. Only two other trials were at least six months in duration[162, 163], though one was excluded because it is only available in abstract form[162]. A second higher-quality systematic review found that 44% of 388 patients with low back pain enrolled in open-label, uncontrolled follow-up studies of randomized trials were still on opioids at the end of follow-up, which varied from 7 to 24 months after initiation of therapy[81].

Twelve out of thirteen additional placebo-controlled trials not included in any previously published systematic reviews found opioids effective for pain relief (Table 7)[91, 95, 97, 102-106, 114, 117, 123, 161]. The exception was a small (N=55), multi-crossover trial of sustained-release morphine, nortriptyline, or their combination versus placebo for radiculopathy with high (nearly 50%) loss to follow-up that found no differences between morphine and placebo on any outcome[120]. The other twelve trials ranged from 2 to 12 weeks in duration, and evaluated sustained-release oxymorphone (3 trials)[97, 102, 106], modified-release tramadol (4 trials)[91, 95, 114, 123], transdermal fentanyl (1 trial)[104], and sustained-release oxycodone (5 trials)[103, 105, 106, 117, 161]. The trials evaluated opioids for low back pain (3 trials[97, 102, 114]), neck pain (1 trial[161]), or osteoarthritis (8 trials[91, 95, 103-106, 117, 123]). Standardized to a 100 point scale, eleven trials found opioids to be superior to placebo by an average of 4 to 23 points for pain relief (slight to moderate magnitude of benefit). A twelfth trial did not report average improvement in pain scores, but found a greater proportion of patients randomized to sustained-release oxycodone experienced at least a two-point improvement in pain scores (10 point scale) compared to placebo (40% vs. 10%)[117]. Opioids were also slightly to moderately superior to placebo in five of six trials that reported WOMAC Physical Function scores[95, 103-106, 123].

Table 7. Placebo-controlled trials of opioids or tramadol not included in systematic reviews

Author, year Type of pain	Number of patients Duration of follow-up	Main results	Quality*
Burch, 2007[91] Osteoarthritis	N=646 (in RCT portion of study) 12 weeks	**Tramadol Contramid OAD (extended-release plus immediate-release tramadol) vs. placebo** Pain Intensity (difference in absolute improvement on a 0 to 10 scale): -0.70, 95% CI -1.02 to -0.38 Improvement in pain score ≥1 point (0 to 10 scale): 94% vs. 89% (p=0.036) Improvement in pain score ≥3 points: 75% vs. 64% (p=0.002) Improvement in pain score ≥5 points: 45% vs. 30% (p<0.001) Patient Global Impression of Change "improved": 80% vs. 69% (p=0.0002)	6/11; 4/5
Gana, 2006[95] Osteoarthritis	N=1020 12 weeks	**Extended-release tramadol 400 mg vs. 300 mg vs. 200 mg vs. 100 mg vs. placebo (change from baseline to week 12)** WOMAC Pain (0 to 500): -108 vs. -104 vs. -112 vs. -107 vs. -74 (p<0.05 vs. placebo for all tramadol arms) WOMAC Physical Function (0 to 1700): -330 vs. -336 vs. -350 vs. -332 vs. -234 (p<0.05 vs. placebo for all tramadol arms) WOMAC Stiffness (0 to 200): -45 vs. -48 vs. -47 vs. -43 vs. -32 (p<0.05 vs. placebo for all tramadol arms) WOMAC Composite Index (0 to 2400): -479 vs. -486 vs. -510 vs. -482 vs. -340 (p<0.05 vs. placebo for all tramadol arms) Arthritis pain intensity, index joint (0 to 100): -28 vs. -30 vs. -30 vs. -28 vs. -20 (p<0.01 vs. placebo for all tramadol arms) Patient global assessment of disease activity (0 to 100): -21 vs. -24 vs. -22 vs. -21 vs. -16 (p<0.05 for tramadol 200 mg versus placebo, NS for other comparisons) SF-36 Physical component (0 to 100): +3.2 vs. +3.6 vs. +3.9 vs. +3.6 vs. +2.4 (NS for all comparisons) SF-36 Mental component (0 to 100): -0.5 vs. -0.7 vs. +0.6 vs. +1.1 vs. -0.3 (NS for all comparisons) Sleep measures: Sleep quality, awakened by pain at night, and trouble falling asleep statistically superior for all tramadol arms vs. placebo	7/11; 4/5
Hale, 2007[97] Low back pain	N=143 12 weeks	**Sustained-release oxymorphone (mean dose 81 mg/day) vs. placebo** Pain intensity, change from baseline: +8.7 vs. +31.6 (p<0.001) Patient global rating "very good" or "excellent": 58% vs. 22% (p<0.001) Discontinuation due to lack of efficacy: 11% (8/70) vs. 53% (39/73)	8/11; 3/5
Katz, 2007[102] Low back pain	N=205 12 weeks	**Sustained-release oxymorphone (mean dose 39 mg/day) vs. placebo** Pain intensity, change from baseline: 26.9 vs.10.0 (p<0.0001) Proportion with ≥30% decrease in pain intensity: 93% (66/71) vs. 72% (34/47) (p=0.002) Proportion with ≥50% decrease in pain intensity: 86% (61/71) vs. 55% (26/47) Patient global rating good, very good, or excellent: 82% vs. 42% vs. 2% (p<0.0001) Discontinuation due to lack of efficacy: 11% (12/105) vs. 35% (35/100)	8/11; 4/5

Table 7. Placebo-controlled trials of opioids or tramadol not included in systematic reviews

Author, year Type of pain	Number of patients Duration of follow-up	Main results	Quality*
Khoromi, 2007[120] Radiculopathy	N=55 9 weeks each intervention (crossover)	**Sustained-release morphine versus benztropine (active placebo)** Average leg pain (mean reduction below benztropine, 0 to 10 scale): 0.3 (p>0.05) Average back pain (mean reduction below benztropine, 0 to 10 scale): 0.2 (p>0.05) Global pain relief "a lot" or "complete": 31% (10/;32) vs. 15% (5/33) Beck Depression Inventory (mean score): 9.6 vs. 9 Oswestry Disability Index (mean score): 15.7 vs. 30.5 No differences on SF-36 scales	5/11; 4/5
Kivitz, 2006[103] Osteoarthritis	N=370 2 weeks	**Sustained-release oxycodone 10 mg vs. 40 mg vs. 50 mg vs. placebo, changes from baseline** Pain (VAS, 0 to 100), change from baseline, least squares mean: -21 vs. -28 vs. -29 vs. -17 (p 0.012 and p=0.006 for 40 mg and 50 mg vs. placebo) WOMAC Composite Index (0 to 2400): -350 vs. -370 vs. -450 vs. -160 (estimated from graph; all oxycodone groups p<0.025 vs. placebo) WOMAC Physical Function score (0 to 1700): -230 vs. -260 vs. -320 vs. -110 (estimated from graph, p<0.025 for all oxycodone groups vs. placebo) SF-36 Physical Component Summary: +3.9 vs. +4.6 vs. +3.6 vs. -0.1 (p<0.001) Chronic Pain Sleep Inventory: -17 vs. -22 vs. -24 vs. -12 (p≤0.05 for 40 mg and 50 mg vs. placebo) Withdrawal due to lack of efficacy: 7% (7/95) vs. 5% (5/93) vs. 4% (4/91) vs. 16% (15/91)	9/11; 5/5
Langford, 2006[104] Osteoarthritis	N=416 6 weeks	**Transdermal fentanyl 25 mcg/hr (median 1.7 patches) vs. placebo (changes from baseline)** VAS pain score (0 to 100): -23.6 vs. -17.9 (p=0.025) WOMAC Overall score (normalized to 0 to 10): -3.9 vs. -2.5 (p=0.009) WOMAC Pain score (0 to 10): -1.5 vs. -0.8 (p=0.001) WOMAC Physical Function score (0 to 10): -1.1 vs. -0.7 (p=0.064) SF-36, Physical component: +3.4 vs. +2.4, p=0.171 SF-36, Mental component: -0.9 vs. +1.1 , p=0.041 SF-36, Pain index: +11.4 vs. +7.1 (p=0.047) Discontinuation due to lack of efficacy: 7% (15/202) vs. 32% (64/197)	9/11; 5/5
Ma, 2007[161] Chronic neck pain	N=116 1 to 4 weeks	**Sustained-release oxycodone vs. placebo at 1 week** Frequency of acute pain flares (>3 flares/day): 79% vs. 55% (p<0.05) Quality of sleep (bad): 9% vs. 53% (p<0.05) Pain (VAS 0 to 10): 3.24 vs. 5.01 (NS) Patient satisfaction scale (0 to 10): 4.74 vs. 4.06 (NS) Functional status (zero to four scale): 1.25 vs. 1.98 (NS)	4/11; 2/5

Table 7. Placebo-controlled trials of opioids or tramadol not included in systematic reviews

Author, year Type of pain	Number of patients Duration of follow-up	Main results	Quality*
Markenson, 2005[105] Osteoarthritis	N=109 Up to 3 months	**Sustained-release oxycodone 10 mg q 12 hours (up to 120 mg/day) vs. placebo (changes from baseline)** Brief Pain Inventory (0 to 10), average pain intensity at day 90: -1.7 vs. -0.6 (p=0.024) WOMAC Pain (0 to 100), at 60 days: -17.8 vs. -2.4 (p<0.05) WOMAC Physical Function (0 to 100), at 60 days: -17.1 vs. -3.8 (p<0.05) WOMAC Stiffness (0 to 100), at 60 days: -21.7 vs. +0.1 (p<0.001) WOMAC Composite Index (0 to 100), at 60 days: -18.9 vs. -2.1 (p<0.05) Proportion experienced ≥30% pain relief at 90 days: 38% vs. 17.6% (p=0.031) Proportion experiencing ≥50% pain relief at 90 days: 20% vs. 5.9% (p=0.045) Brief Pain Inventory, Function composite: -1.9 vs. -0.4 (p=0.001) Withdrawal due to lack of efficacy: 16% vs. 67% (p<0.001)	9/11; 5/5
Matsumoto, 2005[106] Osteoarthritis	N=491 4 weeks	**Sustained-release oxymorphone 40 mg bid vs. sustained-release oxymorphone 20 mg bid vs. sustained-release oxycodone 20 mg bid vs. placebo** Pain Intensity (100 point VAS), mean improvement (estimated from Figure 1): -26 vs. -24 vs. -22 vs. -17 (p not reported) WOMAC Pain (0 to 500), mean improvement (estimated from Figure 3): -118 vs. -102 vs. -88 vs. -60 (p<0.01 for A vs. D, p<0.05 for B vs. D) WOMAC Physical Function (0 to 1700): -315 vs. -300 vs. -220 vs. -190 (p<0.05 for A vs. D and B vs. D) WOMAC Composite Index (0 to 2400): -480 vs. -460 vs. -360 vs. -290 (p<0.05 for A vs. D and B vs. D) Patient's global assessment (VAS 0 to 100): -28.6 vs. -23.2 vs. -25.4 vs. -19.5 (p<0.05 for A vs. D) Withdrawal due to lack of efficacy: 7% (9/121) vs. 4% (5/121) vs. 10% (13/125) vs. 27% (34/124)	9/11; 5/5
Thorne, 2008[123] Osteoarthritis	N=100 4 weeks each intervention (crossover	**Extended-release tramadol once daily (mean dose 340 mg/day) vs. placebo** Mean VAS pain score (0 to 100): 38.2 vs. 47.7 (p=0.0001) Mean ordinal pain score (0 to 4): 1.7 vs. 2.0 (p=0.001) WOMAC pain (0 to 500): 196 vs. 244 (p=0.0001) WOMAC physical function (0 to 1700): 656 vs. 773 (p=0.004) WOMAC stiffness (0 to 200): 23% vs. 20% improvement from baseline (difference NS) Pain and Disability Index (0 to 70): 22.8 vs. 27.2 (p=0.0004) Pain and Sleep Questionnaire (0 to 500): 105 vs. 141 (p=0.0008) SF-36: Tramadol superior to placebo on pain index, general health perception, vitality, and overall physical component score (by 2 to 3 points on 100 point scales); no differences on other scales Patient overall assessment 'moderately' or 'highly' effective: 56% vs. 25% Discontinuation due to lack of efficacy: 4% (2/50) vs. 4% (2/50)	5/11; 4/5

Table 7. Placebo-controlled trials of opioids or tramadol not included in systematic reviews

Author, year Type of pain	Number of patients Duration of follow-up	Main results	Quality*
Vorsanger, 2008[114] Low back pain	N=386 12 weeks	**Extended-release tramadol 300 mg once daily vs. 200 mg once daily vs. placebo** Change in pain since last visit (0 to 100): 37 vs. 37 vs. 32 (estimated from graph, p not reported) at week 12 Current pain intensity (0 to 100): 27 vs. 30 vs. 31 (averaged over weeks 1 to 12, p<0.05 for either dose vs. placebo) Patient global assessment (1 to 5): 3.2 vs. 2.0 vs. 2.7 (averaged over weeks 1 to 12, p<0.05 for either dose vs. placebo) RDQ (0 to 24): 8.2 vs. 8.5 vs. 9.8 (averaged over weeks 1 to 12, p<0.10 for either dose vs. placebo) Overall sleep quality (0 to 100): 50 vs. 54 vs. 45 (averaged over weeks 1 to 12, p<0.01 for either dose vs. placebo) Discontinuation due to lack of efficacy: 10% (13/128) vs. 10% (13/129) vs. 16% (21/129)	7/11; 4/5
Zautra, 2005[117] Osteoarthritis	N=107 3 months	**Sustained-release oxycodone 10 mg q 12 hours (up to 120 mg/day) vs. placebo (all results at 2 weeks)** 2 point or greater improvement in pain score (10-point scale): 40% (22/55) vs. 10% (5/49) (p<0.001) 24-hour pain (0 to 10): 4.96 vs. 6.34 (p<0.001) Positive affect: 2.95 vs. 2.79 (NS) Negative affect: 2.02 vs. 1.94 (NS) Active coping: 3.27 vs. 3.15 (NS) Coping efficacy: 3.39 vs. 3.11 (p=0.006) Arthritis Helplessness: 3.56 vs. 3.77 (p=0.05) Withdrawal due to lack of efficacy: 16% (9/56) vs. 67% (34/51)	7/11; 4/5

*Using Cochrane Back Group criteria, maximum score 11 and Jadad criteria, maximum score 5

Summary of evidence

- Many trials found opioids moderately effective for pain relief and slightly to moderately effective for functional outcomes compared to placebo in patients with chronic noncancer pain. However, almost all data are on short-term (≤12 weeks) outcomes (level of evidence: high).
- About half of patients discontinue opioids in long-term, primarily observational studies (level of evidence: moderate).
- Compared to antidepressants or non-steroidal anti-inflammatory drugs, one systematic review found oxycodone and morphine slightly more effective for pain relief in two trials, but found no differences between propoxyphene, codeine, or tramadol and the non-opioids (6 trials) (level of evidence: moderate).

Key Question 5

What are the harms (including long-term harms) of opioids for chronic noncancer pain? In patients at higher risk for abuse or addiction?

Results of search: systematic reviews

We identified twelve systematic reviews on harms associated with opioids for chronic noncancer pain[74-85]. None of the systematic reviews evaluated patients at higher risk for abuse or addiction. We also included one systematic review of observational studies on risk of hip fractures associated with use of opioids[89].

Results of search: primary studies

We identified thirteen placebo-controlled, randomized trials not included in systematic reviews that evaluated short-term harms associated with opioids for chronic noncancer pain[91, 95, 97, 102-106, 114, 117, 120, 123, 161]. None evaluated patients at higher risk for abuse or addiction. We identified one case-control study on risk of hip fractures in patients on opioids for chronic noncancer pain[164]. We also identified one prospective, small (N=8) before-after study on effects of opioids on cortisol levels[165], a before-after study evaluating QT prolongation associated with methadone[166], a case series on arrhythmias associated with methadone[167], a case-control study on sudden death associated with methadone[168], a retrospective, uncontrolled observational study on sleep apnea in patients prescribed opioids[169], and four cross-sectional studies on associations between opioid use and endocrinologic abnormalities[170-173]. We identified no study of opioid-induced hyperalgesia (abnormal pain sensitivity) that met inclusion criteria. One recent systematic review identified only one case report of hyperalgesia in patients on oral opioids for chronic noncancer pain (out of 139 articles included); most studies included in this review evaluated animals, patients with cancer or post-operative pain, or patients on methadone maintenance for opioid addiction[174].

Although it did not meet inclusion criteria, we briefly discuss results from an ongoing study (the Drug Abuse Warning Network) of emergency room reports of medication misuse[175] and several descriptive reports on deaths associated with opioid use[176-180]. None of these studies

specifically reported the number of deaths in patients prescribed opioids for chronic noncancer pain.

Findings

Short-term adverse events

In all of the systematic reviews, opioids were associated with more short-term adverse events and more withdrawals due to adverse events compared to placebo (Table 8). In the three most comprehensive systematic reviews (all rated higher-quality), the proportion of patients reporting any adverse event ranged from 50% to 80%[79, 81, 83]. The specific adverse events most frequently associated with opioids compared to placebo were nausea, constipation, somnolence, dizziness, vomiting, and pruritus. However, there was great variability between trials in rates of specific adverse events, which is probably related to differences in methods for defining, assessing, or reporting adverse events; differences in populations evaluated; and variable use of run-in periods.

Table 8. Systematic reviews of adverse events associated with opioids for chronic noncancer pain

Author, year	Number of randomized trials included (number rated higher-quality)	Main findings (adverse events)	Quality rating*
Cepeda, 2006[74]	11 (11)	**Tramadol vs. placebo** Minor adverse events: RR=2.27, NNH=5 (95% CI 4 to 8) Withdrawal due to adverse event: RR=2.6, NNH=8 (95% CI 7 to 12)	7/7
Clark, 2004[75]	3 (quality not rated) (trials of noncancer pain patients)	**Sustained-release morphine vs. transdermal fentanyl for noncancer pain (including observational studies)** Any adverse event: 87% vs. 71%, p<0.001 Serious adverse event: 3.9% vs. 3.9%, NS Discontinuation due to adverse event: 19% vs. 20%, NS	2/7
Deshpande, 2007[76]	4 (3)	**Tramadol (with or without acetaminophen) vs. placebo** Headache (risk difference): 9% (95% CI 6% to 12%), 3 trials Nausea (risk difference): 3% (0% to 6%), 3 trials Somnolence (risk difference): 9% (95% CI 5% to 13%), 2 trials Constipation (risk difference): 8% (95% CI 4% to 12%), 2 trials Dry mouth (risk difference): 7% (95% CI 4% to 10%) Dizziness (risk difference): 8% (95% CI 4% to 12%)	7/7
Eisenberg, 2005[78]	8 (8) (trials of opioids for >24 hours)	**Opioid vs. placebo** Nausea: NNH=3.6 (95% CI 2.9 to 4.8) Constipation: NNH=4.6 (95% CI 3.4 to 7.1) Drowsiness: NNH=5.3 (95% CI 3.7 to 8.3) Vomiting: NNH=6.2 (95% CI 4.6 to 11.1) Dizziness: NNH=6.7 (95% CI 4.8 to 10.0)	7/7
Furlan, 2006[79]	39 (34)	**Opioids vs. placebo (rate differences)** Constipation: 16% (95% 10-22%) Nausea: 15% (95% CI 11-19%) Dizziness or vertigo: 8% (5-12%) Somnolence or drowsiness: 9% (95% CI 5-13%) Vomiting: 5% (95% CI 2-7%) Dry skin, itching, or pruritus: 4% (95% CI 1-6%)	7/7

Table 8. Systematic reviews of adverse events associated with opioids for chronic noncancer pain

Author, year	Number of randomized trials included (number rated higher-quality)	Main findings (adverse events)	Quality rating*
Hollingshead, 2006[80]	6 (3)	**Tramadol vs. placebo** Withdrawal due to adverse events: NNH=8.3, 95% CI 5.6 to 17 (3 trials)	6/7
Kalso, 2004[81]	11 (11) (excluding trials of intravenous opioids)	**Oral opioids vs. placebo** At least one adverse event: 80% vs. 56%, NNH=4.2 (3.1 to 6.4) Withdrawal due to adverse event: 24% vs. 15%, NNH=12 (95% CI 8 to 27) Constipation: 41% vs. 11%, NNH=3.4 (95% CI 2.9 to 4.0) Nausea: 32% vs. 12%, NNH=5.0 (95% CI 4.0 to 6.4) Somnolence/sedation: 29% vs. 10%, NNH=5.3 (95% CI 4.3 to 7.0) Vomiting: 15% vs. 3%, NNH=8.1 (95% CI 6.4 to 11) Dizziness: 20% vs. 7%, NNH=8.2 (95% CI 6.3 to 12) Itching: 15% vs. 7%, NNH=13 (95% CI 8.4 to 27)	5/7
Martell, 2007[82]	8 (8) (trials of oral or transdermal opioids)	**Prevalence of aberrant drug-related behaviors (including observational studies):** range 5% to 24%	7/7
Moore, 2005[83]	35 (34)	**Opioid vs. placebo** Any adverse event: 51% (95% CI 49-53%) vs. 30% (95% CI 26-34%) Withdrawal due to adverse event: 22% (95% CI 21-23%) vs. 7% (95% CI 5-9%) Dry mouth: 25% (95% CI 21-29%) vs. 3% (0-7%) Nausea: 21% (95% CI 20-22%) vs. 6% (95% CI 4-7%) Constipation: 15% (95% CI 14-16%) vs. 5% (3-7%) Dizziness: 14% (95% CI 13-15%) vs. 4% (95% CI 3-6%) Drowsiness or somnolence: 14% (95% CI 13-15%) vs. 4% (95% CI 2-6%) Pruritus: 13% (95% CI 11-16%) vs. 2% (95% CI 1-4%) Vomiting: 10% (95% CI 9-11%) vs. 2% (95% CI 1-4%)	6/7
Noble, 2008[84]	1 (0) (9 open-label, uncontrolled observational studies)	**Prevalence of signs of opioid addiction: 0.05% (1/2042)** Prevalence of abuse: 0.43% (3/685) Withdrawals due to adverse events: 32% (95% CI 26% to 40%) for oral opioids and 18% (6% to 39%) for transdermal opioids	7/7

*Using Oxman criteria, maximum score 7

Reliable evidence on rates of abuse, addiction or other aberrant drug-related behaviors is not available from randomized trials of opioids. In the largest systematic review (39 trials), patients with a history of addiction were excluded from 25 trials, and information on addiction history was not reported in the other 14 trials[79]. One lower-quality, open-label head-to-head trial of sustained-release oxymorphone versus sustained-release oxycodone for low back pain that was not included in the systematic reviews (see Key Question 7 for further details) reported drug abuse or diversion in four of 389 patients (all randomized to oxycodone)[181, 182]. However, it did not define drug abuse or diversion or describe how these outcomes were ascertained. No other randomized trial reported these outcomes. A higher-quality systematic review of primarily open-label, uncontrolled observational studies reported opioid addiction in 0.05% (1/2,042) and abuse

in 0.43% (3/685) of patients[84]. Another higher-quality systematic review of opioids for low back pain also included observational studies[82]. It reported estimates of aberrant drug-related behaviors that ranged from 5% to 24%[82]. The studies were generally rated lower quality, used different methods to define aberrant drug-related behaviors, mostly evaluated patients from settings with higher rates of aberrant drug-related behaviors, and did not distinguish between new and pre-existing substance abuse. No trial reported use of active surveillance to identify signs of abuse or addiction.

Thirteen placebo-controlled trials that were not included in the systematic reviews reported findings for short-term harms generally consistent with the systematic reviews (Table 9)[91, 95, 97, 102-106, 114, 117, 120, 123, 161]. The major inconsistency was that rates of withdrawal due to adverse events were not higher in patients randomized to opioids compared to placebo in three trials[97, 102, 114]. This could be explained by the use of run-in periods by all three of these trials to exclude patients who developed early adverse events.

Table 9. Placebo-controlled trials of opioids not included in systematic reviews

Author, year	Number of patients Duration of follow-up	Main results	Quality*
Burch, 2007[91] Osteoarthritis	N=646 12 weeks	**Tramadol Contramid OAD vs. placebo** Nausea: 15% vs. 6% Constipation: 14% vs. 4% Dizziness/vertigo: 10% vs. 4% Somnolence: 7% vs. 4% Withdrawal due to adverse events: 10% (44/432) vs. 5% (11/214) (22% or 225/1028 discontinued Tramadol Contramid OAD during open-label run-in period)	9/11; 5/5
Gana, 2006[95] Osteoarthritis	N=1020 12 weeks	**Extended-release tramadol 400 mg vs. 300 mg vs. 200 mg vs. 100 mg vs. placebo** Any adverse events: 84% vs. 76% vs. 73% vs. 71% vs 56% At least one serious adverse event: 3.0% vs. 1.5% vs. 2.0% vs. 1.5% vs. 1.0%	7/11; 4/5
Hale, 2007[97] Low back pain	N=143 12 weeks	**Sustained-release oxymorphone vs. placebo** Withdrawal due to adverse event: 10% (7/70) vs. 11% (8/72) Withdrawal due to opioid withdrawal symptoms: 0% (0/70) vs. 7% (5/72)	8/11; 3/5
Katz, 2007[102] Low back pain	N=205 12 weeks	**Sustained-release oxymorphone vs. placebo** Withdrawal due to adverse event: 9% (9/105) vs. 8% (8/100) Withdrawal due to opioid withdrawal symptoms: 1% (1/105) vs. 2% (2/100) At least one adverse event: 58% (61/105) vs. 44% (44/100) At least one serious adverse event: 2% (2/105) vs. 3% (3/100)	8/11; 4/5
Khoromi, 2007[120] Radicular low back pain	N=205 12 weeks	**Sustained-release morphine plus nortriptyline versus sustained-release morphine versus nortriptyline versus benztropine (active placebo)** Withdrawal due to adverse events: 12% (4/34) vs. 12% (5/41) vs. 6% (2/34) vs. 3% (1/39) Any adverse event: 89% vs. 93% vs. 68% vs. 50% Constipation: 71% vs. 64% vs. 25% vs. 7% Dry mouth: 29% vs. 21% vs. 36% vs. 21% Headache: 14% vs. 14% vs. 7% vs. 14% Drowsiness: 11% vs. 25% vs. 7% vs. 4% Tired/fatigue: 14% vs. 7% vs. 11% vs. 18% Dizziness: 4% vs. 14% vs. 7% vs. 4% Insomnia: 11% vs. 7% vs. 11% vs. 0% Nausea: 4% vs. 7% vs. 0% vs. 0%	5/11; 4/5
Kivitz, 2006[103] Osteoarthritis	N=370 2 weeks	**Sustained-release oxycodone 10 mg vs. 40 mg vs. 50 mg vs. placebo** Withdrawal due to adverse events: 25% (24/95) vs. 55% (51/93) vs. 52% (47/91) vs. 10% (9/91)	9/11; 5/5
Langford, 2006[104] Osteoarthritis	N=416 6 weeks	**Transdermal fentanyl vs. placebo** Withdrawal due to adverse events: 26% (55/216) vs. 8% (15/200) At least one adverse event: 78% (169/216) vs. 51% (101/200)	9/11; 5/5

Table 9. Placebo-controlled trials of opioids not included in systematic reviews

Author, year	Number of patients Duration of follow-up	Main results	Quality*
Ma, 2007[161] Chronic neck pain	N=116 1 week	**Sustained-release oxycodone vs. placebo** Withdrawal due to adverse event: Not reported Nausea: 31% vs. 12% (p<0.05) Vomiting: 9% vs. 5% Constipation: 22% vs. 3% (p<0.01) Somnolence: 10% vs. 0% Dizziness: 28% vs. 0% (p<0.01) Pruritus: 19% vs. 2% (p<0.01) Agitated: 5% vs. 0%	4/11; 2/5
Markenson, 2005[105] Osteoarthritis	N=109 Up to 3 months	**Sustained-release oxycodone vs. placebo** Withdrawal due to adverse events: 36% (20/56) vs. 4% (2/51) (p<0.001) Any adverse event: 93% (52/56) vs. 55% (28/51) "Serious" adverse event: 5% (3/56) vs. 0% (0/51)	9/11; 5/5
Matsumoto, 2005[106] Osteoarthritis	N=491 4 weeks	**Sustained-release oxymorphone 40 mg bid vs. sustained-release oxymorphone 20 mg bid vs. sustained-release oxycodone 20 mg bid vs. placebo** Withdrawal (overall): 56% (68/121) vs. 48% (58/121) vs. 40% (50/125) vs. 37% (46/124) Withdrawal (adverse events): 47% (57/121) vs. 38% (46/121) vs. 25% (31/125) vs. 27% (34/124) Any adverse events: 91% vs. 95% vs. 88% vs. 57%	9/11; 5/5
Thorne, 2008[123] Osteoarthritis	N=100 4 weeks each intervention (crossover	**Extended-release tramadol once daily (mean dose 340 mg/day) vs. placebo** Any adverse event: 80% vs. 66% Withdrawal due to adverse events: 13% (12/94) vs. 3% (3/88) Serious adverse event: none vs. 1 (atrial flutter) Nausea: 43% vs. 25% (p=0.03) Somnolence: 37% vs. 22% (p=0.08) Constipation: 23% vs. 6% (p=0.001) Anorexia: 6% vs. 1% (p=0.10) Vomiting: 6% vs. 1% (p=-.32) Dizziness: 5% vs. 3% (p=0.41)	5/11; 4/5

Table 9. Placebo-controlled trials of opioids not included in systematic reviews

Author, year	Number of patients Duration of follow-up	Main results	Quality*
Vorsanger, 2008[114] Low back pain	N=386 12 weeks	**Extended-release tramadol 300 mg once daily vs. 200 mg once daily vs. placebo** Any adverse event: 76% vs. 61% vs. 57% (p=0.003) Withdrawal due to adverse events: 10% vs. 10% vs. 14% Nausea: 29% vs. 27% vs. 28% Dizziness: 15% vs. 14% vs. 17% constipation: 23% vs. 26% vs. 19% Headache: 8% vs. 20% vs. 16% Somnolence: 10% vs. 13% vs. 12% Vomiting: 7% vs. 8% vs. 7% Fatigue: 7% vs. 6% vs. 5%	7/11; 4/5
Zautra, 2005[117] Osteoarthritis	N=107 3 months	**Sustained-release oxycodone vs. placebo** Withdrawal (adverse events): 36% (20/55) vs. 4% (2/49)	7/11; 4/5

*Using Cochrane Back Group criteria, maximum score 11 and Jadad criteria, maximum score 5

Long-term adverse events, aberrant drug-related behaviors, endocrinologic adverse events, and falls/fractures

Data on long-term adverse events from randomized trials are sparse. In the longest duration published trial (13 months), 34% of patients (N=680) randomized to transdermal fentanyl or sustained-release morphine withdrew due to adverse events[124]. About 90% of patients randomized to either opioid reported at least one adverse event considered at least possibly related to the trial medication. Constipation and nausea were each reported by over half of the subjects.

One higher-quality systematic review of primarily open-label, uncontrolled studies found that 32% (95% CI 26% to 40%) of patients prescribed oral opioids (N=911) and 18% (95% CI 6% to 39%) prescribed transdermal opioids (N=1399) remained on therapy after six to eighteen months[84]. Another higher-quality systematic review found that less than half of patients with low back pain and prescribed opioids (N=388) remained on opioids in studies that reported long-term (7 to 24 months), open-label follow-up from randomized trials[81]. These results are difficult to interpret because discontinuation of opioids could be due to lack of efficacy, intolerable adverse events, improvement in underlying pain conditions, patient or clinician preferences, or other factors.

One higher-quality systematic review found that rates of aberrant drug-related behaviors ranged from 5% to 24% in observational studies of low back pain patients receiving opioids, but six out of seven studies reporting these outcomes were rated lower-quality, only two studies used a comprehensive and structured clinical assessment to evaluate for presence of aberrant drug-related behaviors, and the studies were not explicit in distinguishing new aberrant drug-related behaviors from pre-existing substance use disorders[82].

For risk of fracture, one higher-quality systematic review of observational studies estimated a relative risk of 1.38 (six studies, 95% CI 1.15 to 1.66) for any fracture in patients on opioids compared to non-use. Risk of hip fractures was similar to the risk for any fracture[89]. Risks associated with opioids were similar to risks associated with benzodiazepines (RR=1.34, 95% CI 1.24 to 1.45), antidepressants (RR=1.60, 95% CI 1.38 to 1.86), and non-barbiturate antiepileptic drugs (RR=1.54, 95% CI 1.24 to 1.93). One case-control study not include in the systematic review found morphine, fentanyl, methadone, oxycodone, tramadol, and codeine all associated with increased fracture risk, but no increase in risk was associated with buprenorphine or combinations of aspirin plus codeine. Increased doses were associated with higher risk of fracture[164]. The main limitation of these results is the possibility of residual confounding, as few studies included in the systematic review controlled for important confounders such as functional status, cognitive impairment, and bone density scores.

Several studies have evaluated the association between use of intraspinal opioids and endocrinologic effects, including suppression of serum testosterone and clinical signs of hypogonadism[183, 184]. One small (N=8) prospective study found that baseline high serum

cortisol levels (possibly related to effects of pain on the adrenal system) decreased to low normal levels after initiation of oral morphine[165]. Pituitary and adrenal response to stimulation with human corticotrophin-releasing hormone remained intact. Several cross-sectional studies evaluated the association between chronic oral opioid use and other endocrinologic abnormalities[170, 171, 173]. One study (N=37) found no association between opioid use or non-use and growth hormone, corticotrophin, cortisol, thyroxine, thyrotropin, prolactin, estradiol, follicle stimulating hormone, luteinizing hormone, or testosterone levels in patients with chronic pain[173]. Three other studies (N=47, 54, and 66) found opioid use associated with hypogonadism and decreased levels of dehydroepiandrosterone sulfate (DHEAS) in men and women[170-172]. A major limitation of these studies is that it is not possible to determine causality because of their cross-sectional design. In addition, it is not clear from the two studies that found an association between opioid use and endocrinologic abnormalities if control patients had chronic pain[170-172]. None of the studies appeared to adjust for potential confounders (such as severity of pain), and methods for selecting patients were poorly described, making it difficult to determine whether patients on opioids with signs of sexual or endocrinologic dysfunction were preferentially enrolled. No evidence exists on endocrinologic effects of short-acting or intermittent opioids, and no randomized trials or controlled observational studies evaluated clinical outcomes associated the different approaches to monitoring or treating hypogonadism or DHEAS deficiency.

There is also limited evidence on the association between arrhythmias and use of methadone. A small (N=17) case series reported episodes of torsades de pointes in patients on high doses of methadone (mean about 400 mg/day)[167]. About half of the cases occurred in patients being treated for chronic pain. A case-control study (N=22 cases) found methadone associated with sudden death (p=0.02)[168]. A subsequently published case series of 104 patients on lower doses (median 110 mg/day) of methadone found that 32% had QTc prolongation, but none had prolongation beyond the value (500 msecs) considered a definite risk for torsades de pointes[166]. These studies are difficult to interpret because they often did not distinguish between patients prescribe methadone for chronic noncancer pain versus those who received methadone for maintenance treatment of heroin addiction or who obtained methadone without a prescription, did not compare risks associated with methadone versus other opioids, or did not account for increased methadone prescription rates over time. A retrospective, uncontrolled study found sleep apnea to be common in patients prescribed chronic opioids for chronic pain[169]. Methadone was the only specific opioid in which an association between dose and severity of apnea-hypopnea was observed.

Other data on harms

The ongoing Drug Abuse Warning Network (DAWN) study reports “mentions” of drug-related visits associated with various prescription and non-prescription opioids in emergency departments across the U.S.[175]. Because this study does not distinguish between prescribed and illicit drug use or use of opioids in maintenance programs or between different modes of administration (e.g. intravenous versus oral), it is not possible to directly use data from DAWN to estimate risk of oral or transdermal opioids in patients with noncancer pain[185]. From 1997

through 2002, analysis of DAWN data found that the proportion of emergency room visits for drug abuse or misuse in which opioids were mentioned increased from 5.75% to 9.85%[186]. However, dispensation of opioids as measured by the Automation of Reports and Consolidated Orders System (ARCOS) also increased substantially over that period.

Because DAWN methods have recently undergone substantial revisions, more recent data starting in 2003 are not directly comparable to the older DAWN data[187]. From 2004 to 2005, the number of emergency room visits associated with nonmedical use of drugs (defined as not taking a pharmaceutical as prescribed or recommended) in which opioids were mentioned increased 24%, from 158,000 to 196,000[188]. The number of suicide attempts was unchanged (1,874 and 1,749).

Several studies describe a recent increase in the number of deaths associated with opioid use. However, none of these studies described the number of deaths specifically in persons prescribed opioids for chronic noncancer pain. The Substance Abuse and Mental Health Services Administration (SAMHSA) issued a report on methadone-associated mortality in 2004[176]. It concluded that observed increases in methadone-associated mortality in several states since the late 1990's appeared largely related to increased accessibility of methadone obtained outside of licensed opioid treatment programs. Methadone-associated deaths were usually associated with other central nervous system depressant agents (such as benzodiazepines, alcohol, and other opioids). In the state of Oregon, methadone deaths increased from 23 in 1999 to 103 in 2002[178]. The increase appeared roughly proportionate to the increase in methadone prescriptions (5-fold increase in grams/100,000 persons between 1997 and 2001). Approximately 28% of the deaths occurred in patients being treated for chronic pain (cancer or noncancer). Another study found that the number of Utah Medical Examiner-reported deaths associated with methadone, hydrocodone, oxycodone, codeine, and fentanyl all increased in 1999 to 2003 compared to 1991 to 1998[189]. The number of deaths associated with methadone, for example, increased from 18 to 164; the number of deaths associated with oxycodone increased from 10 to 111. In contrast to the Oregon data, the Utah deaths did not appear entirely proportionate to increases in opioid prescriptions. A study on accidental poisoning deaths between 1996 and 2002 in Washington State's workers' compensation system found that 32 cases met pre-defined criteria for "definite" or "probable" accidental opioid overdose[177]. Although the study attributed the deaths to increased use of schedule II opioids (from 19.3% of all opioid prescriptions in 1996 to 37.2% in 2002) and an increase in average morphine equivalent dose (from 88 mg/day in 1996 to 132 mg/day in 2002), it reported no statistical analyses on these trends. In addition, the number of annual deaths appeared to peak in 2000 and then decline, though the number of schedule II prescriptions and mean morphine equivalent doses continued to increase through 2002. A U.S. Drug Enforcement Agency survey of medical examiners found a total of 464 deaths probably or "verified" as linked to sustained-release oxycodone[180].

Summary of evidence

- Opioids are associated with increased short-term adverse events compared to placebo. The most frequent adverse events are nausea, constipation, sedation, vomiting, somnolence, and dizziness. Adverse events frequently lead to discontinuation of opioids (level of evidence: high).
- There are no reliable data from randomized trials on risk of aberrant-related behaviors. Data from observational studies estimates rates ranging from 5% to 24%, but studies are characterized by methodological shortcomings, variations in methods used to define and identify aberrant drug-related behaviors, enrollment of higher-risk populations, and failure to distinguish between pre-existing and new substance abuse (level of evidence: low).
- Opioids were associated with a 40% increased risk of fractures, though data are from observational studies and residual confounding is likely (level of evidence: low).
- There is insufficient evidence from cross-sectional studies to determine the association or frequency of oral opioids with endocrinologic dysfunction (level of evidence: low).
- There is insufficient evidence from one retrospective, uncontrolled observational study to determine the association between chronic opioid use in general or methadone use in particular and sleep apnea (level of evidence: low).
- There are case reports of torsades de pointes with high doses of methadone, and prolongation of QT intervals with lower doses of methadone, but the clinical significance of the latter is uncertain. A small case-control study found methadone associated with sudden death in the community (level of evidence: low).
- Emergency room visits for nonmedical use of drugs in which opioids were mentioned increased 24% between 2004 and 2005, but it is not possible to determine how many were in patients prescribed opioids for chronic noncancer pain. Earlier studies suggest that emergency room visit mentions of opioids appear to have increased along with increased rates of distribution.
- Deaths associated with methadone and other opioids have increased along with distribution and use of opioids. However, it is not clear if the increase in opioid-associated deaths is attributable to increased use of opioids in general, increased use of specific opioids (such as methadone or schedule II drugs), higher average doses of opioids, or other factors, and no study reported the number of deaths in patients prescribed opioids for chronic noncancer pain.

Key Question 6

What are the benefits and harms of opioids for noncancer pain in patients with a history of substance abuse or addiction that are undergoing treatment for addiction?

Patients with a history of substance abuse or addiction or who are undergoing treatment for addiction may have less tolerance (see glossary) to pain[190] or may require higher doses of methadone for maintenance treatment due to concomitant pain[191-193]. They may also be at

higher risk for abuse of opioids prescribed for pain relief, though treatment for addiction could potentially mitigate this risk.

Results of search: systematic reviews

We identified no relevant systematic reviews on benefits and harms of opioids for chronic noncancer pain in patients with a history of substance abuse or addiction that are undergoing treatment for addiction that met inclusion criteria.

Results of search: primary studies

We identified no relevant randomized controlled trials on benefits and harms of opioids for chronic noncancer pain in patients with a history of substance abuse or addiction or that are undergoing treatment for addiction that met inclusion criteria. Nearly all randomized trials excluded patients with a history of addiction or substance abuse or did not report information on drug abuse history[79]. We also identified no case-control or cohort studies evaluating benefits or harms of opioids for noncancer pain in patients with a history of substance abuse or addiction or who are undergoing current treatment for addiction. One prospective observational study of a primary care based opioid renewal program with pharmacist and dedicated nurse practitioner support was excluded because it was an uncontrolled study[194].

Findings

The uncontrolled observational study did not meet inclusion criteria but is discussed here because it provides the only evidence on management of high-risk patients[194]. It found that 45% of 171 patients with prior aberrant drug-related behaviors who were referred to an opioid renewal program adhered to the opioid agreement, 38% self-discharged from the program, 13% were referred for addiction treatment, and 4% with consistently negative urine drug screens were weaned from opioids. Methods for monitoring patient outcomes and definitions for aberrant drug-related behaviors were not described in detail, which could make it difficult to apply results of this study.

Summary of evidence

- There are no randomized trials or controlled observational studies on benefits and harms of opioids for chronic noncancer pain in patients with a history of substance abuse or addiction that are undergoing treatment for addiction.

Key Question 7

What are the comparative benefits and harms of different opioids and different formulations of opioids for chronic noncancer pain?

Results of search: systematic reviews

We identified one systematic review on comparative benefits and harms of different sustained-release or transdermal opioids[53].

Results of search: primary studies

We identified six head-to-head trials (reported in seven publications[98, 106, 124, 181, 182, 195, 196]) not included in the systematic review that compared different opioids, six trials[90, 107, 118, 121, 122, 197] on sustained- (twice daily) or extended-release (once-daily) tramadol versus immediate-release tramadol, and three trials[100, 108, 198] on tramadol versus opioids. We also identified three cohort studies based on administrative claims databases that compared risks associated with different sustained-release oral opioids and transdermal fentanyl[199-201].

Findings

Comparisons between one opioid and another opioid

One higher-quality systematic review[53] included two head-to-head trials[202, 203] that compared different opioids and seven trials[119, 204-209] that compared sustained-release versus immediate-release preparations (Table 10). One lower-quality, head-to-head trial (N=212) included in the systematic review found more patients with miscellaneous chronic pain conditions reported good or very good pain control with transdermal fentanyl (40%) compared to sustained-release, oral morphine (19%)[202]. Transdermal fentanyl was associated with less constipation compared to oral morphine, but there was a trend towards more withdrawals due to adverse events with transdermal fentanyl. This trial was rated lower-quality because it was open-label, recorded a high rate of attrition, and did not report intention-to-treat analyses. In addition, three-quarters of patients had previously received morphine. This could have biased results towards transdermal fentanyl if patients were more likely to enroll due to previous poor response to morphine. A second trial (N=295) found no clear differences in efficacy or safety between sustained-release (twice-daily) versus extended-release (once daily) morphine formulations[203].

Table 10. Systematic review evaluating comparative efficacy of different opioids and opioid formulations

Author, year Type of review	Number of relevant randomized trials included (number rated higher-quality)	Total number of patients enrolled Sample sizes for individual trials	Underlying conditions	Interventions evaluated	Quality rating*
Chou, 2003[53] Qualitative	2 (1) head-to-head trials of opioids, 7 (2) trials of sustained- versus immediate-release opioids	984 36 to 295 (median=83)	Back pain (5), osteoarthritis (3), miscellaneous (1)	Transdermal fentanyl (1), morphine (2), oxycodone (4), codeine (1), dihydrocodeine (2)	6/7

*Using Oxman criteria, maximum score 7

Six head-to-head trials not included in the systematic review also found no clear differences in efficacy or safety between different sustained-release oral opioids or sustained-release oral opioids and transdermal fentanyl (Table 11)[98, 106, 124, 181, 182, 195, 196]. Two trials compared sustained-release oral morphine to transdermal fentanyl[124, 196], two compared sustained-release oxycodone to sustained-release oxymorphone[98, 106], and two compared extended-release (once daily) morphine to sustained-release (twice daily) oxycodone[181, 182, 195]. Four out of the six trials

were rated lower-quality, due to methodological shortcomings that included use of open-label designs, poor description of randomization or allocation concealment techniques, high loss to follow-up, and/or lack of intention-to-treat analyses[124, 181, 182, 195, 196]. Although one lower-quality trail found a higher proportion of patients randomized to extended-release morphine (once-daily) compared to sustained-release oxycodone (twice-daily) experienced a >2 point improvement on the Brief Pain Inventory (55% vs. 44%, p=0.03) and better outcomes on sleep assessments, there were no differences in mean changes in Brief Pain Inventory or SF-12 scores[181, 182].

Table 11. Head-to-head trials of opioids not included in systematic reviews

Author, year	Number of patients Duration of follow-up	Main results	Quality*
Allan, 2005[124] Low back pain	N=683 13 months	**Transdermal fentanyl vs. sustained-release morphine** Pain score (mean, 0-100 VAS): 56 vs. 56 Severe pain at rest: No significant difference in intention-to-treat analysis, but data not provided Severe pain at night: No significant difference in intention-to-treat analysis, but data not provided Rescue strong opioids use: 52% (154/296) vs. 53% (154/291) Quality of life (SF-36): No differences Withdrawal (lack of efficacy): 18/335 (5%) vs. 15/342 (4%) Withdrawal (adverse events): 125/335 (37%) vs. 104/337 (31%) (p=0.098) Constipation (ITT): 176/338 (52%) vs. 220/338 (65%) (p<0.05) Any adverse event: 87% vs. 91%	4/11; 2/5
Hale, 2005[98] Low back pain	N=330 (dose titration phase, A vs. B) N=235 (stable intervention treatment phase, A vs. B vs. C) 18 days	**Sustained-release oxymorphone (A) vs. sustained-release oxycodone (B) vs. placebo (C)** Pain Intensity (100 point VAS): Compared to placebo, differences were -18.21 and -18.55 for A and B Pain Relief: 56.8 vs. 54.1 vs. 39.1 Global Assessment "Good", "very good", or "excellent': 59% vs. 63% vs. 27% Withdrawal due to treatment failure (treatment phase) 20% vs. 16% vs. 57% Withdrawal due to treatment failure (dose titration phase) 7/166 (4.2%) vs. 4/164 (2.4%) Withdrawal (adverse events, titration phase): 25/166 (15%) vs. 26/164 (16%) Withdrawal (adverse events, treatment phase): 2/80 (2.5%) vs. 4/80 (5.0%) vs. 5/75 (6.7%) Any adverse events: 85% vs. 86% vs. NR	9/11; 5/5
Matsumoto, 2005[106] Osteoarthritis	N=491 4 weeks	**Sustained-release oxymorphone 40 mg bid vs. sustained-release oxymorphone 20 mg bid vs. sustained-release oxycodone 20 mg bid vs. placebo** Pain Intensity (100 point VAS), mean improvement (estimated from Figure 1): -26 vs. -24 vs. -22 vs. -17 (p not reported) WOMAC Pain (0 to 500), mean improvement (estimated from Figure 3): -118 vs. -102 vs. -88 vs. -60 (p<0.01 for A vs. D, p<0.05 for B vs. D) WOMAC Physical Function (0 to 1700): -315 vs. -300 vs. -220 vs. -190 (p<0.05 for A vs. D and B vs. D) WOMAC Composite Index (0 to 2400): -480 vs. -460 vs. -360 vs. -290 (p<0.05 for A vs. D and B vs. D) Patient's global assessment (VAS 0 to 100): -28.6 vs. -23.2 vs. -25.4 vs. -19.5 (p<0.05 for A vs. D) Overall quality of sleep (VAS 0 to 100): +18.2 vs. +13.8 vs. +15.3 vs. +7.7 (p<0.05 for A vs. D and C vs. D) SF-36 Physical component: +4.5 vs. +3.4 vs. +4.0 vs. +1.8 (p<0.05 for A vs. D and C vs. D) SF-36 Mental component: -0.4 vs. +1.5 vs. -0.8 vs. +2.2 (p<0.05 for C vs. D) Withdrawal {lack of efficacy): 7% (9/121) vs. 4% (5/121) vs. 10% (13/125) vs. 27% (34/124) Withdrawal (adverse events): 47% (57/121) vs. 38% (46/121) vs. 25% (31/125) vs. 27% (34/124) Any adverse event: 91% vs. 95% vs. 88% vs. 57%	8/11; 5/5

Table 11. Head-to-head trials of opioids not included in systematic reviews

Author, year	Number of patients Duration of follow-up	Main results	Quality*
Nicholson, 2006[195] Miscellaneous noncancer pain	N=112 24 weeks	**Extended-release morphine (Kadian) once daily versus sustained-release oxycodone twice daily (mean improvement from baseline)** SF-36 Physical Component Scale: +2.5 vs. +2.1 (NS) SF-36 Mental Component Scale: +0.8 vs. +4.2 (p for differences between groups not reported, but p<0.05 vs. baseline only for sustained-release oxycodone) Pain (0 to 10): -1.9 vs. -1.4 (NS) Sleep Interference Scale (0 to 10): -2.6 vs. -1.6 (p<0.05) Patient Global Assessment (-4 to +4): +2.6 vs. +1.7 (NS) Use of concomitant medications: 80% vs. 88% (NS) Withdrawal (lack of efficacy): 2% (1/53) vs. 7% (4/59) Withdrawal (adverse events): 28% (15/53) vs. 22% (13/59)	4/11; 2/5
Niemann, 2000[196] Chronic pancreatitis	N=18 4 weeks	**Transdermal fentanyl vs. sustained-release oral morphine** Patient Preference rated as "Preference" or "Strong Preference": 47% vs. 41% (NS) Pain Control "Good" or "Very Good": 44% vs. 33% (NS) Quality of Life: No significant differences in physical functioning, general health, role physical, pain intensity, social functioning, mental health, and side effects summary median scores	3/11; 2/5
Rauck, 2006[181, 182] Low back pain	N=392 8 weeks	**Extended-release morphine (Avinza) once daily versus sustained-release oxycodone (Oxycontin) twice daily** Brief Pain Inventory score (0 to 10, mean improvement from baseline): -3.1 vs. -2.8 (p not reported) Proportion with >2 point improvement in BPI: 55% (73/132) vs. 44% (59/134) (p=0.03) Pittsburgh Sleep Quality Index (mean improvement from baseline): 33% vs. 17% (p=0.006) Rescue medication use: 2,595 vs. 3,154 doses (p<0.0001) SF-12 Physical Component Summary (mean improvement from baseline): 23% vs. 19% (NS) SF-12 Mental Component Summary (mean improvement from baseline): 23% vs. 16% (NS) Withdrawal (lack of efficacy): 5% (10/203) vs. 3% (6/189) Withdrawal (adverse events): 19% (38/203) vs. 14% (27/189) Serious adverse events: 3% (7/203) vs. 5% (9/189) Drug abuse or diversion: 0% (0/203) vs. 2% (4/189)	4/11; 2/5

*Using Cochrane Back Group criteria, maximum score of 11; and Jadad criteria, maximum score of 5

Three large, retrospective cohort studies based on administrative claims databases evaluated comparative adverse events associated with different sustained release opioids (oral or transdermal)[199-201]. In patients with noncancer pain, one study of Oregon Medicaid patients found transdermal fentanyl associated with a higher risk of emergency department encounters (adjusted hazards ratio 1.27, 95% CI 1.02 to 1.59) and methadone associated with higher risk of overdose symptoms (adjusted hazards ratio 1.57, 95% CI 1.03 to 2.40), when each was compared to sustained-release morphine. There were no other differences between any evaluated drug (transdermal fentanyl, methadone, sustained-release oxycodone, and sustained-release morphine) on any evaluated outcome (emergency department encounters, mortality, hospitalizations, opioid poisonings, overdose symptoms, or constipation)[200]. Two studies of California Medicaid patients (both sponsored by the manufacturer of transdermal fentanyl) found a greater risk of new constipation in patients prescribed sustained-release oxycodone (adjusted odds ratios=2.55, 95% CI 1.33-4.89[199] and 1.78, 95% CI 1.05-3.03[201]) compared to transdermal fentanyl, after adjusting for patient demographics, co-morbidities, dose of long-acting opioid, and use of short-acting opioids. One of these studies also assessed risk of constipation associated with sustained-release morphine compared to transdermal fentanyl and did not find a statistically significant difference (adjusted odds ratio=1.44, 95% CI 0.80-2.60)[201].

In all three studies, patients on transdermal fentanyl were significantly older and more frequently male compared to patients on oral sustained-release opioids. In addition, doses of opioids, concomitant medications, underlying conditions, and comorbidities varied substantially in patients prescribed different opioids. Such marked differences in measured confounders suggest a high risk for residual confounding due to unmeasured or unknown confounders, especially since administrative databases are frequently limited in their ability to measure important potential confounders[210]. In addition, one study relied on outcomes that are relatively non-specific surrogates for adverse events associated with opioids, such as emergency department encounters, hospitalizations, mortality, and overdose symptoms[200]. The other two studies focused on a single adverse outcome (constipation). Such a narrow focus makes it impossible to assess the overall balance of adverse events, which may be of importance because large randomized trials of transdermal fentanyl and oral sustained-release morphine (reviewed earlier in this section) found transdermal fentanyl associated with lower rates of constipation, but higher rates or a trend towards higher rates of withdrawal due to any adverse event[124, 202].

The ongoing Drug Abuse Warning Network (DAWN) study reports “mentions” of drug-related visits for various prescription and non-prescription opioids in emergency departments across the U.S. (see also Key Question 5)[175]. Analysis of DAWN data from 1997 to 2002 found that rates of mentions for any fentanyl compound increased by 641%, any morphine compound by 113%, and any oxycodone compound by 347%, while prescribing (as measured by the Automation of Reports and Consolidated Orders System [ARCOS] database) increased by 214%, 66%, and 383%, respectively[186]. These rates reflect absolute event rates, and were not adjusted for changes in availiability or use of each opioid. In 2005, the number of emergency room visits involving nonmedical use of drugs that mentioned codeine/codeine combinations was 5,550,

fentanyl/fentanyl combinations was 9160, hydrocodone/hydrocodone combinations was 51,225, hydromorphone/hydromorphone combinations was 5,344, methadone 41,216, morphine/morphine combinations was 15,183, oxycodone/oxycodone combinations was 42,810, and propoxyphene/propoxyphene combinations was 6,813 (estimates of prescribing rates not reported)[188].

Comparisons between sustained-release and immediate-release formulations of opioids or tramadol

One systematic review[53] included seven trials (two rated higher-quality[204, 206]) that found no clear pattern favoring sustained-release or immediate-release opioids for any measured outcome[119, 204-209]. Three trials evaluated sustained- versus immediate-release oxycodone[204, 206, 209], one sustained- versus immediate-release codeine[119], one sustained- versus immediate-release dihydrocodeine[205], one sustained-release dihydrocodeine versus dextropropoxyphene plus paracetamol[208], and one sustained-release morphine plus immediate release oxycodone (titrated doses) versus fixed-dose, immediate release oxycodone[207]. Trials were generally diverse in terms of drugs compared, doses evaluated, and methods for initiating and titrating therapy. However, three trials that evaluated comparable doses of sustained-release versus immediate-release oxycodone were more similar, and also found no pattern favoring one formulation over the other[204, 206, 209].

One higher-quality trial found extended-release (once-daily), scheduled tramadol to be more effective than immediate-release, as-needed tramadol every four to six hours, but the difference was not clinically significant (less than 5 points on a 100 point VAS pain scale)[197]. In addition, the dose of tramadol was lower in the immediate-release arm, and extended-release tramadol was associated with a higher rate of withdrawal due to adverse events and nausea. Five of six other trials (two rated higher-quality[90, 107]) found no clear differences between scheduled extended- (once-daily), sustained-release (twice-daily), or immediate-release formulations of tramadol[90, 107, 118, 121, 122] (Table 12). Two trials compared extended- (once-daily) versus immediate-release tramadol[90, 118], two compared sustained- (twice-daily) versus immediate-release tramadol[121, 122], and one compared extended- versus sustained-release tramadol[107].

Table 12. Head-to-head trials of extended-release (once daily) or sustained-release (twice daily) tramadol versus sustained-release (twice daily) or immediate-release tramadol

Author, year Underlying condition	Number of patients Duration of follow-up	Main results	Quality*
Adler, 2002[90] Osteoarthritis	N=279 21 days	**Tramadol extended-release 400 mg once daily versus tramadol immediate-release 100 mg four times daily** Pain score in morning (0 to 100), adjusted mean difference at end of treatment: -7.2 (NS) (favors immediate-release) Pain score in evening (0 to 100), adjusted mean difference at end of treatment: -0.3 (NS) Mean use of escape medications: No difference Waking with pain on last night: 60% overall Patient global assessment good to excellent: 65% overall (no differences) Withdrawal due to lack of efficacy: 9% (16/188) vs. 9% (8/91)	6/11; 4/5
Beaulieu, 2007[197] Mixed chronic noncancer pain	N=122 2 weeks each intervention (crossover)	**Tramadol extended-release (once daily) scheduled versus tramadol immediate-release (q4 to 6 hours) as-needed** Mean pain intensity week 4 (VAS 0 to 100): 33.4 vs. 37.4 (p<0.007) Mean pain intensity week 4 (ordinal 0 to 4): 1.52 vs. 1.69 Pain and Disability Index: No differences Pain and Sleep score (composite): No differences Patient global rating (1 to 7): 3.1 vs. 3.3 (NS) Patient preferred treatment: 40% vs. 41%	5/11; 3/5
Bodalia, 2003[118] Osteoarthritis	N=134 5 to 8 days	**Tramadol extended-release 150 mg once daily versus tramadol extended-release 200 mg once daily versus tramadol immediate-release 50 mg three times daily (all results reported for first intervention due to carry-over effects)** Median Pain score (0 to 100) prior to morning dose: 33.5 vs. 34.0 vs. 32.5 Median Pain score (0 to 100) following morning dose: 26.1 vs. 27.1 vs. 26.6 Median number of doses of escape medication (acetaminophen): 0.6 vs. 0.5 vs. 0.4 Awakenings from sleep: No differences	5/11; 3/5
Mongin, 2004[107] Osteoarthritis	N=431 12 weeks	**Tramadol extended-release 100-400 mg once daily versus tramadol sustained-release 100-400 mg divided twice daily (percent improvement from baseline to last visit)** WOMAC Pain score: 58% vs. 59% (NS) WOMAC Stiffness score: 49% vs. 49% WOMAC Physical Function score: 52% vs. 50% WOMAC Composite Index: 54% vs. 52% Current pain: 35% vs. 35% Patient global rating "effective" or "very effective": 83% vs. 83%	9/11; 4/5
Raber, 1999[121] Low back pain	N=248 3 weeks	**Tramadol sustained-release 100 mg twice daily versus tramadol immediate-release 50 mg four times daily** Pain relief, improvement in VAS (0 to 100): -25 vs. -25 for per-protocol analysis; ITT results stated as similar but data not reported Functional assessment 'without pain' or 'slight pain possible': >80% in both intervention groups for putting on jacket, putting on shoes, and climbing/descending stairs No awakenings due to low back pain: 41% vs. 47% Global assessment 'good' or 'moderately good': 80% (84/105) vs. 81% (80/99) Global assessment 'good': 47% (49/105) vs. 46% (45/99)	5/11; 3/5
Sorge, 1997[122] Low back pain	N=205 3 weeks	**Tramadol sustained-release 100 mg twice daily versus tramadol immediate-release 50 mg four times daily** Pain relief 'complete', 'good', or 'satisfactory': 88% (52/59) vs. 86% (49/57; results only reported for persons who completed three-week course Pain relief 'complete': 8.5% (5/59) vs. 5.3% (3/57); results only reported for persons who completed three-week course	5/11; 3/5

*Using Cochrane Back Group criteria, maximum score of 11; and Jadad criteria, maximum score of 5

Comparisons between tramadol versus opioids

Three trials found no clear differences in efficacy between tramadol and different opioids (codeine[108], dihydrocodeine[198], or dextropropoxyphene[100]) (Table 13). Only one trial was rated higher-quality[108]. Tramadol appeared associated with higher rates of nausea in two trials (versus dihydrocodeine[198] or dextropropoxyphene[100]), though statistical significance was not reported. On the other hand, tramadol was associated with less constipation than codeine in one trial (11% vs. 21%, p<0.01)[108], but not compared to dextropropoxyphene[100] in another. Data on withdrawals due to adverse events were also mixed, with tramadol associated with more withdrawals than dextropropoxyphene in one trial[100], but no difference between tramadol/acetaminophen and codeine/acetaminophen in a second[108].

Table 13. Head-to-head trials of tramadol versus an opioid

Author, year Underlying condition	Number of patients Duration of follow-up	Main results	Quality*
Jensen, 1994[100] Osteoarthritis	N=264 2 weeks	**Tramadol versus dextropropoxyphene** Mean pain relief (0 to 100): 41 vs. 36 (p=0.12) No intention-to-treat results for other efficacy outcomes Any adverse event: 56% vs. 32% (p not reported) Nausea: 26% vs. 10% (p not reported) Vomiting: 17% vs. 2% (p not reported) Dizziness: 17% vs. 5% (p not reported) Constipation: 8% vs. 8% (p not reported) Withdrawal (overall): 40% (54/135) vs. 16% (20/129) (p not reported) Withdrawal (adverse event): 36% (48/135) vs. 11% (14/129) (p not reported)	6/11; 3/5
Mullican, 2001[108] Osteoarthritis or low back pain	N=462 22 days	Tramadol/acetaminophen vs. codeine/acetaminophen Overall efficacy (1 to 5 scale): 2.9 vs. 2.8 Maximum pain relief (0 to 4): 2.5 vs. 2.4 Constipation: 11% vs. 21% (p<0.01) Somnolence: 17% vs. 24% (p=0.05) Withdrawal (overall): 20% (61/309) vs. 21% (21/153) Withdrawal (adverse events): 12% (37/309) vs. 14% (21/153)	7/11; 4/5
Wilder-Smith, 2001[198] Osteoarthritis	N=57 1 month	**Sustained-release tramadol versus sustained-release dihydrocodeine** Pain intensity at rest at 4 weeks (median, 0 to 4 scale): 0 vs. 1 (p=0.04) Pain intensity with movement at 4 weeks (median, 0 to 4 scale): 1 vs. 1 (NS) Number of bowel movements: No changes Quality of sleep: Results poorly reported Global ratings: Median "excellent" for both drugs Nausea/vomiting: 25% vs. 14% (p not reported) Dizziness: 21% vs. 14% (p not reported) Drowsiness: 54% vs. 28% (p not reported) Headache: 29% vs. 10% (p not reported) Withdrawal (adverse event): Not reported	3/11; 1/5

*Using Cochrane Back Group criteria, maximum score of 11; and Jadad criteria, maximum score of 5

Summary of evidence

- There is insufficient evidence from eight head-to-head trials (three higher-quality) and three observational studies to conclude that any long-acting opioid (sustained-release formulation or transdermal fentanyl) is more beneficial or less harmful than others. Specific drug comparisons were evaluated in one to three trials (level of evidence: moderate).
- Seven trials (two higher-quality) found no clear differences in benefits or harms between sustained- and immediate-release opioids (level of evidence: high).
- Six trials (three higher-quality) found no clear differences in benefits or harms between extended-release, sustained-release, and immediate release tramadol (level of evidence: high).
- Three trials (one higher-quality) found no clear difference in efficacy between tramadol and different opioids. Evidence on differences in harms was inconclusive (for nausea) or inconsistent (for constipation and withdrawals due to adverse events) (level of evidence: moderate).

Key Question 8

Do the comparative benefits and harms of opioids vary in subpopulations defined by demographics (e.g. age, gender, race), specific underlying pain conditions, or co-morbidities (e.g. liver disease, renal disease, respiratory disease, heart disease, HIV, drug misuse, cancer survivors)?

Results of search: systematic reviews

We identified three systematic reviews on benefits[79, 81, 83] or harms[83] of opioids in patients with different underlying pain conditions. We identified no systematic reviews that evaluated efficacy or harms in subpopulations of patients defined by demographics or co-morbidities.

Results of search: primary studies

We identified no relevant randomized trials or controlled observational studies on comparative effectiveness and safety of opioids in different subpopulations of patients with chronic noncancer pain. Nearly all randomized trials excluded patients with significant co-morbidities, including prior or current substance abuse[79]. We excluded one uncontrolled, prospective study of patients with intractable headaches started on opioid therapy and followed for at least three years[211].

Findings

The three systematic reviews on benefits and harms of opioids in patients with different types of underlying pain are summarized in Key Questions 1a and 1b.

One uncontrolled, prospective study found that less than half of patients (70 of 160) started on daily opioids for headache remained on treatment after 3 to 8 years[211]. Twenty-six percent of patients originally started on opioids reported at least 50% improvement in symptoms with

opioids. Among patients that remained on opioids, about 50% had at least one episode of 'problem drug behavior' defined as dose violations, lost prescriptions, obtaining medications from multiple sources.

Summary of evidence

- In indirect comparisons from multiple trials, differences in the type of chronic noncancer pain did not appear to be a useful clinical characteristic for predicting effectiveness of opioids for chronic noncancer pain (see Key Question 1a). There is insufficient evidence from indirect comparisons to conclude that different types of chronic noncancer pain are associated with different risks for short-term, common adverse events (see Key Question 1b) (level of evidence: low to moderate).
- There is insufficient evidence (no studies) to judge benefits or harms of opioids in subpopulations defined by demographic variables or co-morbidities.

Key Question 9

How effective are different strategies for minimizing or treating opioid-related adverse events?

About half of patients randomized to opioids in clinical trials experience at least one adverse event, and about 22% withdraw due to adverse events[83]. The most common adverse events include dry mouth, nausea, constipation, and drowsiness.

Results of search: systematic reviews

We identified no relevant systematic reviews that met inclusion criteria. We excluded one systematic review that evaluated efficacy of cyclo-oxygenase-2-selective non-steroidal anti-inflammatory drugs (NSAIDs) for reducing opioid-related adverse events because it only evaluated patients in post-surgical settings[212] and two systematic reviews of opioid antagonists for treatment of opioid-induced bowel dysfunction because they only included studies of healthy volunteers, persons undergoing surgery, or terminally ill patients[213, 214]. We also excluded one other report of strategies to reduce adverse events associated with oral morphine because it focused on patients with cancer and did not describe use of systematic review methods[215]. Opioid rotation is addressed in Key Question 15.

Results of search: primary studies

We identified two randomized trials[109, 116] of alvimopan (an oral, peripherally acting μ-receptor antagonist) for treatment of opioid-induced bowel dysfunction and one randomized trial[115] of ultralow-dose oral naltrexone (in combination with oxycodone) for prevention of physical dependence (see glossary) and opioid-associated adverse events. We excluded seven trials (six randomized and one non-randomized) of naloxone or methylnaltrexone for treatment of opioid-induced constipation in patients with cancer or other advanced illness[216-220] or patients enrolled in a methadone maintenance program[221, 222]. We identified no prospective studies on

strategies for minimizing or treating other opioid-induced adverse events, including nausea/vomiting, sedation, and pruritus.

Findings

One short-term (3 weeks) trial (N=168) found alvimopan 1 or 0.5 mg/day associated with a greater likelihood of a bowel movement within eight hours compared to placebo (54% and 43% vs. 29%, p<0.001)[109] (Table 14). The alvimopan 1 mg/day dose was also associated with a greater number of weekly bowel movements compared to placebo after 1 (8.4 vs. 5.5) and 2 weeks (6.9 vs. 5.0), but there was no significant difference at 3 weeks (6.4 vs. 5.5). There was no difference in laxative use or pain scores. Alvimopan 1 mg/day was associated with a trend towards increased adverse events compared to placebo (48% vs. 33% reporting at least one adverse event), primarily related to gastrointestinal adverse events (nausea, diarrhea, vomiting).

The second trial (N=522) found alvimopan 0.5 mg bid, 1 mg once daily, and 1 mg bid all associated with an increased number of weekly spontaneous bowel movements (+1.71, +1.64, and +2.52, respectively; p<0.05 for all results versus placebo) after six weeks, with no changes in pain scores[116]. Alvimopan was also associated with decreased laxative use at all doses. Effects on opioid-induced bowel dysfunction-related symptoms and constipation-related quality of life scores generally favored alvimopan at all doses, but were not always statistically significant. There was no difference in incidence of any adverse events, withdrawals due to adverse events, or serious adverse events. However, there appeared to be a dose-related trend in risk of abdominal pain (15% in placebo vs. 28% with 1 mg bid) and diarrhea (5% vs. 14%).

Table 14. Trials of medications for treatment of opioid-induced bowel dysfunction

Author, year	Number of patients Duration of follow-up	Main results	Quality*
Paulson, 2005[109]	N=168 3 weeks	**Alvimopan 1 mg qD versus alvimopan 0.5 mg qD versus placebo** Average proportion reporting a bowel movement within 8 hours of study drug administration: 54% (p<0.001 vs. placebo) vs. 43% (p<0.001 vs. placebo) vs. 29% Number of weekly bowel movements: 4.7 vs. 4.1 (p<0.01 vs. placebo) vs. 5.0 Proportion reporting "improved" during treatment: 70% (p=0.046 vs. placebo) vs. 58% (p=0.04 vs. placebo) vs. 50% Proportion reporting "improved" during follow-up: 11% vs. 18% vs. 22% (NS) Laxative use: No change Pain scores: No change	10/11; 4/5
Webster, 2006[115]	N=719 18 weeks intervention, 3 days following study medication discontinuation	**Oxycodone 20 mg + naltrexone 0.001 mg qid vs. oxycodone 40 mg + naltrexone 0.001 mg bid vs. oxycodone 20 mg qid vs. placebo** Mean Short Opiate Withdrawal Scale score (day 1): 2.3 vs. 1.2 vs. 2.7 vs. -0.1 (p<0.05 for naltrexone bid vs. oxycodone alone) Mean number of moderate to severe opioid-related adverse events during treatment: Constipation: 0.55 vs. 0.40 vs. 0.71 vs. 0.28 (p<0.05 for naltrexone bid vs. oxycodone alone) Dizziness: 0.32 vs. 0.35 vs. 0.37 vs. 0.13 (p>0.05 for all comparisons) Somnolence: 0.61 vs. 0.56 vs. 0.83 vs. 0.50 (p<0.05 for naltrexone bid vs. oxycodone alone) Pruritus: 0.28 vs. 0.25 vs. 0.51 vs. 0.05 (p<0.05 for naltrexone qid and naltrexone bid vs. oxycodone alone) Nausea: 0.53 vs. 0.52 vs. 0.60 vs. 0.21 (p>0.05 for all comparisons) Vomiting: 0.19 vs. 0.22 vs. 0.23 vs. 0.09 (p>0.05 for all comparisons)	6/11; 4/5
Webster, 2008[116]	N=522 6 weeks	**Alvimopan 1 mg bid vs. 1 mg qD vs. 0.5 mg bid vs. placebo** Spontaneous bowel movements per week: 2.52 (95% CI 1.40-3.64) vs. 1.64 (95% CI 0.88 to 2.40) vs. 1.71 (95% CI 0.83 to 2.58) (p<0.05 for all doses versus placebo) Proportion with >3 spontaneous bowel movements per week: 68% vs. 63% vs. 63% vs. 39% (p<0.001 for all doses versus placebo) Opioid-induced bowel dysfunction global improvement (at least moderately improved): 42% vs. 40% vs. 39% vs. 14% (p<0.03 for all doses versus placebo) Rescue laxative use (tablets per week compared to placebo): -0.78 vs. -1.28 vs. -1.12 (p=0.01 for all doses)	7/11; 4/5

*Using Cochrane Back Group criteria, maximum score of 11; and Jadad criteria, maximum score of 5

Alvimopan has not been approved for use in patients with chronic pain by the U.S. Food and Drug Administration, in part because of unpublished results from a longer-term (12 month) trial that reported a trend towards increased risk of myocardial infarctions[223]. Most myocardial infarctions occurred after one to four months of treatment. In the short-term trials, one myocardial infarction and one case of angina were reported in the larger (N=522) study[116].

One higher-quality randomized trial found the combination of oxycodone plus ultralow-dose naltrexone (0.001 mg in each dose) twice daily, but not four times daily, superior to similar doses of oxycodone alone four times daily for withdrawal symptoms after an 18 week course of therapy[115]. However, differences on the Short Opiate Withdrawal Scale appeared small (on the order of 1.5 points on a 30 point scale). During treatment, oxycodone plus ultralow-dose naltrexone twice daily was associated with fewer moderate-to-severe constipation, somnolence, and pruritus events compared to oxycodone alone four times daily, but differences also appeared small (around 0.25 average number of events for all outcomes). There were no differences in pain relief or measures of function. Results of this trial are difficult to interpret because differences between oxycodone four times daily and oxycodone plus ultralow-dose naltrexone twice daily could be related to dosing frequency, rather than to effects of naltrexone. In addition, although this trial met pre-defined criteria for a higher-quality study, results may be seriously compromised because less than 50% of enrolled patients were analyzed on the main outcome (withdrawal symptoms). The combination of oxycodone plus ultralow-dose naltrexone is not yet available in the U.S.

Summary of evidence

- Alvimopan was more effective than placebo for inducing bowel movements in patients with opioid-induced constipation in two higher-quality, short-term trials (level of evidence: fair). Alvimopan is not approved by the U.S. Food and Drug Administration for use in patients with chronic pain, in part because of an increased risk of cardiovascular events observed in a longer-term, unpublished trial.
- The combination of oxycodone plus ultra-low dose naltrexone was associated with fewer withdrawal symptoms, constipation, somnolence, and pruritus compared to oxycodone alone in one higher-quality trial, but differences appear small and results are difficult to interpret because of differences between interventions in dosing frequency and very high loss to follow-up (level of evidence: low). Oxycodone plus ultra-low-dose naltrexone is not approved by the U.S. Food and Drug Administration for treatment of opioid-induced bowel dysfunction.
- There is insufficient evidence to evaluate efficacy of other strategies for minimizing or treating opioid-induced constipation or other opioid-related adverse events in patients with chronic noncancer pain, though oral naloxone, subcutaneous methylnaltrexone, and oral methylnaltrexone have been evaluated in patients with cancer or other advanced illness and persons on opioid maintenance for management of addiction. Opioid rotation is addressed in Key Question 15.

Key Question 10

How does initial or chronic use of opioids impact driving or work safety?

Opioids are associated with adverse events such as sedation and dizziness that could potentially impact driving or work safety[83]. However, some studies suggest that opioids do not necessarily impair or may improve psychomotor and cognitive functioning in patients on opioids for chronic noncancer pain[224-227].

Results of search: systematic reviews

We identified two systematic reviews on effects of opioids on driving safety in mixed populations[86, 87]. We identified no systematic reviews on effects of opioids on work safety.

Results of search: primary studies

We identified four prospective cohort studies[228-231] and one before-after study[232] on effects of opioids on driving safety. We identified no studies on effects of opioids on outcomes related to work safety (such as work-related injuries).

Findings

One systematic review (25 studies) found no clear evidence that opioids are associated with intoxicated driving, motor vehicle accidents, or motor vehicle accident fatalities[86]. Most of the evidence included in this systematic review consisted of large, cross-sectional descriptive epidemiologic studies that reported the proportion of sampled patients with an adverse outcome associated with driving in whom opioids were identified. There was no information from most studies regarding duration of opioid use and whether opioids were used illicitly, prescribed for chronic pain, or for opioid maintenance treatment. The systematic review also included four controlled studies that evaluated driving safety in heroin users and patients enrolled in methadone maintenance programs. No study specifically evaluated patients on opioids for chronic noncancer pain. The systematic review based most of its conclusions on comparisons of estimates of opioid use from studies of intoxicated drivers or drivers involved in motor vehicle accidents and fatalities relative to estimates of opioid use from epidemiologic studies in the general population.

A second systematic review (48 studies) found consistent evidence for no driving impairment as measured by driving simulators or in road driving tests in opioid-maintained patients (3 studies) and no greater incidence of motor vehicle violations or motor vehicle accidents in opioid-maintained patients versus comparable controls (4 studies)[87]. It also found consistent evidence for no impairment of psychomotor abilities in opioid-maintained patients or immediately after a dose of opioids. Two of the three studies of driving simulators or road driving tests evaluated patients with chronic noncancer pain.

Four other prospective studies evaluated driving tests in patients prescribed opioids for chronic noncancer pain compared to healthy volunteers[228, 229, 231], chronic pain patients not taking opioids[228], or cognitively impaired patients who had undergone rehabilitation[230] (Table 15). In three studies, there were no clear differences in driving test results between patients on opioids for chronic noncancer pain and healthy volunteers or chronic pain patients not taking opioids[228, 229, 231]. In one study, patients prescribed opioids for chronic noncancer pain performed better than cognitively impaired patients who passed their driving test[230]. A fifth, before-after study found no differences in driving performance after adding transdermal fentanyl to up to 15 mg/day of chronic oxycodone (or equivalent)[232].

Table 15. Controlled studies in driving safety in patients on opioids for chronic noncancer pain

Author, year	Number of patients on opioids for chronic noncancer pain Control(s)	Main results	Type of study
Byas-Smith, 2005[228]	21 Chronic pain, no opioid No chronic pain, no opioid	**Chronic pain and on opioid (A) vs. chronic pain, no opioid (B) vs. no chronic pain, no opioid (C)** Community Drive Test, Obstacle Course, and Test of Variables of Attention: No differences Digit Symbol Substitution Test: C superior to A on Digit Symbol Substitution Test (59.66 vs. 48.13, p<0.05), but no difference between A and B (48.13 vs. 49.82)	Cohort
Gaertner, 2006[229]	30 Healthy volunteers	**Chronic pain and on opioid vs. healthy volunteers** Number of passed tests (primary outcome, out of 5): 4.0 vs. 4.1 (p=0.18) Proportion passing all 5 tests: 37% vs. 56% (p=NS)	Cohort
Galski, 2000[230]	16 Cognitively impaired patients who passed driving test	**Chronic pain on opioid (A) vs. cognitively impaired patients (B)** A superior to B on WAIS-R Digit Symbol Scaled Score, Rey Complex Figure Test-Time to Copy, Threat Recognition Braking % Valid, Following Directions. No other differences between A and B on pre-driver evaluation, simulator evaluation, or behaviors	Cohort
Menefee, 2004[232]	23 Before starting transdermal fentanyl	**Before vs. after starting treatment with transdermal** Driving simulator: No differences Cognitive performance: Improved on some measures, no measures worsened. Balance: No differences	Before-after
Sabatowski, 2003[231]	30 Healthy volunteers	**Chronic pain on opioid vs. healthy volunteers** Sum score of Z-transformed German driving tests: 0.60 vs. -0.20, p=0.38 for non-inferiority test (0.19 for superiority test) Percentage of passed tests (60% vs. 74% (p=0.22)	Cohort

Interpretation of these results is a challenge because in all studies it was unclear how patients on opioids were selected for inclusion. Patients who volunteered for enrollment or presented for driving tests may have been more likely to perform well and may not be representative of the general population of patients with chronic noncancer pain who are on opioids. In addition, it is not clear in any of the studies if outcomes assessors were blinded to opioid use status. Finally, results of driving tests and simulators may not correlate precisely with actual driving safety as measured by motor vehicle accidents, traffic fatalities, or other outcomes. However, we identified no prospective or controlled studies of chronic pain patients evaluating such outcomes.

Summary of evidence

- There is insufficient evidence to conclude that use of chronic opioids impairs driving safety. Limitations of the evidence include a reliance on cross-study comparisons to interpret epidemiologic studies, use of simulated and other controlled driving tests that may not completely reflect real-world driving condition, and probable selection bias (level of evidence: low).

- There is insufficient evidence to judge effects of opioids on work safety (no evidence).

Key Question 11

What are the benefits and harms of different methods for initiating and titrating opioids for chronic noncancer pain?

Results of search: systematic reviews

We identified no relevant systematic reviews that met inclusion criteria.

Results of search: primary studies

We identified two randomized trials that evaluated different methods for initiating tramadol for chronic noncancer pain[110, 112]. Two other trials compared sustained-release versus immediate-release opioids for titrating patients to stable pain control[207, 209].

Findings

One higher-quality trial (N=465) found slower rates of dose titration of tramadol (target dose 200 mg/day) associated with fewer withdrawals due to adverse events compared to faster dose titration (31% vs. 24% vs. 15% for 10-days, 4-days, and 1-day titration, respectively [p<0.001 for trend])[112] (Table 16). A second higher-quality trial (N=163) found 13- and 16-day dose titration schedules associated with fewer withdrawals due to adverse events compared to dose titration over 10 days (30% vs. 34% vs. 54%)[110]. Target doses for the 10- and 16-day titrations were 200 mg/day and for the 13-day titration 150 mg/day. In both trials, there were no differences in outcomes related to efficacy (withdrawals due to lack of efficacy, pain scores, or patient ratings).

One lower-quality trial found no difference between dose titration with sustained-release versus immediate-release oxycodone in the time to stable pain control or the proportion of patients who achieved stable analgesia (84% of subjects were previously on opioids)[209]. A second lower-quality trial found titrated doses of sustained-release morphine plus immediate-release oxycodone slightly superior (around 5 points on a 100 point scale) to fixed-dose, immediate-release oxycodone for pain intensity, but found no differences in measures of function, sleep, and psychologic distress[207]. Results of this trial are difficult to interpret because maximum doses of opioids varied in the two arms (up to 200 mg/day equivalent of morphine in titrated dose arm, versus up to 20 mg/day in the fixed-dose oxycodone arm), and average doses of opioids were not reported.

Table 16. Trials of different methods for initiating and titrating opioids

Author, year	Number of patients Duration of follow-up	Main results	Quality*
Jamison, 1998[207]	N=36 16 weeks	**Sustained-release morphine + short acting oxycodone + naproxen (maximum 200 mg/day morphine equivalent) vs. immediate-release oxycodone + naproxen (maximum 20 mg/day oxycodone) vs. naproxen** Average pain (means, 0-100 VAS): 54.9 vs. 59.8 vs. 65.5 Current pain (means, 0-100 VAS): 51.3 vs. 55.3 vs. 62.7 Highest pain (means, 0-100 VAS): 71.4 vs. 75.5 vs. 78.9 Anxiety (means): 11.2 vs. 15.0 vs. 31.6 Depression (means): 10.8 vs. 16.4 vs. 26.9 Irritability (means): 17.7 vs. 20.5 vs. 33.7 Level of activity (means, 0-100 scale): 49.3 vs. 49.3 vs. 51.5 Hours of sleep (means): 5.9 vs. 5.9 vs. 6.1	3/11; 2/5
Petrone, 1999[110]	N=163 28 days	**Tramadol 10 days to 200 mg/day versus 16 days to 200 mg/day versus 13 days to 150 mg/day** Pain intensity (improvement from baseline, 0 to 10 scale): -1.4 vs. -1.5 vs. -1.6 Patient rated study medication as very good or good: 63% vs. 67% vs. 61% Withdrawal (lack of efficacy): 2% (1/56) vs. 3% (2/59) vs. 0% (0/54) Withdrawal due to adverse events: 54% (29/54) vs. 34% (20/59) vs. 30% (16/54) ($p \leq 0.008$ for 16 or 13 day versus 10 day titration)	7/11; 3/5
Ruoff, 1999[112]	N=465 14 days	**Tramadol 1 day to 200 mg/day versus 4 days to 200 mg/day versus 10 days to 200 mg/day versus placebo** Withdrawal (lack of efficacy): 0.8% (1/130) vs. 1.6% (2/129) vs. 1.5% (2/132) vs. 0% (0/69) Withdrawal (adverse events): 31% (40/130) vs. 24% (31/129) vs. 15% (20/132) vs. 4% (3/68) ($p<0.001$ for trend)	8/11; 5/5
Salzman, 1999[209]	N=57 10 days	**Sustained-release oxycodone vs. immediate-release oxycodone** Mean decrease in pain intensity (0 to 3 scale): 1.1 vs. 1.3 (NS) Proportion achieving stable analgesia: 87% (26/30) vs. 96% (26/27) ($p = 0.36$) Time to stable pain control: 2.7 vs. 3.0 days ($p = 0.90$) Mean number of dose adjustments: 1.1 vs. 1.7 adjustments ($p = 0.58$)	3/11; 2/5

*Using Cochrane Back Group criteria, maximum score of 11; and Jadad criteria, maximum score of 5

Summary of evidence

- Slower dose titration schedules of tramadol were associated with fewer withdrawals due to adverse events in two higher-quality trials (level of evidence: moderate).
- There is insufficient evidence from two lower-quality trials to accurately judge benefits and harms of methods for initiating and titrating opioids (level of evidence: low).

Key Question 12

What are the benefits and harms of round-the-clock versus as needed dosing of opioids, or round-the-clock with as needed dosing versus as needed dosing alone for chronic noncancer pain?

Round-the-clock dosing of opioids is recommended over as needed dosing in several guidelines[16-19]. Proposed advantages of round-the-clock dosing include an increase in the consistency of pain relief, reduction in pain related behaviors, and decrease in the risk of addiction or tolerance.

Results of search: systematic reviews

We identified no systematic reviews that evaluated around-the-clock versus as needed dosing of opioids that met inclusion criteria.

Results of search: primary studies

We identified one trial of around-the-clock dosing of codeine versus as needed dosing[119] and one trial of scheduled extended-release tramadol versus as-needed, immediate-release tramadol[197].

Findings

One higher-quality trial found scheduled extended-release (once-daily) tramadol to be more effective than as-needed, immediate-release (every four to six hours) tramadol for pain intensity (Table 17)[197]. However, differences on pain intensity did not reach statistical significance (less than 5 mm on a 100 point pain scale), there were no differences on other outcomes, and there were more withdrawals due to adverse events in the scheduled-dose arm. One lower-quality trial found no clear difference between round-the-clock, sustained-release codeine (with acetaminophen as rescue medication) and as needed, immediate-release codeine plus acetaminophen in average pain intensity after five days, though round-the-clock dosing was associated with fewer fluctuations in pain intensity[119]. Interpretation of both trials is a challenge because the interventions varied on factors other than whether the opioid was dosed round-the-clock or as needed, including use of a sustained-release versus immediate-release preparation, higher mean doses in the round-the-clock arm (200 versus 71 mg/day of codeine and 281 vs. 154 mg/day of tramadol), and differential doses of acetaminophen.

Table 17. Trial of round-the-clock versus as needed dosing of opioids

Author, year	Number of patients Duration of follow-up	Main results	Quality*
Beaulieu, 2007[197] Mixed chronic noncancer pain	N=122 2 weeks each intervention (crossover)	**Tramadol extended-release (once daily) scheduled versus tramadol immediate-release (q4 to 6 hours) as-needed** Mean pain intensity week 4 (VAS 0 to 100): 33.4 vs. 37.4 (p<0.007) Mean pain intensity week 4 (ordinal 0 to 4): 1.52 vs. 1.69 Pain and Disability Index: No differences Pain and Sleep score (composite): No differences Patient global rating (1 to 7): 3.1 vs. 3.3 (NS) Patient preferred treatment: 40% vs. 41%	5/11; 3/5
Hale, 1997[119]	N=104 5 days	**Sustained-release codeine + acetaminophen (round-the-clock) vs. immediate-release codeine/acetaminophen (as needed)** Mean pain intensity, improvement from baseline to day 5 (0 to 3 scale): 0.8 vs. 0.5 (estimated from Fig. 1, p not reported) Number of fluctuations in pain intensity ratings: 6.1 vs. 8.6 (p=0.011) Rescue medication use at night: 0.7 vs. 0.9 (p=NS) Rescue medication use during day: 1.0 vs. 1.5 (p=0.018) Acceptability Overnight: 1.97 vs. 1.61 (p=0.13) Acceptability During Daytime: 2.12 vs. 1.84 (p=0.32)	5/11; 3/5

*Using Cochrane Back Group criteria, maximum score of 11; and Jadad criteria, maximum score of 5

Summary of evidence

- Two trials (one higher-quality and one lower-quality) found no clear differences between scheduled dosing of sustained-release opioids versus as-needed dosing of immediate-release opioids, but results are difficult to interpret because of other differences between interventions, including higher doses in the scheduled dose arms (level of evidence: low).

Key Question 13

What are the benefits and harms of regular intramuscular, subcutaneous, intranasal, buccal, or rectal versus oral or transdermal administration of opioids for chronic noncancer pain?

Opioids can be administered using a variety of routes. Some guidelines specifically recommend against use of intramuscular opioids for noncancer pain[17], or recommend use of injectable opioids only in very limited circumstances and with pain specialist consultation[16]. Other routes of administration are not specifically addressed in published guidelines.

Results of search: systematic reviews

We identified no relevant systematic reviews that met inclusion criteria.

Results of search: primary studies

We identified no randomized trials or controlled observational studies on regular intramuscular, subcutaneous, intranasal, buccal, or rectal versus oral or transdermal administration of opioids in patients with chronic noncancer pain that met inclusion criteria. We excluded five trials on different routes of administration in patients with cancer pain[233-237].

Findings

No studies met inclusion criteria. However, there is some potentially relevant evidence from trials of patients with cancer pain. Two trials found intramuscular administration of methadone or pentazocine associated with no advantages over oral administration[234, 235]. Three trials of patients with cancer pain found no clear differences between rectal and oral administration of morphine[233, 236], other than faster onset of pain relief with rectal morphine in one of the trials[236]. Another trial found no differences between oral and rectal administration of tramadol[237].

Summary of evidence

- No trials directly compared regular intramuscular, subcutaneous, intranasal, buccal, or rectal versus oral or transdermal administration of opioids in patients with chronic noncancer pain. Trials of patients with cancer pain suggest no advantages of intramuscular over oral administration of opioids, and similar efficacy between oral and rectal routes.

Key Question 14

What are the comparative benefits of different strategies for treating acute exacerbations of pain or a new acute pain problem in patients on chronic opioids for chronic noncancer pain?

Acute exacerbations of pain, or breakthrough pain, are common in patients on opioids with controlled baseline pain[238-240]. Patients on chronic opioids for chronic noncancer pain may also develop a new acute pain problem.

Results of search: systematic review

We identified no relevant systematic reviews that met inclusion criteria.

Results of search: primary studies

We identified three higher-quality randomized, placebo-controlled trials on buccal fentanyl[111, 113] or intranasal ketamine[92] for breakthrough pain in patients prescribed opioids for chronic noncancer pain. We excluded one observational study[239] and two randomized trials on strategies for treating breakthrough pain in patients with cancer[241, 242], and one small (N=15), uncontrolled, prospective observational study that evaluated a protocol for managing acute exacerbations of chronic noncancer pain in the emergency department[243]. We excluded a low-quality, placebo-controlled trial of round-the-clock, sustained-release oxycodone for chronic neck pain with frequent acute flares (see Key Questions 4 and 5)[161].

Findings

Two randomized trials (N=77 and 79) found buccal fentanyl tablets to be superior to placebo for treating episodes of breakthrough pain in patients with chronic low back pain[111] or chronic neuropathic pain[113] over a three-week period. For chronic low back pain, a larger proportion of patients randomized to buccal fentanyl tablets experienced >50% pain relief versus placebo from thirty minutes through two hours after treatment (two hour data 48% vs.16%, p<0.0001)[111]. For neuropathic pain, one trial found buccal fentanyl to be superior to placebo for ≥50% relief of breakthrough pain at 15 minutes through 2 hours after treatment (15 minutes data 12% vs. 5%, p<0.0001)[113]. Three out of 156 subjects in the two trials withdrew due to adverse events. Use of a run-in period in both trials may limit generalizability of findings to patients not previously exposed to buccal fentanyl, as about one-quarter of patients were excluded during an open-label run-in period due to lack of efficacy or adverse events.

A crossover randomized trial (N=20) of patients with chronic pain (4 cancer, 16 noncancer) and frequent (two to seven) daily episodes of breakthrough pain found intranasal ketamine more effective than placebo for achieving >40% pain relief (45% vs. 5%, p=0.008)[92] (Table 18). Half of the patients reported dissociative symptoms such as fatigue, dizziness, feeling of unreality, changes in vision, or nausea following treatment with ketamine, though no serious adverse events or withdrawals due to adverse events were reported.

Table 18. Trials of strategies for treatment of acute exacerbations of pain in patients on chronic opioid therapy

Author, year Medication	Number of patients Duration of follow-up	Main results	Quality*
Carr, 2004[92] Intranasal ketamine	N=22 2 breakthrough pain episodes	**Intranasal ketamine vs. placebo** Reduction in pain score (>40%): 45% (9/20) vs. 5% (1/20) (p=0.0078) Pain score <2.2 (0 to 10 scale): 55% (11/20) vs. 10% (2/10) Mean reduction in pain score (0 to 10): -2.65 vs. -0.81 (p<0.0001)	9/11; 5/5
Portenoy, 2007[111] Buccal fentanyl	N=77 3 weeks	**Buccal fentanyl vs. placebo** Proportion of breakthrough pain episodes with ≥50% reduction in pain intensity after 30 minutes: 30% (122/413) vs. 13% (27/207) (p≤0.0001) ≥50% reduction in pain intensity after 120 minutes: 48% (198/413) vs. 16% (33/207) (p≤0.0001)	9/11; 5/5
Simpson, 2007[113] Buccal fentanyl	N=79 3 weeks	**Buccal fentanyl vs. placebo** Proportion of breakthrough pain episodes with 'meaningful' pain reduction: 69% vs. 36% (p<0.0001) Proportion of breakthrough pain episodes with ≥50% reduction in pain intensity after 15 minutes: 12% vs. 5% (p≤0.0001), p<0.0001 for each subsequent time point from 30 to 120 minutes Use of supplemental medication: 14% (59/432) vs. 36% (77/213) (OR=0.28, 95% CI 0.18 to 0.42)	9/11; 5/5

*Using Cochrane Back Group criteria, maximum score of 11; and Jadad criteria, maximum score of 5

None of the three trials were designed to evaluate long-term benefits or harms. The trial of intranasal ketamine evaluated two breakthrough pain episodes[92] and the trials of buccal fentanyl[111, 113] evaluated up to nine breakthrough pain episodes over a three-week period.

Summary of evidence

- Short-term use of buccal fentanyl is substantially more effective than placebo for treatment of breakthrough pain episodes in patients already on opioids for chronic low back pain or chronic neuropathic pain (2 higher-quality trials), though evidence on longer-term use is not available and use of an open-label run-in period may limit generalizability of results (level of evidence: moderate).
- Short-term use of intranasal ketamine is more effective than placebo for treatment of breakthrough pain episodes in patients on opioids for chronic pain (1 small [N=22], higher-quality trial), though adverse events were common and evidence on longer-term use is not available (level of evidence: low).
- There are no trials on use of short-acting or as-needed opioids other than buccal fentanyl for treatment of breakthrough pain in patients already on opioids for chronic noncancer pain.

Key Question 15

What are the benefits and harms of opioid rotation versus continued treatment or dose escalation with the same opioid in patients with chronic noncancer pain?

Patients may vary substantially in the amount of pain relief or adverse events they experience with different opioids[244]. In addition, patients on one opioid may develop incomplete cross-tolerance towards other opioids. Opioid rotation or opioid switching refers to the practice of changing opioids in order to improve analgesia or reduce side effects[245].

Results of search: systematic reviews

We identified no systematic reviews on benefits and harms of opioid rotation or switching in patients with chronic noncancer pain. Two systematic reviews were excluded because they exclusively[246] or almost exclusively (51 of 52 trials)[247] focused on patients with cancer pain. Neither systematic review included any relevant randomized trial.

Results of search: primary studies

We identified no randomized trials or controlled observational studies on opioid rotation versus continued treatment or dose escalation with the same opioid in patients with chronic noncancer pain. We identified three reports from two small prospective studies[248-250] and three retrospective studies on outcomes following opioid rotation or switching in patients with chronic noncancer pain[251-253]. We excluded one study on opioid switching between methadone and morphine in patients on maintenance treatment for opioid dependence[254].

Findings

Both prospective studies used a before-after design[249, 250]. One study (N=42) of patients with primarily (64%) musculoskeletal pain and inadequate pain relief or intolerable side effects on morphine at ≥120 mg/day found that 76% of patients reported good or very good pain relief after switching to a transdermal buprenorphine patch, compared to 5% before the switch[250]. Although 12% of patients switched to transdermal buprenorphine experienced local irritation at the patch site, no serious adverse events or adverse events that resulted in withdrawal of buprenorphine occurred. The other, smaller (N=12) prospective study found that 7 of 12 patients with chronic noncancer pain switched from oral morphine to methadone preferred methadone after 9 months[249]. However, four patients had switched back to oral morphine. In addition, one patient experienced sedation during initiation of methadone that required naloxone. In this same population, eight patients experienced small but statistically significant increases in corrected QT intervals during initiation of methadone (0.416 to 0.436 seconds, p=0.01), though no arrhythmias or clinically significant cardiac events were reported[248].

Three retrospective studies found opioid rotation successful in the majority of patients with chronic noncancer pain[251-253]. However, one of the studies found that most patients required multiple switches before experiencing improved analgesia[253]. In addition, symptoms of withdrawal and overdose were frequent during rotation. In the two largest studies (N=97 and N=86), the first rotation was deemed effective in 36% to 73% of patients[252, 253].

Summary of evidence

- We identified no randomized trials or controlled observational studies on effectiveness or safety of opioid rotation versus continued treatment or dose escalation with the current opioid that met inclusion criteria.
- There is insufficient evidence from two small, uncontrolled prospective studies and uncontrolled retrospective studies to accurately assess benefits and harms of opioid rotation in patients with chronic noncancer pain (level of evidence: low).

Key Question 16

What are the benefits and harms of different methods for switching patients on opioids for chronic noncancer pain from one opioid to another?

Equianalgesic dose tables for various opioids are primarily based on single dose studies in patients with limited previous exposure to opioids[255]. It is uncertain how applicable such data are to patients with long-term exposure to opioids for chronic noncancer pain.

Results of search: systematic reviews and primary studies

We identified no systematic reviews or primary studies on benefits and harms of different methods for switching patients on opioids for chronic noncancer pain from one opioid to another that met inclusion criteria.

Summary of evidence

- There is insufficient evidence (no studies that met inclusion criteria) to determine benefits and harms of different methods of switching patients on opioids for chronic noncancer pain from one opioid to another.

Key Question 17

How accurate are patient characteristics or features for predicting lack of response to high doses of opioids for chronic noncancer pain?

Patients with chronic noncancer pain may not experience improvements in pain or function even on higher doses of opioids[21]. Evidence on patient characteristics or features useful for predicting lack of response to higher doses of opioids could help guide decisions that result in avoidance of unnecessary exposure to progressive dose escalations.

Results of search: systematic reviews and primary studies

We identified no systematic reviews or primary studies on accuracy of patient characteristics or features for predicting lack of response to higher doses of opioids for chronic noncancer pain that met inclusion criteria.

Summary of evidence

- There is insufficient evidence (no studies that met inclusion criteria) to determine accuracy of patient characteristics or features for predicting lack of response to higher doses of opioids.

Key Question 18

How do dose-related responses for opioids change at different dose ranges or with long-term use?

Dose-related responses to opioids may vary at different doses or with long-term use due to the development of tolerance.

Results of search: systematic reviews and primary studies

We identified no systematic reviews, randomized trials, or controlled observational studies evaluating differences in dose-related responses to opioids at varying dose ranges or with long-term use that met inclusion criteria.

Summary of evidence

- There is insufficient evidence (no studies that met inclusion criteria) to determine if dose-related responses for opioids change at different dose ranges or with long-term use.

Key Question 19

What are the benefits and harms of high (>200 mg/day of morphine or equivalent) versus lower doses of opioids for chronic noncancer pain?

Previous guidelines for treatment of cancer and noncancer pain suggested no pre-defined maximum or ceiling dose for opioids, and noted that some patients require very high doses to achieve adequate symptom relief[16, 19, 256]. However, higher doses of opioids (defined in this report as >200 mg/day of morphine or equivalent) may be associated with a less favorable balance of benefits to risks compared to lower doses, particularly in patients with chronic noncancer pain[21].

Results of search: systematic reviews and primary studies

We identified no systematic reviews, randomized trials, or controlled observational studies on outcomes associated with dose escalation above 200 mg/day of morphine (or equivalent) versus maintaining the current dose, switching to an alternative opioid, or discontinuation of therapy in patients with chronic noncancer pain and inadequate symptom relief on moderate doses (100 to 200 mg/day of morphine or equivalent) of opioids. In trials included in systematic reviews of opioids[79, 81], the highest daily dose permitted was 240 mg/day of morphine[257], but the highest average dose was 120 mg/day[138]. In a prospective, long-term open-label registry study of patients originally enrolled in clinical trials, 3 of 219 patients (1.4%) were prescribed >200 mg/day at any time through up to three years of follow-up[258].

Summary of evidence

- There is insufficient evidence (no studies that met inclusion criteria) to evaluate benefits and harms of high (>200 mg/day) doses of opioids versus lower doses.

Key Question 20

Are high doses of opioids associated with different or unique harms compared to lower doses?

It is not clear if high doses (>200 mg/day of morphine or equivalent) of opioids are associated with different or unique harms (such as arrhythmia, endocrinologic effects, or others) compared to lower doses.

Results of search: systematic reviews and primary studies

We identified no relevant systematic reviews or randomized trials that met inclusion criteria. We identified one cross-sectional study evaluating sex hormone levels in men receiving >120 mg/day of methadone compared to lower doses[170]. Another study evaluated effects of methadone dose on QT intervals[166].

Findings

A cross-sectional observational study found no difference in sex hormone levels in men on 70-120 mg/day of morphine (N=23) versus those on >120 mg/day (N=16), though both were

associated with lower testosterone levels compared to men on 20-60 mg methadone/day (N=15)[170]. The clinical significance of the difference (free testosterone 41.7 to 44.8 pg/ml versus 74.3 pg/ml) is uncertain. In addition, results are difficult to interpret because it is not clear how patients were selected for inclusion in the study, a cross-sectional design was used (making it difficult to establish cause and effect), and there was no analysis of potential confounders such as duration of opioid use, severity of pain, body mass index, and underlying condition.

Torsades de pointes was reported in a case series (N=17) of patients in methadone maintenance or at a pain clinic on high doses of methadone (range 65 to 1000 mg/day, mean 397 mg/day)[167]. However, a before-after study evaluating effects of methadone on prolongation of QT intervals found no association with methadone dose (range 20 to 1200 mg/day, mean 110 mg/day)[166].

Summary of evidence

- There is insufficient evidence from cross-sectional and before-after studies to judge whether high doses of opioids are associated with different or unique toxicities compared to lower doses.

Key Question 21

How effective are patient education methods or clinician advice for improving outcomes associated with chronic opioid therapy?

Patient education and clinician advice could help patients understand expectations of benefits and potential side effects, and could alleviate anxiety or uncertainty about use of opioids or improve clinical outcomes such as pain, function, and outcomes associated with the abuse potential of opioids. Some guidelines recommend patient education prior to initiation of opioids[27].

Results of search: systematic reviews and primary studies

We identified no studies on effectiveness of patient education methods or clinician advice for improving outcomes associated with chronic opioid therapy that met inclusion criteria.

Summary of evidence

- There is insufficient evidence (no studies that met inclusion criteria) to determine effectiveness of different patient education methods or clinician advice for improving outcomes associated with chronic opioid therapy.

Key Question 22

How effective is co-prescription with other pain-attenuating medications or combining opioids for improving pain control or decreasing adverse events associated with opioid analgesics?

Results of search: systematic reviews

We identified no relevant systematic reviews that met inclusion criteria. We excluded one systematic review that evaluated co-administration of cyclo-oxygenase-2 selective NSAIDs for post-surgical pain[212].

Results of search: primary studies

We identified seven randomized trials (results reported in four publications) on dual therapy with gabapentin[96], dextromethorpan[94, 101], or nortriptyline[120] plus an opioid versus opioid monotherapy in patients with chronic noncancer pain and one trial on the addition of oxycodone to chronic stable doses of gabapentin in patients with painful diabetic neuropathy[99] (Table 19). One lower-quality trial on the efficacy of titrated doses of sustained-release morphine plus immediate release oxycodone versus fixed-dose immediate-release oxycodone is summarized in Key Question 1[207]. We excluded one retrospective cohort study based on insurance claims data on effects of gabapentin on opioid prescriptions in patients with post-herpetic neuralgia[259]

Findings

One higher-quality randomized crossover trial found the combination of gabapentin (mean dose 1700 mg) plus morphine (mean dose 34 mg) superior to morphine alone (mean dose 45 mg) for short-term (5 weeks) pain intensity (difference of about 0.64 points on a 10 point scale) and the McGill Pain Questionnaire (difference about 3.2 points on a 45 point scale)[96]. Combination therapy was associated with more dry mouth than morphine alone (21% vs. 5%), but a trend towards decreased constipation (21% vs. 39%).

One lower-quality randomized multi-crossover trial found the combination of morphine plus nortriptyline no better than morphine alone on any outcome in patients with radiculopathy[120]. However, results of this trial are difficult to interpret due to very high (50%) loss to follow-up.

Five trials (reported in two publications[94, 101]) that evaluated combinations of morphine plus dextromethorphan versus morphine alone reported mixed results. In three higher-quality trials of patients with non-neuropathic pain, there were no differences between either fixed- or titrated doses of combination therapy and morphine monotherapy in pain intensity, amount of morphine, or withdrawals due to lack of efficacy[94]. Two lower-quality trials of patients (75% and 83% noncancer pain), on the other hand, found no differences between combination therapy and morphine monotherapy for pain relief, but morphine requirements were significantly lower with combination therapy[101]. Based on data combined from these two trials, there was a trend towards increased constipation with morphine monotherapy (possibly related to higher morphine

requirements), but less nausea. One of the higher-quality trials also reported a trend towards more nausea with combination therapy[94].

One higher-quality trial found the addition of sustained-release oxycodone to chronic stable doses of gabapentin to be associated with small effects on pain (0.55 points on a 0 to 10 scale, 95% CI 0.15 to 0.95) and rescue medication use (0.5 doses/day) in patients with painful diabetic neuropathy[99]. Oxycodone was also associated with higher rates of gastrointestinal adverse events, fatigue, somnolence, dizziness, withdrawal due to adverse events, and overall adverse events.

Table 19. Trials of strategies for treatment of acute exacerbations of pain in patients on chronic opioid therapy

Author, year Underlying condition	Number of patients Duration of follow-up	Main results	Quality*
Galer, 2005a[94] Non-neuropathic pain	N=327 12 weeks	**Immediate-release morphine versus immediate-release morphine/dextromethorphan (1:1)** Difference in change in baseline pain intensity (0 to 10): 0.1 (95% -0.2 to 0.4) Withdrawal due to lack of efficacy: 32% (54/167) vs. 31% (50/160) Other outcomes: No differences (data not reported)	8/11; 3/5
Galer, 2005b[94] Non-neuropathic pain	N=308 12 weeks	**Immediate-release morphine versus immediate-release morphine/dextromethorphan (1:1) (fixed-dose)** Percent change in average daily morphine dose: -5.4 vs. -7.6 vs. -5.9 (NS for all comparisons) Average daily pain intensity score: 3.8 vs. 3.2 vs. 3.1 (NS for all comparisons) Withdrawal due to lack of efficacy: 5% (5/101) vs. 2% (2/100) vs. 1% (1/107) Other outcomes: No differences (data not reported)	6/11; 3/5
Galer, 2005b[94] Non-neuropathic pain	N=193 12 weeks	**Immediate-release morphine versus immediate-release morphine/dextromethorphan (1:1)** Percent change in average daily morphine dose: -5.4 vs. -7.6 vs. -5.9 (NS for all comparisons) Average daily pain intensity score: 3.8 vs. 3.2 vs. 3.1 (NS for all comparisons) Withdrawal due to lack of efficacy: 5% (5/101) vs. 2% (2/100) vs. 1% (1/107) Other outcomes: No differences (data not reported)	7/11; 3/5
Gilron, 2005[96] Neuropathic pain	N=57 5 weeks	**Sustained-release morphine (A) vs. gabapentin (B) vs. sustained-release morphine + gabapentin (C) vs. lorazepam (D)** Mean pain intensity (baseline 5.72 +/- 0.23): 3.70 +/- 0.34 vs. 4.15 +/- 0.33 vs. 3.06 +/- 0.33 vs. 4.49 +/- 0.34 (C superior to A, B, and D) Brief Pain Inventory, general activity (baseline 4.7): 3.1 vs. 3.0 vs. 2.9 vs. 4.5 SF-36 Physical functioning (baseline 51.7): 57.8 vs. 61.1 vs. 62.4 vs. 56.0 Beck Depression Inventory (baseline 10.3): 6.7 vs. 6.4 vs. 6.0 vs. 8.5	7/11; 4/5

Table 19. Trials of strategies for treatment of acute exacerbations of pain in patients on chronic opioid therapy

Author, year Underlying condition	Number of patients Duration of follow-up	Main results	Quality*
Hanna, 2008[99] Diabetic neuropathy	N=338 12 weeks	**Sustained-release oxycodone vs. placebo (each added to chronic stable doses of gabapentin)** Pain (0 to 10, mean treatment difference): 0.55 (95% CI 0.15 to 0.95) Escape medication use (mean treatment difference): -0.48 (95% CI -0.91 to -0.05) Global assessment of pain relief "good" or "very good": 56% vs. 41% (p=0.003)	8/11; 5/5
Katz, 2000a[101] Mixed pain conditions	N=89 2 weeks	**Immediate-release morphine versus immediate-release morphine/dextromethorphan (1:1)** Mean proportion of days with satisfactory pain relief: 79% vs. 78% (NS) Change from baseline in average daily morphine dose (mg), during first intervention phase: +20 mg vs. -50 mg (p<0.001)	4/11; 2/5
Katz, 2000b[101] Mixed pain conditions	N=232 2 weeks	**Immediate-release morphine versus immediate-release morphine/dextromethorphan (1:1)** Mean proportion of days with satisfactory pain relief: 81% vs. 82% (NS) Change from baseline in average daily morphine dose (mg): +16 mg vs. +1.6 mg (p=0.025) Global rating "better" than run-in morphine: 43% vs. 55%	4/11; 2/5
Khoromi, 2007[120] Radiculopathy	N=55 9 weeks per intervention	**Sustained-release morphine plus nortriptyline versus sustained-release morphine versus nortriptyline versus benztropine (active placebo)** Average leg pain (mean reduction below benztropine, 0 to 10 scale): 0.3 vs. 0.3 vs. 0.5 (p>0.05 for all interventions versus benztropine) Average back pain (mean reduction below benztropine, 0 to 10 scale): 0.2 vs. 0.2 vs. 0.4 (p>0.05 for all interventions versus benztropine) Global pain relief "a lot" or "complete": 25% (7/28) vs. 31% (10/;32) vs. 19% (6/31) vs. 15% (5/33) Beck Depression Inventory (mean score): 6 vs. 9.6 vs. 7.3 vs. 9 Oswestry Disability Index (mean score): 27.4 vs. 15.7 vs. 27.5 vs. 30.5 No differences on SF-36 except for Role emotional: 83 vs. 69 vs. 72 vs. 63 (p=0.03 for combination treatment versus benztropine)	5/11; 4/5

*Using Cochrane Back Group criteria, maximum score of 11; and Jadad criteria, maximum score of 5

Summary of evidence

- For neuropathic pain, one higher-quality trial found the combination of gabapentin plus morphine slightly more effective than morphine monotherapy for short-term pain intensity and function, at slightly lower doses of morphine. Combination therapy was associated with increased dry mouth (level of evidence: moderate).
- For neuropathic pain, one higher-quality trial found the combination of sustained-release oxycodone plus gabapentin slightly more effective than gabapentin monotherapy for short-term pain intensity and rescue medication use. Combination therapy was associated with increased gastrointestinal adverse events, somnolence, fatigue, and withdrawals due to adverse events (level of evidence: moderate).

- For radicular pain, one small (N=55), lower-quality trial found the combination of nortriptyline plus morphine no better than morphine monotherapy on any outcome (level of evidence: low).
- For non-neuropathic or mixed pain, five trials (three higher-quality) reported inconsistent results regarding effects of dextromethorphan plus morphine versus morphine monotherapy, though the three higher-quality trials consistently found no differences (level of evidence: moderate).
- There is insufficient evidence from one lower-quality trial that evaluated non-equivalent doses of a combined opioid regimen (sustained-release morphine plus immediate-release oxycodone) versus a single opioid (immediate-release oxycodone) to determine efficacy (see Key Question 11) (level of evidence: low).

Key Question 23

What is the effect of concomitant use of drugs with CNS effects on adverse events associated with opioids for chronic noncancer pain?

Use of drugs with central nervous system effects is associated with driving accidents[260-262], accidental overdose[176], and hip fractures[263, 264]. We evaluated evidence on whether concomitant use of drugs with central nervous system effects increases risks associated with opioids in patients with chronic noncancer pain.

Results of search: systematic reviews

We identified no systematic reviews that met inclusion criteria.

Results of search: primary studies

We identified no randomized trials or controlled observational studies that met inclusion criteria. We excluded a retrospective study on the association between opioids and other medication use and sleep apnea because it was an uncontrolled study (see Key Question 5)[116].

Findings

No studies met inclusion criteria. However, descriptive case reports and series frequently reported identification of additional psychoactive drugs (frequently in the setting of polypharmacy, often with benzodiazepines) in a high proportion of fatal methadone overdoses[176]. In one case-control study, use of two or more psychoactive drugs was associated with a higher risk of injury motor vehicle accidents compared to use of a single drug, but the drugs were not specified[260]. An uncontrolled observational study found that severity of apnea-hypopnea correlated with dose of benzodiazepines[169].

Summary of evidence

- There is insufficient evidence (no studies that met inclusion criteria) to estimate increased risk associated with concomitant use of additional psychoactive drugs in patients on opioids for chronic noncancer pain.

Key Question 24

What are the benefits associated with behavioral therapy, multidisciplinary rehabilitation and/or functional restoration/work hardening in addition to or instead of opioids for chronic noncancer pain?

Behavioral therapy, multidisciplinary rehabilitation, and functional restoration/work hardening have been shown to be effective in patients with chronic noncancer pain. Most guidelines recommend referral of chronic pain patients who do not respond adequately to opioids or who exhibit aberrant drug-related behaviors to a multidisciplinary team (including a psychologist or psychiatrist) for further assessment and management[16, 18, 27, 81].

Results of search: systematic reviews

We identified no systematic reviews on effectiveness of behavioral therapy and/or functional restoration/work hardening in addition to or instead of opioids for chronic noncancer pain that met inclusion criteria. We excluded a number of systematic reviews that evaluated effectiveness of behavioral therapy and functional restoration/work hardening in general, but did not evaluate these interventions in comparison with or in addition to opioids[265-273].

Results of search: primary studies

We identified no randomized trials that directly evaluated the efficacy of behavioral therapy, multidisciplinary rehabilitation, and/or functional restoration versus or in addition to opioids in patients with chronic noncancer pain. We identified two randomized trials of multidisciplinary rehabilitation and functional restoration that evaluated opioid use as a secondary outcome[274, 275].

Findings

One trial found that use of opioids after nine to 18 months decreased from 32% to 14% in patients enrolled in a multidisciplinary rehabilitation program and from 33% to 22% in patients enrolled in an outpatient multidisciplinary rehabilitation program, but increased from 50% to 67% in control patients[275]. Statistical significance of these results was not reported. Results were based on a small sample size (N=52) and are susceptible to attrition bias (33 patients enrolled did not return for follow-up).

A second trial found no significant difference in rates of opioid intake (pills/week) between patients randomized to functional restoration versus usual care after 17 months[274]. Attrition was not clearly reported in this trial.

Summary of evidence

- No trial directly compared behavioral therapy, multidisciplinary rehabilitation, and/or functional restoration/work hardening to opioid therapy or in addition to opioid therapy in patients with chronic noncancer pain. Two trials that evaluated opioid use as a secondary outcome were

methodologically flawed and reported inconclusive and inconsistent results (level of evidence: low).

Key Question 25

How effective are opioid agreements/contracts for improving clinical benefits and reducing harms, including abuse, addiction, or other aberrant drug-related behaviors associated with opioids for chronic noncancer pain?

Opioid agreements/contracts are formal written agreements between opioid prescribers and patients that define key aspects of opioid therapy, including potential risks and benefits of treatment, prescribing policies, methods for monitoring opioid use, expected behaviors, and consequences of violating the agreement[276, 277]. Proposed functions of opioid agreements/contracts include the potential to enhance adherence to opioid therapy and reduce aberrant drug-related behaviors, facilitate and document the informed consent process, reduce clinicians' legal risk, and improve practice efficiency[276, 278]. Potential harms are uncertain, but may include stigmatization of opioid therapy, a tendency to promote undertreatment of pain, or negative effects on patient-clinician relationships. Opioid contracts are in widespread use, and published guidelines generally recommend written opioid agreements/contracts in all patients initiating therapy[17, 19, 20, 27] or in patients at higher risk for aberrant drug-related behaviors[18].

Results of search: systematic reviews and primary studies

We identified no systematic reviews or randomized trials on effects of opioid agreements/contracts on clinical outcomes. One small (N=20) retrospective study evaluated the association between signing an opioid contract and outcomes[279].

Findings

The only study on clinical outcomes associated with signing an opioid contract retrospectively evaluated 20 patients on chronic opioid therapy with a history of substance abuse[279]. It found that signing of an opioid contract was not associated with a "successful outcome," though this outcome was not defined. Of the nine patients who signed a contract, four subsequently violated it.

Summary of evidence

- There is insufficient evidence from one small retrospective study to evaluate effects of opioid contracts/agreements on clinical outcomes (level of evidence: low).

Key Question 26

In patients receiving opioids for chronic noncancer pain, how accurate are formal screening instruments for identifying aberrant drug-related behaviors?

A number of screening instruments have been proposed for evaluating the risk of aberrant drug-related behaviors in patients prescribed opioids for chronic noncancer pain. A reliable

instrument for identifying aberrant drug-related behaviors could be valuable for ongoing monitoring of risks and benefits of chronic opioid therapy.

Results of search: systematic reviews

We identified no systematic reviews that met inclusion criteria.

Results of search: primary studies

We identified nine studies (N=1530) on utility of screening instruments for identifying aberrant drug-related behaviors in patients prescribed opioids for chronic noncancer pain[135, 144, 280-286]. We excluded four studies of formal screening instruments that did not assess chronic pain patients prescribed opioids[287, 288] or did not evaluate diagnostic accuracy for aberrant opioid drug-related behaviors[134, 146, 289]. Instruments evaluated in the excluded studies include the Screening Instrument for Substance Abuse Potential (SISAP)[287], the Screening Tool for Addiction Risk (STAR)[288], and the Pain Assessment and Documentation Tool (PADT)[289].

Findings

Six of nine studies on diagnostic accuracy of screening instruments for identifying aberrant drug-related behaviors in patients prescribed opioids for chronic noncancer pain met our threshold for a higher-quality study (Table 20)[144, 280, 282, 283, 285, 286]. However, all studies had methodological shortcomings. No study described whether investigators assessing the reference standard for aberrant drug-related behaviors were blinded to results of the screening instrument. In addition, methods for identifying aberrant drug-related behaviors varied across studies, and did not distinguish well between new and pre-existing aberrant drug-related behaviors (particularly substance abuse or illicit drug use) or between less and more serious behaviors. In two studies, methods for identifying drug-related behaviors were not well described[281, 284]. Five studies incorporated urine toxicology results of illicit drugs or unprescribed opioids into definitions of aberrant drug-related behaviors[144, 281, 282, 284, 285]. All of the studies evaluated different screening instruments, with the exception of two studies that assessed the Pain Medication Questionnaire[135, 280]. Of the eight instruments evaluated, two were self-administered[280, 282], four interviewer-administered[144, 283, 285, 286], and in two the method of administration was unclear[281, 284]. The instruments varied in complexity, with the number of assessment items ranging from three[144] to 42[283]. One screening instrument focused on history of alcohol or substance abuse[144] and one focused on psychosocial factors[285]. The others assessed multiple domains including coping strategies, pain medication behaviors, abuse of substances other than prescribed opioids, and/or psychosocial factors[135, 144, 280-286]. One instrument[285] was based on a subset of psychiatric items included in another screening instrument (the Prescription Drug Use Questionnaire[283]). Only one study reported pain scores (average 6 on a 0 to scale)[282]. No study reported doses of opioids prescribed and none adjusted or controlled for demographic and intervention variables.

Table 20. Studies of formal screening instruments for identifying aberrant drug-related behaviors in patients prescribed opioid

Author, year Instrument evaluated	Number of patients Type of study	Definition of aberrant drug-related behaviors	Main results	Quality*
Adams, 2004[280] Pain Medication Questionnaire (PMQ) Self-administered, 26 items	111 patients on opioids Cross-sectional	Physician Risk Assessment tool used to identify opioid misuse; based on a set of six dimensions, each rated on a 5-point Likert scale	Known opioid misuse (N=12) versus no known history of opioid misuse (matched sample) Mean PMQ score: 33.9 vs. 25.5 (p=0.045 based on 1-sided t-test)	6/9
Atluri, 2004[281] 6-item instrument Method of administration unclear, 6 items	107 cases, 103 controls Case-control	Inappropriate opioid use included inappropriate urine drug screen (not defined), intentional 'doctor shopping', alteration of opioid prescription to obtain more opioids, criminal activity involving prescription opioids (89% inappropriate urine drug screen)	Risk of inappropriate opioid use Score >3 (out of 6) positive items (high risk) versus score <3 (low risk): OR 16.6 (95% CI 8.3 to 33)	2/9
Butler, 2007[282] Current Opioid Misuse Measure (COMM) Self-administered, 17 items	227 Cross-sectional (for assessing diagnostic accuracy)	Aberrant Drug Behavior Index positive if Patient Drug Use Questionnaire score >11 or urine toxicology screen positive (presence of illicit drug or non-prescribed opioid) and Prescription Opioid Therapy Questionnaire score ≥3	Area under receiver operating curve for Current Opioid Misuse Measure on the Aberrant Drug Behavior Index: 0.81 (95% CI 0.74 to 0.86) COMM score ≥9: sensitivity 0.77, specificity 0.66 for positive Aberrant Drug Behavior Index COMM score ≥10: sensitivity 0.74 and specificity 0.73	5/9
Compton, 1998[283] Prescription Drug Use Questionnaire (PDUQ) Interviewer-administered, 40 items	52 Cross-sectional	American Society of Addiction Medicine criteria for substance abuse and substance dependence as evaluated by a single addiction medicine specialist	Score (number of positive items) on 40-item PDUQ questionnaire (p<0.0005 on ANOVA) Nonaddicted: 6 to 15 Substance-abusing: 11 to 25 Substance-dependent: 15 to 28	7/9
Holmes, 2006[135] Pain Medication Questionnaire (PMQ) Self-administered, 26 items	271 Prospective cohort	Individuals with a known history of substance abuse (alcohol, prescription drugs, illicit drugs) based on self-admission, referring physician report, or initial psychologist evaluation; Physician Risk Assessment score; requests for early prescription refills	Known history of substance abuse (N=68) versus no known history of substance abuse (N=68) Pain Medication Questionnaire score (mean): 28.8 vs. 23.9 (p=0.01) High vs. low Pain Medication Questionnaire score Request for early refills: 61.5% vs. 33.3% (p=0.02); OR 3.2 (95% CI 1.21 to 8.44)	3/9

Table 20. Studies of formal screening instruments for identifying aberrant drug-related behaviors in patients prescribed opioid

Author, year Instrument evaluated	Number of patients Type of study	Definition of aberrant drug-related behaviors	Main results	Quality*
Manchikanti, 2004[284] Based on Atluri et al[281] Method of administration unclear, 4 items	150 Case-control	Controlled substance abuse defined as: Misuse of controlled substances in a clinical setting, including obtaining controlled substances from other physicians or other identifiable sources, dose escalations with inappropriate use, and/or violation of controlled substance agreement Illicit drug abuse not defined	No controlled substance abuse/no illicit drug use vs. no controlled substance abuse/positive illicit drug use vs. positive controlled substance abuse/no illicit drug use vs. positive controlled substance abuse/positive illicit drug use Total score 0 or 1 out of 4 items: 100% vs. 94% vs. 20% vs. 23% (p values >0.05 for all comparisons) Total score ≥2 out of 4: 0% vs. 6% vs. 80% vs. 77% (significant for 6% vs. 0% and for 80% or 77% vs. 0% or 6%)	3/9
Michna, 2004[144] Abuse questions Items (3 questions) Interviewer-administered, 3 items	145 Cross-sectional	A: unanticipated positive results in urine toxicology tests B: episodes of lost or stolen prescription C: multiple unsanctioned escalations in dose D: frequent unscheduled pain center or emergency room visits E: concern expressed by a significant other about the patient's use of opioids F: excessive phone calls	High risk (2-3 positive responses) versus low risk (0-1 positive responses) Positive urine screen: 38% vs. 15%, p<0.01 Lost/stolen prescriptions: 33% vs. 17%, p<0.05 Unsanctioned dose escalations: 33% vs. 22%, p>0.05 Unscheduled clinic/ER visits: 18% vs. 12%, p>0.05 Concern from significant others: 18% vs. 10%, p>0.05 Multiple clinic phone calls: 9% vs. 7%, p>0.05	7/9
Wasan, 2007[285] Psychiatric items from the Prescription Drug Use Questionnaire (PDUQ) Interviewer-administered, 5 items	228 Prospective cohort	Drug Misuse Index: Misuse or abuse defined as positive scores on the self-reported Screener and Opioid Assessment for Pain Patients and the Current Medication Misuse Measure; or positive scores on the urine toxicology screen (presence of illicit substance or a non-prescribed opioid) and the Perception of Opioid Therapy Questionnaire	High psychiatric comorbidity (≥2 positive items out of 5 psychiatric items on the PDUQ) vs. low psychiatric comorbidity (<2 positive items) Drug Misuse Index positive: 52% vs. 22% (p<0.001)	6/9
Wu, 2006[286] Addiction Behaviors Checklist (ABC) Interviewer-administered, 20 items	136 Prospective cohort	Interviewer's global clinical judgment (yes or no to "Do you think patient is using medications appropriately?")	Addiction Behaviors Checklist score Diagnostic accuracy on Interviewer's Global Clinical Judgment assessment based on cut-off score of 3 or greater (0 to 20 scale): sensitivity 88%, specificity 86% (optimal sensitivity/specificity combination, receiver operating curve characteristics not reported)	4/9

*Using six criteria described in Methods section (maximum score 9)

One higher-quality study derived the 17-item, self-administered Current Opioid Misuse Measure (COMM) from 40 original items and evaluated the diagnostic test characteristics of the final instrument[282]. It found an area under the receiver operating curve of 0.81 (95% CI 0.74 to 0.86). Based on an optimal cut-off score of ≥10 (out of a maximum possible score 68), the sensitivity and specificity were 0.74 (95% CI 0.63 to 0.84) and 0.73 (95% CI, 0.65 to 0.80), respectively, with a PLR of 2.77 (95% CI 2.06 to 3.72), NLR of 0.35 (95% CI 0.24 to 0.52), and DOR of 7.90 (95% CI 4.25 to 14.7) (Table 21).

A second, lower-quality study found the 20-item, interviewer-administered Addiction Behavior Checklist (ABC, 20 items) associated with a sensitivity of 0.88 and specificity of 0.86 (PLR 6.29 and NLR 0.14) at the optimal cut-off score of ≥3 out of 20 (confidence intervals not calculable)[286]. Items included in the ABC were selected prior to evaluation in the study. The interpretation of this study is challenging, however, because the presence of aberrant drug-related behaviors was defined by the response of the treating pain physician to a single question of uncertain reliability or validity—"Do you think patient is using medications appropriately?"

The screening instrument in four other studies showed poor diagnostic accuracy[144, 285] or the results were difficult to interpret due to serious methodological shortcomings[281, 284]. One higher-quality study found that positive responses to at least two of three pre-selected questions had only modest sensitivity and specificity for various behaviors associated with opioid misuse or abuse, resulting in small or trivial likelihood ratios (Table 21)[144]. Another higher-quality study found that the presence of psychiatric comorbidity (defined as two or more positive responses on the five psychiatric items of the previously developed Prescription Drug Use Questionnaire) was associated with a sensitivity of 0.74 (95% CI 0.63 to 0.82) and a specificity of 0.57 (95% CI 0.49 to 0.65) for positive findings on the Drug Misuse Index (which combines results from the SOAPP, COMM, other risk assessment instruments, and urine toxicology results)[285]. The PLR was 1.72 (95% CI 1.37 to 2.17) and the NLR 0.46 (95% CI 0.31 to 0.67). One study found a 6-item instrument associated with small positive and negative likelihood ratios for aberrant drug-related behaviors[281]. Another study found a 4-item instrument associated with a large PLR and small NLR (Table 21)[284]. However, both of these studies used a retrospective case-control design, were rated lower-quality, and derived and validated the instrument in the same population.

In three studies, higher scores on various screening instruments generally correlated with presence of variably defined aberrant drug-related behaviors, but sensitivity, specificity, and other standard measures of diagnostic accuracy were not reported and could not be calculated (Table 21)[135, 280, 283]. No study evaluated the utility of formal monitoring instruments compared to informal clinical assessments alone, or compared one screening instrument to another. In addition, no study assessed effects of applying formal screening instrument for aberrant drug-related behaviors on clinical outcomes in patients prescribed opioids for chronic noncancer pain.

Table 21. Results, diagnostic accuracy of instruments for identifying aberrant drug-related behaviors in patients prescribed opioids

Author, year Instrument evaluated	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio
Adams, 2004[280] Pain Medication Questionnaire (PMQ) Self-administered, 26 items	Not calculable	Not calculable	Not calculable	Not calculable
Atluri, 2004[281] 6-item instrument Method of administration unclear, 6 items	0.77 (95% CI 0.68 to 0.84), for score ≥4	0.84 (95% CI 0.76 to 0.91) for score ≥4	4.93 (95% CI 3.11 to 7.83) for score ≥4	0.28 (95% CI 0.19 to 0.39) for score ≥4
Butler, 2007[282] Current Opioid Misuse Measure (COMM) Self-administered, 17 items	0.77 (95% CI 0.66 to 0.86) for COMM score ≥9 0.74 (95% CI 0.63 to 0.84) for COMM score ≥10	0.66 (95% CI 0.58 to 0.73) for COMM score ≥9 0.73 (95% CI 0.65 to 0.80) for COMM score ≥10	2.25 (95% CI 1.74 to 2.90) for COMM score ≥9 2.77 (95% CI 2.06 to 3.72) for COMM score ≥10	0.35 (95% CI 0.23 to 0.50) for COMM score ≥9 0.35 (95% CI 0.24 to 0.52) for COMM score ≥10
Compton, 1998[283] Prescription Drug Use Questionnaire (PDUQ) Interviewer-administered, 40 items	Not calculable	Not calculable	Not calculable	Not calculable
Holmes, 2006[135] Pain Medication Questionnaire (PMQ) Self-administered, 26 items	Not calculable	Not calculable	Not calculable	Not calculable
Manchikanti, 2004[284] Based on Atluri et al[281] Method of administration unclear, 4 items	0.49 (95% CI 0.37 to 0.60) for score ≥2	1.00 (95% CI 0.95 to 1.0) for score ≥2	69.2 (95% CI 4.33 to 1106) for score ≥2	0.52 (95% CI 0.42 to 0.64) for score ≥2

Table 21. Results, diagnostic accuracy of instruments for identifying aberrant drug-related behaviors in patients prescribed opioids

Author, year Instrument evaluated	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio
Michna, 2004[144] Abuse questions Items (3 questions) Interviewer-administered, 3 items	2-3 positive responses A: 0.53 (95% CI 0.35 to 0.71) B: 0.47 (95% CI 0.29 to 0.65) C: 0.40 (95% CI 0.25 to 0.58) D: 0.40 (95% CI 0.19 to 0.64) E: 0.44 (95% CI 0.22 to 0.69) F: 0.36 (95% CI 0.11 to 0.69)	2-3 positive responses A: 0.75 (95% CI 0.66 to 0.83) B: 0.74 (95% CI 0.64 to 0.81) C: 0.72 (95% CI 0.63 to 0.80) D: 0.70 (95% CI 0.62 to 0.78) E: 0.71 (95% CI 0.62 to 0.79) F: 0.69 (95% CI 0.61 to 0.77)	2-3 positive responses A: 2.14 (95% CI 1.36 to 3.39) B: 1.77 (95% CI 1.09 to 2.85) C: 1.46 (95% CI 0.89 to 2.39) D: 1.35 (95% CI 0.74 to 2.46) E: 1.53 (95% CI 0.85 to 2.73) F: 1.19 (95% CI 0.52 to 2.70)	2-3 positive responses A: 0.62 (95% CI 0.42 to 0.92) B: 0.72 (95% CI 0.51 to 1.02) C: 0.82 (95% CI 0.62 to 1.10) D: 0.85 (95% CI 0.58 to 1.24) E: 0.78 (95% CI 0.51 to 1.20) F: 0.92 (95% CI 0.58 to 1.45)
Wasan, 2007[285] Psychiatric items from the Prescription Drug Use Questionnaire (PDUQ) Interviewer-administered, 5 items	0.74 (95% CI 0.63 to 0.83) for ≥2 items on PDUQ	0.57 (95% CI 0.48 to 0.66) for ≥2 items on PDUQ	1.72 (95% CI 1.37 to 2.17) for ≥2 items on PDUQ	0.46 (95% CI 0.31 to 0.67) for ≥2 items on PDUQ
Wu, 2006[286] Addiction Behaviors Checklist (ABC) Interviewer-administered, 20 items	0.88 for ABC score ≥3 (confidence intervals not calculable)	0.86 for ABC score ≥3 (confidence intervals not calculable)	Not calculable	Not calculable

A=unanticipated positive results in urine toxicology tests, B=episodes of lost or stolen prescription, C=multiple unsanctioned escalations in dose, D=frequent unscheduled pain center or emergency room visits, E=concern expressed by a significant other about the patient's use of opioids, F=excessive phone calls

Summary of evidence

- One prospective derivation study found that the COMM may be useful for identifying drug-related behaviors in patients prescribed opioids for chronic noncancer pain. However, the COMM is a relatively weak predictor and results require validation in other populations and settings. There is insufficient evidence from other studies to determine the diagnostic accuracy or other screening instruments for identifying aberrant drug-related behaviors, due to methodological shortcomings. All studies used poorly standardized or described methods for identifying aberrant drug-related behaviors and did not evaluate the seriousness of the identified behaviors. No study has evaluated the utility of formal screening instruments compared to informal clinician assessments (level of evidence: low).

Key Question 27a

In patients receiving opioids for chronic noncancer pain, what is the diagnostic accuracy of urine drug screening and different urine drug screening methods for detecting illicit drug use?

Patients with chronic pain may underreport or conceal illicit drug use[290-293]. Regular or periodic urine drug screening has been proposed as a method for identifying patients using illicit drugs[294]. Most urine drug screening tests utilize immunoassays, but cross-reactivity between various drugs and chemicals can cause false positive results[295-297]. Urine tests based on gas chromatography-mass spectrometry assays are considered the most specific test for identifying individual drugs and metabolites and are often used to confirm positive results on immunoassays[298, 299].

Results of search: systematic reviews

We identified no systematic reviews that met inclusion criteria.

Results of search: primary studies

We identified one study that evaluated sensitivity of urine toxicology screening for illicit drug use compared to patient self-report during a psychiatric examination[290]. A second study did not meet inclusion criteria because it calculated sensitivity and specificity of point-of-care urine toxicology tests versus gas chromatography-mass spectrometry in laboratory samples, with no clinical data reported[297]. We identified no other studies evaluating diagnostic test accuracy of urine drug screening for detecting illicit drug use.

Findings

One retrospective study (N=226) found sensitivities of urine drug samples performed with gas chromatography-mass spectrometry were 86% for cannabinoids and 76% for benzodiazepines, compared to patient self-report during psychiatric examination[290]. Interpretation of these results is a challenge because it is not clear if the investigators that evaluated patient self-reports were blinded to results of urine drug screening, or when illicit drug use last occurred relative to timing of urine sampling.

A study that did not meet inclusion criteria found specificities of 100% and sensitivities of 99-100% for two point-of-care urine drug screening tests (Signifiy ER Drug Screen Test and Triage Drug of Abuse Panel plus TCA) compared to routine (non-point-of-care) immunoassays in laboratory samples[297].

Summary of evidence

- Urine toxicology testing with gas chromatography/mass spectrometry was associated with sensitivities of 76% for benzodiazepines and 86% for cannabinoids compared to patient self-report in one retrospective study of chronic pain patients, but results are difficult to interpret due to methodological shortcomings (level of evidence: low).

Key Question 27b

In patients receiving opioids for chronic noncancer pain, what is the diagnostic accuracy of urine drug screening and different urine drug screening methods for identifying the presence or absence of prescribed and non-prescribed opioids and estimating doses of opioids?

Patients may not take opioids as prescribed, underestimate opioid use, or use non-prescribed opioids[291, 293, 300]. In addition to detecting illicit drug use, urine drug screening could also be useful for assessing adherence to therapy or use of non-prescribed opioids.

Results of search: systematic reviews

We identified no systematic reviews that met inclusion criteria.

Results of search: primary studies

We identified one study evaluating sensitivity of urine drug screening for opioid use compared to patient self-report during a psychiatric examination[290]. We identified no other studies evaluating diagnostic test accuracy of urine drug screening. A second study evaluated urine concentrations of fentanyl with application of different doses of transdermal fentanyl[301].

Findings

One retrospective study (N=226) found a sensitivity of urine drug samples performed with gas chromatography-mass spectrometry of 88% compared to patient self-report of opioid use during psychiatric examination[290]. Interpretation of these results is a challenge because it is not clear if the investigators that evaluated patient self-reports were blinded to results of urine drug screening, or when opioid use last occurred relative to timing of urine sampling.

A second study found poor correlation between the dose of transdermal fentanyl and urine concentrations in 142 samples[301].

Summary of evidence

- Urine toxicology testing with gas chromatography/mass spectrometry was associated with a sensitivity of 88% for opioid use compared to patient self-report in one retrospective study of

chronic pain patients, but results are difficult to interpret due to methodological shortcomings (level of evidence: low).

- One study found poor correlation between the dose of transdermal fentanyl and urine concentrations of fentanyl (level of evidence: low).

Key Question 28

In patients receiving opioids for chronic noncancer pain, how effective is urine drug screening and different urine drug screening methods for reducing abuse, addiction, and other aberrant drug-related behaviors, or increasing adherence to taking opioids as prescribed?

Results of search: systematic reviews

We identified no systematic reviews that met inclusion criteria.

Results of search: primary studies

We identified two observational studies that appeared to be conducted in the same patient cohort that compared rates of illicit drug use in patients who underwent random urine drug testing[292] or adherence monitoring[302] compared to historical controls.

Findings

One observational study of 500 consecutive patients prescribed opioids for CNCP reported marijuana in 11% of samples, cocaine in 5%, and methamphetamines or amphetamines in 2% in a setting in which all patients agreed to random urine drug screening.[292] Compared to an earlier cohort in the same setting, the prevalence of marijuana in urine was lower (11% vs. 18%, p-value not reported), but the prevalence of other illicit drug use was similar. A second study that appeared to be conducted in the same patient cohort found that institution of adherence monitoring (signed controlled substance agreement, periodic monitoring, periodic drug testing, pill counts, and education when necessary) was associated with a rate of controlled substance abuse of 9%, defined as receiving controlled substances from any place or source other than the prescribing physician, compared to 18% in an earlier cohort[302]. Results of both of these studies are difficult to interpret because they used historical controls, did not report statistical significance of differences in rates of aberrant behaviors, did not describe monitoring protocols well, and did not describe how the monitoring protocols (and other factors) differed compared to the historical cohort. We identified no other studies that met the prespecified inclusion criteria.

Summary of evidence

- There is insufficient evidence from two observational studies of the same (or a similar) patient cohort with methodological shortcomings to determine effectiveness of urine drug screening or adherence monitoring for reducing abuse, addiction, and other aberrant drug-related behaviors in patients prescribed chronic opioid therapy for chronic noncancer pain (level of evidence: low).

Key Question 29

In patients receiving opioids for chronic noncancer pain, how effective are other methods (pill counts, limited prescriptions, monitoring blood levels) for detecting or reducing abuse, addiction, other aberrant drug-related behaviors, or whether patients are taking opioids as prescribed?

Results of search: systematic reviews and primary studies

We identified no systematic reviews or primary studies on effectiveness of pill counts, limited prescriptions, monitoring of blood levels, or other methods for detecting or reducing abuse, addiction, other aberrant drug-related behaviors, or whether patients are taking opioids as prescribed. Prescription monitoring programs are evaluated in Key Question 34.

Summary of evidence

- We identified no studies that met inclusion criteria.

Key Question 30

Is re-evaluation of patients on chronic opioid therapy at different intervals associated with different outcomes?

All guidelines for use of opioids in patients with chronic noncancer pain recommend regular monitoring for response to treatment, adverse events, and evidence of aberrant drug-related behaviors[18-20, 27]. However, optimal intervals for re-evaluation are uncertain.

Results of search: systematic reviews and primary studies

We identified no systematic reviews, randomized trials, or observational studies that evaluated effects of re-evaluation of patients on chronic opioid therapy at different intervals on clinical outcomes.

Summary of evidence

- We identified no relevant studies that met inclusion criteria.

Key Question 31

What are the benefits and harms associated with different methods for evaluating outcomes in patients receiving opioids for chronic noncancer pain?

Results of search: systematic review and primary studies

We identified no relevant systematic reviews or primary studies. One tool, the Pain Assessment and Documentation Tool (PADT), has been recently developed to assist clinicians in evaluation and documentation of outcomes related to use of opioids in four key domains: analgesia, activities of daily living, adverse events, and aberrant drug-related behaviors[289, 303]. However, no study has evaluated the effect of using this or any other outcomes assessment tool on clinical outcomes.

Summary of evidence

- We identified no studies that met inclusion criteria.

Key Question 32

In patients receiving opioids for chronic noncancer pain, what is the accuracy of tools for differentiating drug-related behaviors due to inadequate symptom relief from true aberrant drug-related behaviors?

Requests for additional opioid medications in patients on chronic opioids may be related to inadequate symptom relief due to progression of underlying disease, a new disease process, development of tolerance, or other factors. The term "pseudoaddiction" has been used to describe a pattern of behaviors in patients with unrelieved pain that mimic behaviors in patients who are addicted to opioids such as escalating doses, using higher doses than prescribed, and increasing demands and exaggeration of symptoms[304]. In such patients, it is believed that effective treatment of the pain should result in resolution of the behaviors.

Results of search: systematic reviews and primary studies

We identified no systematic reviews or primary studies on accuracy of tools for differentiating drug-related behaviors due to inadequate symptom relief from true aberrant drug-related behaviors. The few studies that evaluated drug-related behaviors due to inadequate symptom relief in patients with chronic noncancer pain have not attempted to validate criteria for diagnosing this condition[305, 306].

Summary of evidence

- We identified no relevant studies that met inclusion criteria.

Key Question 33

In patients receiving opioids for chronic noncancer pain, what is the effect of diagnosing drug-related behaviors due to inadequate symptom relief on clinical outcomes?

Results of search: systematic reviews and primary studies

We identified no systematic reviews, randomized trials, or observational studies on effects of diagnosing drug-related behaviors due to inadequate symptom relief on clinical outcomes.

Summary of evidence

- We identified no relevant studies that met inclusion criteria.

Key Question 34

What patient features or characteristics predict improved outcomes with discontinuation of long-term opioids versus continued treatment?

Discontinuation of opioid therapy may be considered in patients who fail to experience adequate efficacy, those whose underlying pain condition improves (e.g. after surgery or other interventions), those who exhibit aberrant drug-related behaviors, and those who wish to discontinue therapy for other reasons.

Results of search: systematic reviews and primary studies

We identified no relevant systematic reviews, randomized trials or observational studies. We excluded one small, retrospective, uncontrolled observational study that found that 21 of 23 patients on high-dose opioid and chronic noncancer pain experienced a significant decrease in pain following opioid discontinuation, but did not evaluate patient features or characteristics predicting better outcomes[307].

Summary of evidence

- We identified no studies that met inclusion criteria.

Key Question 35

What are the benefits and harms of different methods for discontinuing opioids?

Results of search: systematic reviews

We identified no systematic reviews on the benefits and harms of different methods for discontinuing opioids in patients with chronic noncancer pain. We excluded systematic reviews that evaluated benefits and harms of different maintenance methods for treating opioid (heroin) dependence[308, 309].

Results of search: primary studies

We identified one randomized trial[93] and two prospective, non-randomized trials[310, 311] on methods for reducing or discontinuing opioids in patients with chronic noncancer pain. One trial that evaluated differences in short-term withdrawal symptoms after discontinuation of oxycodone plus ultralow-dose naltrexone versus oxycodone alone is reviewed for Key Question 9[115].

Findings

One small (N=10), higher-quality crossover trial found abrupt cessation of morphine associated with increased pain and decreased function (duration of intervention 60 hours) compared to continuation of morphine[93] (Table 22). Three patients (30%) reported opioid withdrawal symptoms following abrupt cessation of morphine, though there were no differences in physiologic parameters (vital signs and pupil size). Average dose of morphine prior to entry into was 42 mg/day (range 30 to 120 mg/day). Results of this trial may not apply to the general

population of patients with chronic noncancer pain, as patients who did not have pain adequately controlled by immobilization and alternative medications were excluded from study entry.

Two lower-quality, non-randomized prospective clinical trials reported similar rates of opioid abstinence after three to six months in patients randomized to different methods for opioid detoxification. In the first study, patients were randomized to inpatient, patient-controlled reduction of opioids or to a fixed reduction schedule[310]. In the second, patients were randomized to detoxification plus counseling or to detoxification with maintenance therapy if detoxification was unsuccessful[311]. Neither study evaluated effects of different methods for discontinuing opioids on pain, function, or withdrawal symptoms.

Table 22. Trials of methods for discontinuing opioids in patients with chronic noncancer pain

Author, year	Number of patients Duration of follow-up	Main results	Quality*
Cowan, 2005[93]	N=10 60 hours	**Continued sustained-release morphine vs. abrupt cessation** Brief Pain Inventory, average pain in last 24 hours (0 to 10): 3.2 vs. 5.3 (p<0.026) Pain interference with general activity in last 24 hours (0 to 10): 0.2 vs. 4.3 (p,0.027) Physiologic parameters: No differences Adverse events during cessation of opioids: 3/10 (30%) Proportion reporting craving for opioid during cessation of opioids: 0/10 (0%)	8/11; 4/5
Ralphs, 1994[310]	N=108 6 months	**Patient-controlled reduction versus cocktail method** Abstinent at discharge: 68% vs. 89% (p<0.05) Abstinent 6 months after discharge: 54% (27/50) vs. 56% (18/32) Use of other drugs, pain, or psychological variables at 6 months: No differences between groups	2/11; 0/5
Tennant, 1983[311]	N=42 3 months	**Detoxification/counseling vs. detoxification/maintenance** Proportion remaining in treatment past 3 weeks: 24% (5/21) vs. 95% (20/21) Abstinent after 90 days: 10% (2/21) vs. 19% (4/21)	2/11; 1/5

*Using Cochrane Back Group criteria, maximum score of 11; and Jadad criteria, maximum score of 5

Summary of evidence

- Abrupt cessation of chronic opioids was associated with increased pain, decreased function, and withdrawal symptoms in patients on moderate doses of morphine for chronic noncancer pain in one small (N=10), higher-quality trial of selected patients (level of evidence: low).
- There is insufficient evidence to evaluate efficacy and safety of other methods for discontinuing opioids in patients with chronic noncancer pain (two lower-quality, non-randomized trials) (level of evidence: low).

Key Question 36

What are the benefits and harms of continuing opioids versus switching to alternative analgesics in women with chronic noncancer pain who become pregnant or are planning to become pregnant?

Opioid use during pregnancy is associated with neonatal withdrawal syndrome and other adverse consequences including lower birth weight and difficulties breastfeeding[312, 313]. All opioids are classified as Pregnancy Class C (uncertain safety, no human studies; animal studies show an adverse effect). Nearly all studies on use of opioids during pregnancy are in women receiving methadone maintenance for heroin addiction.

Results of search: systematic reviews and primary studies

We identified no systematic reviews or primary studies evaluating different treatment strategies in women with chronic noncancer pain prescribed opioids that become pregnant or are planning to become pregnant.

Summary of evidence

- We identified no studies that met inclusion criteria.

Key Question 37

What are the effects of opioid prescribing policies on clinical outcomes?

State or federal regulations, laws, or guidelines designed to minimize diversion or abuse of opioids could have unintended negative consequences if they lead to underutilization of opioids for patients with pain[314-316]. Other policies, such as formulary restrictions on which opioids can be prescribed or prior authorization requirements for certain drugs could also have effects on patient outcomes.

Results of search: systematic reviews and primary studies

We identified no relevant systematic reviews, randomized trials, or observational studies on effects of opioid prescribing policies on clinical outcomes that met inclusion criteria.

Findings

Although several studies found implementation of prescription monitoring programs for Schedule II opioids associated with a decrease in prescription rates for Schedule II opioids and a shift towards increased rates of Schedule III, non-monitored opioid prescribing, the studies were not designed to determine whether the changes were due to a decrease in inappropriate or unnecessary Schedule II opioid use, or if these changes resulted in subsequent undertreatment of pain[317, 318]. No study has evaluated patient outcomes such as pain relief, functional status, ability to work, and abuse/addiction associated with implementation of a prescription monitoring program, formulary restriction, or other policies related to opioids prescribing. Claims of positive effects of prescription monitoring programs on reducing

diversion are primarily based on anecdotal reports of impressions of efficacy from policymakers and law enforcement officials[316].

Summary of evidence

Although prescription of schedule II opioids decreases after implementation of prescription monitoring programs, we identified no studies on effects of opioid prescribing polices on patient outcomes (level of evidence: low).

SUMMARY AND DISCUSSION

Specific findings from this review are summarized in the executive summary. We highlight several key research gaps:

Nearly all randomized trials of opioids are efficacy trials conducted in ideal settings and selected populations, usually with short-term follow-up. More effectiveness studies assessing long-term outcomes in less highly-selected populations are needed to help confirm the usefulness of opioids for chronic noncancer pain in real-world settings.

Methods to identify patients who are more likely to benefit from opioids, experience adverse events, or exhibit aberrant-drug related behaviors would be extremely helpful to guide the decision to initiate opioid therapy, but evidence is very sparse. A critical research need is for more studies that evaluate formal screening instruments that can be reliably used by clinicians in a variety of settings.

Reliable evidence to estimate the incidence of aberrant drug-related behaviors in patients prescribed chronic opioids for chronic noncancer pain is not available. More research is needed on risk of aberrant drug-related behaviors in more representative populations, using validated methods for assessing such outcomes.

Additional studies on the risk of driving and work-related safety in patients on stable doses of opioids or being initiated on therapy are needed to clarify appropriate driving or work-related recommendations.

More research is needed to determine whether high doses of opioids are associated with different harms compared to lower doses, and whether there are patient characteristics that reliably predict lack of response to high doses of opioids.

There is no reliable evidence on benefits and harms of opioid rotation in patients with chronic noncancer pain.

There is no reliable evidence on diagnostic accuracy of urine drug testing in clinical setting, or on effects of urine drug screening on patient outcomes.

More research is needed on benefits and harms associated with use of opioid contracts and agreements.

Effects of opioid prescribing policies on clinical outcomes are poorly understood. All studies focus on prescription rates rather than on patient-centered outcomes. Studies that evaluate effects of opioid prescribing policies on patient outcomes are needed.

We identified no full cost-effectiveness analyses of opioids for chronic noncancer pain. Such studies could help clarify choices between different opioids when risks and benefits appear similar, or when multiple trade-offs between different risks and benefits need to be considered.

Evidence on optimal methods for managing acute or new episodes of pain in patients with chronic noncancer pain that are on opioids is sparse, even though such patients are frequently encountered in urgent illness, inpatient, and outpatient settings.

GLOSSARY

Term	Definition
Aberrant drug-related behavior	A behavior outside the boundaries of the agreed upon treatment plan which is established as early as possible in the doctor-patient relationship[319].
Abuse	Any use of an illegal drug, or the intentional self-administration of a medication for a nonmedical purpose such as altering one's state of consciousness, e.g. getting high[320].
Addiction	A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving[321].
Breakthrough pain	Transient or episodic exacerbation of pain that occurs in patients with pain that is otherwise considered stable but persistent[322].
Chronic opioid therapy	Daily or near-daily use of opioids for at least 90 days, often indefinitely (adapted from Von Korff et al)[323].
Diversion	The intentional transfer of a controlled substance from legitimate distribution and dispensing channels[320].
Hyperalgesia	An increased response to a stimulus which is normally painful[2].
Misuse	Use of a medication (for a medical purpose) other than as directed or as indicated, whether willful or unintentional, and whether harm results or not[320].
Physical dependence	A state of adaption manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist[321].
Tolerance	A state of adaption in which exposure to a drug induces changes that result in a diminution of one or more opioid effects over time[321].

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APPENDIX 1. VETERANS AFFAIRS/DEPARTMENT OF DEFENSE GUIDELINES

Grade of recommendation definitions in Veterans Affairs/Department of Defense guidelines[27] on use of opioids in noncancer pain

Grade	Definition
A	A strong recommendation that the intervention is always indicated and acceptable
B	A recommendation that the intervention may be useful/effective
C	A recommendation that the intervention may be considered
D	A recommendation that a procedure may be considered not useful/effective, or may be harmful
I	Insufficient evidence to recommend for or against—the clinician will use clinical judgment

APPENDIX 2. VETERANS AFFAIRS/DEPARTMENT OF DEFENSE GUIDELINES

Recommendation statements receiving grades of A or B in the Veterans Affairs/ Department of Defense guidelines[27] for use of opioids in noncancer pain

Recommendation	Quality of evidence	Grade
Evaluate function related to pain	Good	A
Consider use of other treatment approaches, which should be coordinated with opioid therapy	Good	A
Long-acting agents are effective for continuous, chronic pain	Good	A
An opioid trial for either nociceptive or neuropathic pain	Good	A
Time-contingent dosing schedule	Good	A
Set dose levels based on patient needs, not predetermined maximal dose	Good	A
Titrate until an adequate level of analgesia is obtained	Good	A
Evaluate function related to chronic pain after initiation of therapy	Good	A
Recommend modifying the dose or rotating the opioid agent to minimize adverse effects	Good	A
For constipation • Prophylactic mild peristaltic stimulant for all patients • Increase the dose if no bowel movement in 48 hours • If no bowel movement in 72 hours, perform a rectal exam • If not impacted provide additional therapy (i.e. suppository, enema, magnesium citrate, etc.)	Good	A
For nausea and vomiting • Consider prophylactic antiemetic therapy • Add or increase non-opioid adjuvants • If analgesia is satisfactory, decrease opioid dose by 25% • Treat based on cause	Good	A
In cases of non-efficacy • Individual dose titration. Increase dose by 25-100% • Do not increase dose more frequently than every 5 half lives • Titrate only one drug at a time, while observing the patient for additive effects • Increase medication until limited by adverse effects or clear evidence of lack of efficacy	Good	A
In cases of non-efficacy • Rotate to another opioid based on equianalgesic table and titrate • Provide a drug holiday	Fair	B
Assess gender (prior to starting opioids)	Fair	B
Evaluate pain intensity using 0-10 scales	Fair	B
Refer to multidisciplinary pain clinic	Fair	B
No single agent is superior; in most patients, trials with several medications may be required; rotation among opioids may improve long-term efficacy	Fair	B
Treat adverse effects by modifying dose or by drug rotation	Fair	B
Consultation/referral to substance use disorder specialty for predicting addiction behaviors and continue opioid therapy	Fair	B
Assess effectiveness of treatment; revise treatment plan when pain rating is greater than 3	Fair	B

APPENDIX 2. VETERANS AFFAIRS/DEPARTMENT OF DEFENSE GUIDELINES

Recommendation statements receiving grades of A or B in the Veterans Affairs/ Department of Defense guidelines[27] for use of opioids in noncancer pain

Recommendation	Quality of evidence	Grade
For sedation • Determine whether sedation is due to the opioid; eliminate nonessential central nervous system depressants • If analgesia is satisfactory, reduce opioid dose by 10-15% • Add or increase non-opioid or non-sedating adjuvant for additional pain relief so that the opioid can be reduced • Add stimulant drug during the day such as caffeine • Change opioid	Fair	B
For itching • Consider treatment with antihistamines • Change opioids	Fair	B
For hallucination/dysphoria • Evaluate underlying cause • Eliminate nonessential central nervous system-acting medications (e.g. steroids)	Fair	B
For sexual dysfunction • Dose reduction • Testosterone injections may be helpful for men	Fair	B

APPENDIX 3. SEARCH STRATEGIES

Cochrane Database of Systematic Reviews: through 3rd Quarter 2008

1 opioid$.mp. (217)
2 narcotic$.mp. (133)
3 (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp.
4 (((intract$ or chronic$ or severe$ or unbearabl$) adj3 pain$) or agony or agoniz$).mp. (426)
5 (or/1-3) and 4 (126)

Cochrane Central Register of Controlled Trials: through 3rd Quarter 2008

General search

1 opioid$.mp. (6570)
2 narcotic$.mp. (3094)
3 (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp.
4 exp Narcotics/
5 exp Analgesics, Opioid/
6 or/1-5
7 (((intract$ or chronic$ or severe$ or unbearabl$) adj3 pain$) or agony or agoniz$).mp. (4644)
8 6 and 7 (1139)

Abuse

1 exp Narcotics/ (8863)
2 exp Analgesics, Opioid/ (9170)
3 narcotic$.mp. (3094)
4 opioid$.mp. (6570)
5 (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp. (16914)
6 exp Patient Compliance/ (5247)
7 exp Health Services Misuse/ (96)
8 exp "drug and narcotic control"/ (57)
9 (abuse$ or abusing or misus$ or diversion$ or divert$).mp. (4210)
10 exp Substance-Related Disorders/ (6065)
11 or/1-5 (19614)
12 or/6-10 (13513)
13 11 and 12 (1505)
14 (((intract$ or chronic$ or severe$ or unbearabl$) adj3 pain$) or agony or agoniz$).mp. (4644)
15 13 and 14 (26)

APPENDIX 3. SEARCH STRATEGIES

Driving

1 exp Narcotics/ (8863)
2 exp Analgesics, Opioid/ (9170)
3 narcotic$.mp. (3094)
4 opioid$.mp. (6570)
5 (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp. (16914)
6 or/1-5 (19614)
7 exp Automobile Driving/ (418)
8 exp Motor Vehicles/ (95)
9 exp Accidents, Traffic/ (193)
10 exp Accident Prevention/ (2426)
11 (car or cars or truck$ or automobil$ or motor vehicl$).mp. (878)
12 ((traffic$ or occupat$ or work$ or job or jobs or career$) adj7 (accident$ or injur$ or safe or safety or safer or safely)).mp. (870)
13 ((traffic$ or drive or driver$ or driving) adj7 (accident$ or injur$ or safe or safety or safer or safely)).mp. (427)
14 or/7-13 (4015)
15 6 and 14 (109)

Drug monitoring

1 exp Narcotics/ (8863)
2 exp Analgesics, Opioid/ (9170)
3 narcotic$.mp. (3094)
4 opioid$.mp. (6570)
5 (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp. (16914)
6 or/1-5 (19614)
7 ((medication$ or opioid$ or pain$) adj7 (contract$ or agree$)).mp. (407)
8 exp Drug Monitoring/ (663)
9 (adher$ adj5 monitor$).mp. (192)
10 ((pill or pills or tablet$ or dose or doses or prescript$) adj7 (limit$ or count$ or ration$ or monitor$)).mp. (3900)
11 or/7-10 (5051)
12 6 and 11 (344)

Prognosis

1 exp Narcotics/ (8863)
2 exp Analgesics, Opioid/ (9170)
3 narcotic$.mp. (3094)
4 opioid$.mp. (6570)
5 (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or

APPENDIX 3. SEARCH STRATEGIES

hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp. (16914)
6 or/1-5 (19614)
7 exp "Sensitivity and Specificity"/ (8664)
8 Prognosis/ (6775)
9 exp risk/ (16062)
10 "outcome and process assessment (health care)"/ or "outcome assessment (health care)"/ or "process assessment (health care)"/ (3328)
11 diagnostic accuracy.mp. (753)
12 receiver operating characteristic.mp. or ROC Curve/ (650)
13 6 and (or/7-12) (436)
14 (((intract$ or chronic$ or severe$ or unbearabl$) adj3 pain$) or agony or agoniz$).mp. (4644)
15 13 and 14 (36)

Pseudoaddiction
1 exp Narcotics/ (8863)
2 exp Analgesics, Opioid/ (9170)
3 narcotic$.mp. (3094)
4 opioid$.mp. (6570)
5 (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp. (16914)
6 or/1-5 (19614)
7 pseudoaddict$.mp. (0)
8 ((fake$ or faking or false$ or mislead$ or deceiv$) adj7 (addict$ or depend$)).mp. (16)
9 7 or 8 (16)
10 6 and 9 (1)

Urine testing
1 exp Narcotics/ (8863)
2 exp Analgesics, Opioid/ (9170)
3 narcotic$.mp. (3094)
4 opioid$.mp. (6570)
5 (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp. (16914)
6 or/1-5 (19614)
7 exp Substance Abuse Detection/ (214)
8 (urine adj7 (screen$ or test$ or detect$)).mp. (1019)
9 6 and (7 or 8) (187)

APPENDIX 3. SEARCH STRATEGIES

Ovid MEDLINE®: 1996 to November Week 1 2008

General search

1 opioid$.mp. (34446)
2 narcotic$.mp. (21927)
3 (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp. (39524)
4 exp Narcotics/ (25596)
5 exp Analgesics, Opioid/ (29000)
6 or/1-5 (64206)
7 (((intract$ or chronic$ or severe$ or unbearabl$) adj3 pain$) or agony or agoniz$).mp. (23075)
8 6 and 7 (3925)

Abuse

1 exp Narcotics/ (25596)
2 exp Analgesics, Opioid/ (29000)
3 narcotic$.mp. (21927)
4 opioid$.mp. (34446)
5 (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp. (39524)
6 exp Patient Compliance/ (20962)
7 exp Health Services Misuse/ (3191)
8 exp "drug and narcotic control"/ (8370)
9 (abuse$ or abusing or misus$ or diversion$ or divert$).mp. (71458)
10 exp Substance-Related Disorders/ (70229)
11 or/1-5 (64206)
12 or/6-10 (143539)
13 11 and 12 (15648)
14 (((intract$ or chronic$ or severe$ or unbearabl$) adj3 pain$) or agony or agoniz$).mp. (23075)
15 13 and 14 (537)

Driving

1 exp Narcotics/ (25596)
2 exp Analgesics, Opioid/ (29000)
3 narcotic$.mp. (21927)
4 opioid$.mp. (34446)
5 (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp. (39524)
6 or/1-5 (64206)

APPENDIX 3. SEARCH STRATEGIES

7 exp Automobile Driving/ (5186)
8 exp Motor Vehicles/ (5392)
9 exp Accidents, Traffic/ (11642)
10 exp Accident Prevention/ (28546)
11 (car or cars or truck$ or automobil$ or motor vehicl$).mp. (18562)
12 ((traffic$ or occupat$ or work$ or job or jobs or career$) adj7 (accident$ or injur$ or safe or safety or safer or safely)).mp. (27933)
13 ((traffic$ or drive or driver$ or driving) adj7 (accident$ or injur$ or safe or safety or safer or safely)).mp. (13868)
14 or/7-13 (66825)
15 6 and 14 (625)

Drug monitoring
1 exp Narcotics/ (25596)
2 exp Analgesics, Opioid/ (29000)
3 narcotic$.mp. (21927)
4 opioid$.mp. (34446)
5 (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp. (39524)
6 or/1-5 (64206)
7 ((medication$ or opioid$ or pain$) adj7 (contract$ or agree$)).mp. (1333)
8 exp Drug Monitoring/ (7452)
9 (adher$ adj5 monitor$).mp. (558)
10 ((pill or pills or tablet$ or dose or doses or prescript$) adj7 (limit$ or count$ or ration$ or monitor$)).mp. (15371)
11 or/7-10 (24204)
12 6 and 11 (970)

Prognosis
1 exp Narcotics/ (25596)
2 exp Analgesics, Opioid/ (29000)
3 narcotic$.mp. (21927)
4 opioid$.mp. (34446)
5 (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp. (39524)
6 or/1-5 (64206)
7 exp "Sensitivity and Specificity"/ (222915)
8 Prognosis/ (133602)
9 exp risk/ (378028)
10 "outcome and process assessment (health care)"/ or "outcome assessment (health care)"/ or "process assessment (health care)"/ (37910)
11 diagnostic accuracy.mp. (8869)
12 receiver operating characteristic.mp. or ROC Curve/ (15685)
13 6 and (or/7-12) (4118)
14 (((intract$ or chronic$ or severe$ or unbearabl$) adj3 pain$) or agony or agoniz$).mp. (23075)
15 13 and 14 (260)

APPENDIX 3. SEARCH STRATEGIES

Pseudoaddiction

1 exp Narcotics/ (25596)
2 exp Analgesics, Opioid/ (29000)
3 narcotic$.mp. (21927)
4 opioid$.mp. (34446)
5 (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp. (39524)
6 or/1-5 (64206)
7 pseudoaddict$.mp. (13)
8 ((fake$ or faking or false$ or mislead$ or deceiv$) adj7 (addict$ or depend$)).mp. (183)
9 7 or 8 (196)
10 6 and 9 (13)

Urine testing

1 exp Narcotics/ (25596)
2 exp Analgesics, Opioid/ (29000)
3 narcotic$.mp. (21927)
4 opioid$.mp. (34446)
5 (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp. (39524)
6 or/1-5 (64206)
7 exp Substance Abuse Detection/ (3270)
8 (urine adj7 (screen$ or test$ or detect$)).mp. (8471)
9 6 and (7 or 8) (1232)
10 from 9 keep 1-181 (181)

APPENDIX 4. QUALITY RATING SYSTEMS

Systematic Reviews

Criteria for assessing scientific quality of research reviews*

Criteria	*Operationalization of criteria*
1. Were the search methods reported? *Were the search methods used to find evidence (original research) on the primary questions stated?* **"Yes" if the review states the databases used, date of most recent searches, and some mention of search terms.**	The purpose of this index is to evaluate the scientific quality (i.e. adherence to scientific principles) of research overviews (review articles) published in the medical literature. It is not intended to measure literary quality, importance, relevance, originality, or other attributes of overviews. The index is for assessing overviews of primary ("original") research on pragmatic questions regarding causation, diagnosis, prognosis, therapy, or prevention. A research overview is a survey of research. The same principles that apply to epidemiological surveys apply to overviews: a question must be clearly specified, a target population identified and accessed, appropriate information obtained from that population in an unbiased fashion, and conclusions derived, sometimes with the help of formal statistical analysis, as is done in "meta-analyses". The fundamental difference between overviews and epidemiological studies is the unit of analysis, not the scientific issues that the questions in this index address. Since most published overviews do not include a methods section, it is difficult to answer some of the questions in the index. Base your answers, as much as possible, on information provided in the overview. If the methods that were used are reported incompletely relative to a specific question, score it as "can't tell", unless there is information in the overview to suggest either the criterion was or was not met.
2. Was the search comprehensive? *Was the search for evidence reasonably comprehensive?* **"Yes" if the review searches at least 2 databases and looks at other sources (such as reference lists, hand searches, queries experts).** *Note: EMBASE was launched in 1972, and CDSR was launched in 1994, therefore papers prior to 1994 can be graded "Yes" if only one database is searched.*	
3. Were the inclusion criteria reported? *Were the criteria used for deciding which studies to include in the overview reported?*	
4. Was selection bias avoided? Was bias in the selection of studies avoided? **"Yes" if the review reports how many studies were identified by searches, numbers excluded, and gives appropriate reasons for excluding them (usually because of pre-defined inclusion/exclusion criteria).**	
5. Were the validity criteria reported? *Were the criteria used for assessing the validity of the included studies reported?*	
6. Was validity assessed appropriately? *Was the validity of all the studies referred to in the text assessed using appropriate criteria (either in selecting studies for inclusion or in analyzing the studies that are cited)?* **"Yes" if the review reports validity assessment and did some type of analysis with it (e.g. sensitivity analysis of results according to quality ratings, excluded low-quality studies, etc.)**	

APPENDIX 4. QUALITY RATING SYSTEMS

Systematic Reviews

Criteria for assessing scientific quality of research reviews*

Criteria	*Operationalization of criteria*
7. Were the methods used to combine studies reported? *Were the methods used to combine the findings of the relevant studies (to reach a conclusion) reported?* **"Yes" for studies that did qualitative analysis if there is some mention that quantitative analysis was not possible and reasons that it could not be done, or if 'best evidence' or some other grading of evidence scheme used.**	For Question 8, if not attempt has been made to combine findings, and no statement is made regarding the inappropriateness of combining findings, check "No". if a summary (general) estimate is given anywhere in the abstract, the discussion, or the summary section of the paper, and it is not reported how that estimate was derived, mark "No" even if there is a statement regarding the limitations of combining the findings of the studies reviewed. If in doubt, mark "Can't tell". For an overview to be scored as "Yes" in Question 9, data (not just citations) must be reported that support the main conclusions regarding the primary question(s) that the overview addresses. The score for Question 10, the overall scientific quality, should be based on your answers to the first nine questions. The following guidelines can be used to assist with deriving a summary score: If the "Can't tell" option is used one or more times on the preceding questions, a review is likely to have minor flaws at best and it is difficult to rule out major flaws (i.e. a score of 4 or lower). If the "No" option is used on Question 2, 4, 6 or 8, the review is likely to have major flaws (i.e. a score of 3 or less, depending on the number and degree of the flaws).
8. Were the findings combined appropriately? *Were the findings of the relevant studies combined appropriately relative to the primary question the overview addresses?* **"Yes" if the review performs a test for heterogeneity before pooling, does appropriate subgroup testing, appropriate sensitivity analysis, or other such analysis.**	
9. Were the conclusions supported by the reported data? *Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview?*	
10. What was the overall scientific quality of the overview? *How would you rate the scientific quality of this overview?*	
Each Question is scored as Yes, Partially/Can't tell or No	

Extensive Flaws		**Major Flaws**		**Minor Flaws**		**Minimal Flaws**
1	2	3	4	5	6	7

*Table created using information from Oxman & Guyatt, J Clin Epidemiol. 1991;44(11):1271-8 and Furlan, Clarke, et al., Spine. 2001 Apr 1;26(7):E155-62.

APPENDIX 5. QUALITY RATING SYSTEMS

Primary Studies

Criteria list for methodological quality assessment*

Criteria	*Operationalization of Criteria*	*Score*
***A. Was the method of randomization adequate*?**	A random (unpredictable) assignment sequence. An example of adequate methods is a computer generated random number table and use of sealed opaque envelopes. Methods of allocation using DOB, date of admission, hospital numbers, or alternation should not be regarded as appropriate.	Yes/No/ Don't Know
B. Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	Yes/No/ Don't Know
C. Were the groups similar at baseline regarding the most important prognostic factors? *"Yes", if similar:* • *Age & gender* • *Description of type of pain* • *Intensity, duration or severity of pain*	In order to receive a "yes", groups have to be similar in baseline regarding demographic factors, duration or severity of complaints, percentage of patients with neurologic symptoms, and value of main outcome measure(s).	Yes/No/ Don't Know
D. Was the patient blinded to the intervention?	The reviewer determines if enough information about the blinding is given in order to score a "yes": Use the author's statement on blinding, unless there is a differing statement/reason not to (no need for explicit information on blinding). If a study notes it is double-blind, code "yes" for patient, care provider and outcome assessor (unless it is clear that one of these is not blinded).	Yes/No/ Don't Know
***E. Was the care provider blinded to the intervention*?**		
F. Was the outcome assessor blinded to the intervention?		
G. Were cointerventions avoided or similar?	Cointerventions should either be avoided in the trial design or similar between the index and control groups. Code "yes" if there is a statement about co-intervention medications being used or not use. e.g.: rescue analgesics not allowed or note about which rescue analgesics were permitted or if rescue analgesics are outcomes.	Yes/No/ Don't Know
H. Was the compliance acceptable in all groups?	The reviewer determines if the compliance to the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). Code "yes" if protocol violations are reported or if actual compliance data is reported.	Yes/No/ Don't Know

APPENDIX 5. QUALITY RATING SYSTEMS

Primary Studies

Criteria list for methodological quality assessment*

Criteria	*Operationalization of Criteria*	*Score*
I. Was the drop-out rate described and acceptable? *≤15% drop out rate is acceptable.*	The number of participants who are included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 15% and does not lead to substantial bias, a "yes" is scored.	Yes/No/ Don't Know
J. Was the timing of the outcome assessment in all groups similar?	Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.	Yes/No/ Don't Know
K. Did the analysis include an intention-to-treat analysis? *"Yes" if less than 5% of no-treatment excluded.*	All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of noncompliance and cointerventions.	Yes/No/ Don't Know
This list includes only the internal validity criteria (N=11) that refer to characteristics of the study that might be related to selection bias (criteria A and B), performance bias (criteria D, E, G, and H), attrition bias (criteria I and K and detection bias (criteria f and J). The internal validity criteria should be used to define methodologic quality in meta-analysis.		

* Table adapted from methods developed by the Cochrane Back Review Group (van Tulder, Furlan, Bombardier, Bouter, and Editorial Board of the Cochrane Collaboration Back Review Group) Spine. 2003;28(12):1290-9.

Jadad Quality Rating for Primary Studies*

Criteria	*Scoring*	*Operationalization of Criteria*	*Criteria Score*
Randomization: Was the study described as randomized (use of words such as randomly, random, and randomization)?	Yes = 1 No = 0	***Add 1 point if:*** Method to generate the sequence of randomization was described *and* was appropriate (e.g. computer-generated, table of random numbers, etc.) and adequate method used for allocation concealment (e.g. centralized randomization or opaque, sealed envelopes) ***Subtract 1 point if:*** Method of randomization described and inappropriate (e.g.: alternating patients, different hospital, etc.)	0 - 2
Blinding: Was the study described as double-blind?	Yes = 1 No = 0	***Add 1 point if:*** Method of double blinding described and appropriate (identical placebo, active placebo, term "double-dummy " used) ***Subtract 1 point if***: Method of double blinding described and inappropriate (comparison of tablets that are not identical-appearing)	0 - 2
Withdrawals and drop-outs: Was there a description of withdrawals and dropouts?	Yes = 1 No = 0	**Only 0 or 1 possible.**	0 or 1
		OVERALL SCORE = 1 – 5 (max score is 5)	

* Jadad AR et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Controlled Clin Trials 1996; 17:1-12.

APPENDIX 6. SYSTEMATIC REVIEWS EVIDENCE TABLES

Included systematic reviews on efficacy of opioids for chronic noncancer pain

Author, year, title	Key Question(s)	Purpose of study	Databases searched, date of last search	Number of studies	Types of studies included/ limitations of primary studies	Methods for rating methodological quality of primary studies	Methods for synthesizing results of primary studies	Number of patients (treatment and control)	Interventions	Results	Adverse events	Overall quality rating*
Cepeda, 2006[74] Tramadol for osteoarthritis	4 5	1. To determine the analgesic effectiveness of oral tramadol or tramadol/paracetamol for osteoarthritic pain. 2. To determine the effectiveness of tramadol for improving physical function in people with OA. 3. To assess the duration of any benefit. 4. To determine the safety of tramadol.	Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and LILACS databases up to August 2005. No language restrictions.	11	RCTs that evaluated the effect of tramadol or tramadol plus paracetamol on pain levels and/or physical function in people with primary or secondary osteoarthritis (excluded studies of other types of arthritis & back pain). Published & unpublished studies were eligible. Limitations: Average length of follow-up of the trials was 35 days. High loss to follow-up in all trials. All but one trial funded by pharmaceutical industry. There is evidence suggesting that industry funded studies could overestimate treatment effects.	Separately rated & described whether the trial reported: a description of the randomization; allocation concealment; masking process; whether withdrawals were 20% or more; similarity between baseline characteristics of treatment groups; and analysis of outcomes according to the intention-to-treat principle.	Separately analyzed placebo-controlled and active controlled trials; analyzed together trials that evaluated tramadol alone or tramadol plus acetaminophen. Used a fixed-effect model for the quantitative analysis because results were similar across trials.	1019 received tramadol or tramadol/ para-cetamol 920 received placebo or active-control	200mg oral tramadol per day, or an NSAID or different pain reliever for one week to 3 months.	Pain: tramadol vs. placebo tramadol less pain (-8.5 units on a 0 to 100 scale; 95% confidence interval [CI] -12.0 to -5.0) 12% relative decrease in pain intensity from baseline. Patients taking tramadol had a 37% increase (95% CI 1.2 to 1.5) in the likelihood of reporting moderate improvement. Number needed to treat to benefit (NNTB) = 6 (95% CI 4 to 9).	Tramadol : 2.27 X risk of developing minor adverse events 2.6 X risk of developing major adverse vs. placebo. Of every eight patients who receive tramadol or tramadol/paracetamol, one will stop taking the medication because of adverse events. Number needed to treat to harm (NNTH)= 8 (95% CI 7 to 12) for major adverse events.	7

* Detailed consensus quality ratings provided in Appendix 7

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Chou, 2003[53] Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review	7	Summarize and assess comparative efficacy and safety of long-acting opioids in the management of chronic non-cancer pain.	Cochrane Library (2002, Issue 1), MEDLINE, and EMBASE (both through October 2002) Language: English	24 total: 16 RCTs 8 observ-ational studies	Randomized trials (for comparative efficacy and adverse events) and observational studies (for adverse events only) that included non-parenteral long-acting opioids for treatment of adults with chronic non-cancer pain. Limitations: No randomized trial was rated good quality and observational studies were of generally poorer quality than the trials. Lack of high-quality evidence to answer key questions. Included studies were of relatively short duration: 5 days-16 weeks.	Tool with pre-defined criteria used to assess internal and external validity.	Strength of evidence for body of literature pertaining to each key question was assessed in standardized manner based on criteria developed by the US Preventive Task Force and the National Health Service Center for reviews and Dissemination (UK). Evidence was synthesized and evaluated in response to key questions established prior to the evidence search.	RCTs: 1427 Observ-ational: 1190	Long-acting and short-acting opioids used for treating adults with chronic non-cancer pain. Studies found investigated transdermal fentanyl, long-acting oral oxycodone, morphine, codeine and dihydro-codeine.	Efficacy for pain and functional outcomes Head-to head comparisons Insufficient evidence for efficacy determination. 1 poor-quality study and 1 fair-quality trial of 1x/day vs. 2x/day morphine: Pain control: NS Sleep quality: 1 of 7 measures showed slight but significant improvement in 1x/day (morning dose but not evening dose) vs. 2x/day dose. Long-acting opioids vs. other drugs or placebo 14 trials of insufficient quality to compare efficacy of long-acting opioids. Long-acting vs. short-acting opioids Insufficient evidence in 7 fair-quality trials to suggest efficacy of long-acting opioids as a class vs. short-acting opioids. Long-acting vs. short-acting oxycodone Clinical efficacy: NS (3 trials) Pain control: equally effective (3 trials, fair evidence).	Head-to head comparisons I fair quality trial of 1x/day vs. 2x/day morphine: > constipation, < asthenia. Other AE rates: NS Insufficient evidence favoring any particular long-acting opioid for AEs. Long-acting opioids vs. other drugs or placebo 13 trials of insufficient quality to determine relative risk of assessed adverse events. Rates of abuse and addiction not reported in the trials. Observational studies also of insufficient quality to provide reliable information on relative risk.	6

* Detailed consensus quality ratings provided in Appendix 7

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Clark, 2004[75] Efficacy and safety of transdermal fentanyl and sustained-release oral morphine in patients with cancer and chronic non-cancer pain	4 5	To evaluate effectiveness and safety of transdermal fentanyl (TDF) and sustained release morphine (SRM) in cancer pain (CP) and chronic noncancer pain (CNCP) using a pooled analysis on datasets of published, open label, uncontrolled (no comparator group) and randomized controlled (with SRM as comparator) studies of TDF.	MEDLINE (to February 2004) Language: English	8 total: 4 trials with CNCP patients reported here	Open label, uncontrolled and randomized controlled (with SRM as comparator) clinical studies of TDF with minimum treatment duration of 28 days. Limitations: Short (28-day) treatment period. Studies not quality rated. Highly selected patient population limits generalizability.	Studies not quality rated	All variables summarized with descriptive statistics. Between-treatment differences tested with 2-sided *t*-test for comparison of independent samples. Within-treatment differences for change from baseline to day 28 tested using 2-sided, paired *t*-test. Between-treatment incidence of AEs were compared using Fisher's exact test.	1220 total for pooled efficacy data	Transdermal fentanyl vs. sustained-release oral morphine, 28-day treatment for patients with cancer and chronic non-cancer pain.	NCP subgroup results Normalized pain scores on 0-100 scale, change from baseline to Day 28 Average pain, SRM vs. TDF -17.7 ± 26.2 (N=121) vs. -21.0 ± 24.4 (N=271) NS Pain 'right now', SRM vs. TDF -16.5 ± 28.9 (N=121) vs. -24.1 ± 28.7 (N=272) p=0.017	AEs 1st 28 days of treatment, NCP subgroup results SRM (N=488) vs. TDF (N=1285) Patients with any AE: 87.3% vs. 71.2%, p<0.001 Patients with serious AE: 3.9% vs. 3.9%, NS Patients with drug-related AE: 80.7% vs. 62.3%, p<0.001 Drugs discontinued due to AE: 19.3% vs. 20.4%, NS Deaths: 0 vs.0.2%, NS Constipation: 52% vs. 17%, p<0.001 Nausea: 39% vs. 30%, p<0.001 For CNCP and CP groups together: Somnolence: 25% vs. 13%, p<0.001	2

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Deshpande, 2007[76] Opioids for chronic low-back pain (Cochrane Review)	4 5	To evaluate efficacy of opioids for chronic low back pain	Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, PsychINFO (all to May 2006); MEDLINE and EMBASE (to May 2007) Language: No restriction	4	Randomized and quasi-randomized controlled trials of opioids for chronic low back pain Limitations: Narrowly and/or poorly defined study populations, high drop out rates. Small number of trials (4).	Cochrane Collaboration system	Meta-analysis with RevMan, reporting standardized mean difference or absolute risk difference (for harms); also qualitative synthesis based on five levels of evidence	944 total	All trials evaluated oral opioid or tramadol	Tramadol (with or without acetaminophen) vs. placebo Pain relief (SMD): -0.71 (95% CI -1.02 to -0.39), 3 trials Roland Disability Questionnaire (SMD): -0.17 (955 CI -0.3 to -0.04), 3 trials Set-dose or titrated dose opioid versus naproxen alone Pain relief (SMD): -0.58 (955 CI -1.42 to 0.26), 1 trial Function: No difference, 1 trial	Tramadol (with or without acetaminophen) vs. placebo Headache (risk difference): 9% (95% CI 6% to 12%), 3 trials Nausea (risk difference): 3% (0% to 6%), 3 trials Somnolence (risk difference): 9% (95% CI 5% to 13%), 2 trials Constipation (risk difference): 8% (95% CI 4% to 12%), 2 trials Dry mouth (risk difference): 7% (95% CI 4% to 10%) Dizziness (risk difference): 8% (95% CI 4% to 12%)	7

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Devulder, 2005[77] Impact of long-term use of opioids on quality of life in patients with chronic, non-malignant pain	4 5	Objective: To present the results of quality of life (QoL) and patient functioning in long-term opioid treatment for the management of non-malignant pain.	MEDLINE (1966-November/December 2004), EMBASE (1974-November/December 2004), the Oxford Pain Relief Database (Bandolier; 1954–1994) and the Cochrane Central Register of Controlled Trials (CENTRAL). Language: English, German, and French papers included.	11	Eligible studies were blinded or open-label trials with either a randomised, controlled, or an observational design.	Jadad	Unknown - each trial was summarized independently within review & in effects of treatment table.	2877	Transdermal fentanyl (TDF) - 25, 50, 75, or 100 µg/hr patches; sustained-released oral morphine (SRM) -10, 30, 60, 100, or 200mg for a variety of chronic pain conditions: LBP, CNCP, OA of the knee, post-herpetic neuralgia, diabetic neuropathy, non-malignant pain.	Six RCTs: four studies in which baseline QoL was reported, three showed an improvement in QoL. Five observational studies: In general, had higher Jadad rating scores for the quality of the paper than RCTs. A significant improvement in QoL was reported in four studies.	TDF: 10 reported constipation (ranged from 4.7-52%); 8 studies reported nausea (ranged from 11.2-93%); 5 reported vomiting (ranged from 4.2-54%) and somnolence (ranged from 8-22.5%); 3 reported excessive sweating (ranged from 3-68%); 4 reported dizziness (ranged from 25-53%); 2 reported fatigue (ranged from14-57%); and one study reported poor appetite (14%) and headache (68%). SRM: 3 studies reported constipation (ranged from 41-68%), 2 reported nausea (ranged from 18-50%), vomiting (ranged from 26-39%), and dizziness (ranged from 24-37%); one reported somnolence (30%), poor appetite (39%), abdominal pain (22%), and fatigue (22%). Placebo: one study reported nausea (32%), blurred vision (20%), sleeplessness (17%), confusion (158%), and diarrhea (13%).	2

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APPENDIX 6. SYSTEMATIC REVIEWS EVIDENCE TABLES

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Eisenberg, 2005[78] Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin	4 5	To assess the efficacy and safety of opioid agonists for the treatment of neuropathic pain based on published RCTs.	MEDLINE (through November 2004), Cochrane Central Register of Controlled Trials (through 4th quarter, 2004). Language: not specified.	22 total 8 intermed-iate term trials reported here	Trials in which opioid agonists were used to treat central or peripheral neuropathic pain of any etiology, pain was assessed using validated instruments, and adverse events were reported. Limitations: Most trials not long enough to estimate duration of efficacy of opioids for chronic pain, the potential for opioid tolerance, or long-range adverse effects. Trials had only narrow ranges of fixed doses. Drop-outs not reported. Intermediate term trials reviewed here were of crossover (5) and parallel design (3), which are more likely to have unbiased results than RCTs.	Jadad scale	For intermediate term trials: Meta-analyses for overall mean pain intensity. Hetero-geneity within and between trials evaluated with Chi Square test. Fixed effects model used for all analyses as studies combined appeared homogenous. Funnel chart used to determine lack of publication bias. P values < .05 considered significant. Relative risks calculated for adverse events, along with number needed to harm (NNH) when possible.	670 total 403 in intermediate term trials, data reported here	Opioid agonists used to treat central or peripheral neuropathic pain of any etiology. In intermediate term trial results reported here, drugs used were morphine, oxycodone, methadone and levorphanol.	Only intermediate term trial (duration of treatment 8 days to 8 weeks) results reported here. Total of 8 trials (5 crossover, 3 parallel design), 403 patients. Opioid vs. placebo, overall mean pain intensity: opioid 14 points lower 95% CI, -18 to -10, p<.001 (meta-analysis 263 opioid, 258 placebo-treated patients). Dose-dependent analgesic effect found in 2 studies. Secondary outcomes of disability, sleep, cognition, depression measured in 6 trials but not quantitatively combined due to varied measurement tools. No consistent reduction in disability with opioids. No findings showing improvement in depression with opioids.	Data based on 5 intermediate term trials and 2 additional studies. Nausea: NNH 3.6; 95% CI, 2.9-4.8 Constipation: NNH 4.6; 95% CI, 3.4-7.1 Drowsiness: NNH 5.3; 95% CI, 3.7-8.3 Vomiting: NNH 6.2; 95% CI, 4.6-11.1 Dizziness: NNH 6.7; 95% CI, 4.8-10.0 Number of drop-outs due to AEs in 4 studies: 13.5% (33/244) opioids vs. 7.6% (12/156) placebo.	7

* Detailed consensus quality ratings provided in Appendix 7

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Fishbain, 2002[86] Can patients taking opioids drive safely? A structured evidence-based review	10	To determine if there is epidemiological evidence of an association between opioid use and intoxicated driving, motor vehicle accidents (MVA) and MVA fatalities. To rate the quality of evidence using AHCPR type, strength and consistency criteria. To determine whether patients taking opioids can drive safely.	Medline, Psychological Abstracts, Science Citation Index, National Library of Medicine Physician Data Query (PDQ), all through 2000 Language: No language restrictions	25	All available studies addressing intoxicated driving and opioids, MVA and opioids, and MVA fatalities and opioids. Limitations: Heterogeneity of design among included studies, diversity of included populations. Studies not quality rated. Lack of relevant control groups. Potential confounders include lack of control for: adequate reference group, risk due to use of opioids vs. other drugs, and effects of underlying disease process for which drug was prescribed	Studies not quality rated	Included studies sorted into 3 topic areas: (1) intoxicated driving and opioids, (2) MVA and opioids, (3) MVA fatalities and opioids. For each topic area, studies were categorized using AHCPR guidelines, and strength and consistency of evidence in each topic area was categorized according to AHCPR guidelines.	Not explicitly reported - sample sizes reported in tables	Whether patients taking opioids can drive safely was assessed	Intoxicated driving: 6 studies total, 5 non-experimental, 1 experimental. All studies reported opioid use prevalence approx-imately 1/10 that of the point prevalence in the general population. Authors conclude this suggests opioids are probably not associated with intoxicated driving. MVA: 9 studies total, 5 quasi-experimental and 4 experimental. All but 1 indicated opioids are not associated with MVA. Authors conclude the evidence overall is that opioids are not associated with MVA. MVA fatalities: 10 studies total, non-experimental. For most of the studies, prevalence percentages for an opioid association with MVA fatalities was 1/5 the point prevalence percentage for opioid use reported in the general population. only 1 study reported a possible association between opioid use and MVA fatalities.	Not reported.	3

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Fishbain, 2003[87] Are opioid dependent/tolerant patients impaired in driving-related skills? A structured evidence-based review	10	To review evidence on whether opioids affect driving abilities of patients on stable doses of opioids or who would be presumed to have tolerance to sedative effects. To evaluate the strength of the evidence using a structured evidence-based review process and the AHCPR categories	Medline, Psychological Abstracts, Science Citation Index, National Library of Medicine Physician Data Query (PDQ), all through 2001 Language: No language restrictions	48	All available studies addressing whether opioid-dependent/tolerant patients are impaired in driving-related skills. Limitations: Heterogeneity of design among included studies, diversity of included populations (addicts, cancer patients, methadone users, CNCP). No quality rating of studies. Multiple measures of impairment with no standard measurement used. Lack of relevant control groups. Potential confounders include lack of control for: pain, education level, disease-associated symptoms, non-opioid drug abuse history. Some populations highly selected and evaluated in highly defined settings, limiting applicability.	Studies not quality rated	Included studies sorted into 5 topic areas: (1) psychomotor abilities, (2) cognitive function, (3) effect of opioid dosing on psychomotor abilities, (4) motor vehicle driving violations and accidents, (5) driving impairment as measured in driving simulators and off/on road driving studies. For each topic area, studies were categorized using AHCPR guidelines, and strength and consistency of evidence in each topic area was categorized according to AHCPR guidelines and a quantitative method.	Not explicitly reported - sample sizes reported in tables	Driving-related skills in opioid tolerant/dependent patients were assessed.	Psychomotor abilities: moderate, generally consistent evidence for no impairment among opioid-maintained patients Cognitive function: inconclusive evidence, multiple studies, for no impairment in opioid-maintained patients Effect of opioid dosing on psychomotor abilities: strong, consistent evidence from multiple studies for no impairment immediately after being given doses of opioids Motor vehicle driving violations and accidents: strong, consistent evidence for no greater incidence in motor vehicle violations/motor vehicle accidents versus comparable controls of opioid maintained patients Driving impairment as measured in driving simulators and off/on road driving studies: consistent evidence for no impairment	Not reported	3

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Furlan, 2006[79] Opioids for non-cancer pain: a meta-analysis of effectiveness and side effects	1a 4 5 8	1. To determine efficacy of opioids for CNCP versus placebo. 2. To compare effectiveness of opioids for CNCP with that of other drugs. 3. To identify categories of CNCP with better response to opioids. 4. To determine the most common side effects and complications of opioids for CNCP, including incidence of opioid addiction and sexual dysfunction.	MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, ACP Journal Club, DARE (through April 2005). Language: English, French or Spanish language trials.	41	Trials of any opioid administered by oral, transdermal or rectal routes ≥ 7 days with outcome data on pain, function or side effects. Limitations: Most trials not long enough to estimate duration of efficacy of opioids for chronic pain, the potential for opioid tolerance, or long-range adverse effects. Reliance on self-report measures for function measures. Most trials not adequately designed as equivalence or noninferiority trials. Only 17 of the trials were adequately randomized. High drop-out rates in opioid (33%) and control (38%) groups.	Jadad scale	Meta-analyses with standard mean differences for pain and functional outcomes. Absolute risk differences calculated for side effects. Statistical heterogeneity tested by Q test. Random effects model for meta-analyses. Sensitivity analyses calculated within subgroups of studies. Cumulative meta-analyses with STRATA. Side effects clinically significant if incidence ≥ 10% in either group.	6019	Any opioid administered by oral, transdermal or rectal routes > 7 days.	Efficacy opioids vs. placebo Pain: SMD -0.60, 95% CI -0.69 to -0.50 (28 trials, meta-analysis) Cumulative meta-analysis (28 trials) showed efficacy reached stable effect size in 2002, prior to 8 trials published since. NS for patient category of mixed pain (single trial, small n). Function: SMD -0.31, 95% CI -0.41 to -0.22 (20 trials, meta-analysis). Sensitivity analysis: for long-acting morphine, patients with mixed pain and low quality studies, effect in favor of opioids but CI included null effect. Cumulative meta-analysis (20 trials) corroborated those of pain outcomes. Tramadol vs placebo (sensitivity analysis): Pain: SMD -0.57, 95% CI -0.70 to -0.44 (9 trials, 1378 patients) Function: SMD -0.30 95% CI -0.45 to -0.16 (6 trials, 1122 patients) Effectiveness opioids vs other drugs: Pain relief: NS, SMD -9.95, 95% CI -0.32 to 0.21 (8 trials, meta-analysis). Sensitivity analysis: no change with type of drug (NSAID, TCA, methodological quality), but strong opioids (oxycodone, morphine) > effective than other drugs, SMD -0.34, 95%CI -0.67 to -0.01. 1 trial not in meta-analysis: codeine + acetaminophen > acetaminophen at 7 days follow-up, but not later. Function: Opioids < effective. SMD 0.16, 95% CI 0.03 to 0.30.	Opioids vs. placebo constipation: RD 16%, 95% CI 10-22% nausea: RD 15%, 95% CI 11%-19% dizziness/vertigo: RD 8%, 95% CI 5%-12% somnolence/drowsiness: RD 9%, 95% CI 5%-13% vomiting: RD 5%, 95% CI 2%-7% dry skin/itching/pruritus: RD 4%, CI 1%-6% Opioids vs. other drugs nausea: 14% (95%CI 4%-25%) constipation: 9% (1%-17%) drowsiness: 6% (0-11%) Tramadol vs. placebo Diarrhea: < frequent in opioids, RD -2%, 95%CI -3% to 0	7

Detailed consensus quality ratings provided in Appendix 1, Table 2.

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Hollingshead, 2006[80] Tramadol for neuropathic pain (Cochrane Review)	4 5	Systematically review the evidence from randomized control trials for the efficacy of tramadol in treating neuropathic pain	Cochrane Neuromuscular Disease Group Trials Register, MEDLINE, EMBASE and LILACS (all to June 2005)	6	Randomized and "quasi-randomized" controlled trials comparing tramadol with placebo, other pain relieving treatment, or no treatment in people of both sexes and all ages with neuropathic pain of all degrees of severity. Limitations: Differences in methodology among included studies. Pain relief rated on different scales. Short duration: 4-7 weeks.	Cochrane Collaboration system	Tested heterogeneity with RevMan; fixed effects model to calculate RR with 95% CI. Quality analysis of trials used to explore any significant heterogeneity between them. (Unable to perform intended subgroup analysis on painful peripheral neuropathy as all trials examined only that condition alone.) 3 trials comparing tramadol with placebo were combined in a meta-analysis.	399 total	Any form of tramadol treatment	Tramadol vs. placebo In 3 trials, proportion of subjects with 50% pain relief: combined relative benefit 1.7 (95% CI 1.36 to 2.14). Adding 4th trial with 40% pain relief: combined relative benefit 1.8 (95% CI 1.4 to 2.3). NNT for 50% pain relief = 3.8 (95% CI 2.8 to 6.3) Tramadol vs. clomipramine NS (1 poor quality trial) Tramadol vs. morphine Not able to draw conclusions (1 poor quality trial) Touch evoked pain Tramadol reduced > placebo ($p<0.001$). NS at 50% pain relief threshold.	No life-threatening AEs or AEs requiring hospitalization or prolonged hospital stays. Withdrawal due to side effects: RR 5.4 (1.6 to 17.8); NNH 7.7 (95% CI 4.6 to 20) based on combined data from 2 trials. NNH 8.3 (95% CI 5.6 to 17) based on data from 3 placebo-controlled trials.	5

* Detailed consensus quality ratings provided in Appendix 7

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Included systematic reviews on efficacy of opioids for chronic noncancer pain

Author, year, title	Key Question(s)	Purpose of study	Databases searched, date of last search	Number of studies	Types of studies included/ limitations of primary studies	Methods for rating methodological quality of primary studies	Methods for synthesizing results of primary studies	Number of patients (treatment and control)	Interventions	Results	Adverse events	Overall quality rating*
Kalso, 2004[81] Opioids in chronic non-cancer pain: systematic review of efficacy and safety	1a 4 5 8	To analyze available randomized, placebo-controlled trials of WHO step 3 opioids for efficacy and safety in chronic non-cancer pain.	MEDLINE, EMBASE, (through August 2003) Cochrane Library (on-line September 2003) and the Oxford Pain Relief Database (1950-1994). Language: report notes no restriction of language.	15 total 11 trials of oral opioids reported here (IV interven-ions not included here)	Randomized comparisons of WHO step 3 opioids with placebo in chronic non-cancer pain. Double blind studies reporting on pain intensity outcomes using validated pain scores. Trails reported here included neuropathic pain (6), musculoskeletal pain (4), and mixed pain (1). Limitations: Most trials not long enough to estimate duration of efficacy of opioids for chronic pain, the potential for opioid tolerance, or long-range adverse effects. High drop-out rate; only 66% completed. In the 5 studies that tested concealment of blinding, majority of patients and investigators distinguished opioid from active and inactive placebo.	Jadad scale for quality with addition of 5-item validity scale (Smith, et al, 2000)	Relative risk (RR) calculated with 95% confidence intervals using a fixed effect model and was considered statistically significant when the confidence interval did not include 1. When the RR was significant, NNH was calculated using the Cook and Sacket method (1995) with a 95% confidence interval. Homogeneity was examined visually.	1145 total 1025 in oral trials, reported here	Oral opioid vs. placebo 4 days to 8 weeks. Morphine (5 trials), morphine or methadone (1 trial), oxycodone (4 trials). Active placebo (benztropine) in 2 trials. One trial had 3 treatment arms, including an anti-depressant. IV trials not reported here.	Only oral opioid results reported here. 6 crossover design and 5 parallel group trials. Mean pain relief: $\geq$ 30% with opioids in both neuropathic and nociceptive pain ($p<0.05$ to $p<0.0001$ in 7 trials) Allodynia: mean weekly VAS for steady pain, brief pain and dynamic mechanical: reduction for oxycodone vs. placebo Sleep quality: improvement with opioids in all 7 studies reporting, 2 noting improved sleep only when pain relief Depression: NS in 6 studies Mood: improved in opioids with pain relief in 2 studies Self-reported activity levels, pain-related interference in daily activity, pain disability index, physical function, pain interference with walking or general activity: NS (5 studies). Improvement of pain-related disability closely correlated with pain relief (1 study). Disability scores lower with oxycodone vs. placebo (2 studies) Quality of life: 3 studies used validated questionnaires; 1 showed improvement with oxycodone.	Opioid vs. placebo, RR and NNH with 95%CI Any adverse event: 80% vs. 56%, RR 1.4 (1.3-1.6), NNH 4.2 (3.1-6.4), 4 trials Discontinuation due to AE: 24% vs.15%, RR 1.4 (1.1-1.9), NNH 12 (8.0-27), 8 trials Constipation: 41% vs. 11%, RR 3.6 (2.7-4.7), NNH 3.4 (2.9-4.0), 8 trials Nausea: 32% vs. 12%, RR 2.7 (2.1-3.6), NNH 5.0 (4.0-6.4), 8 trials Somnolence/sedation: 29% vs. 10%, RR 3.3 (2.4-4.5), NNH 5.3 (4.3-7.0), 7 trials Vomiting: 15% vs. 3%, RR 6.1 (3.3-11), NNH 8.1 (6.4-11), 7 trials Dizziness: 20% vs. 7%, RR 2.8 (2.0-4.0), NNH 8.2 (6.3-12), 8 trials Itching: 15% vs. 7%, RR 2.2 (1.4-3.3), NNH 13 (8.4-27), 6 trials Dry mouth: 15% vs. 9%, RR 1.5 (1.0-2.1) NS, NNH not calculated, 7 trials Headache: 8% vs. 12%, RR 0.8 (0.5-1.3) NS, NNH not calculated, 4 trials.	7

* Detailed consensus quality ratings provided in Appendix 7

APPENDIX 6. SYSTEMATIC REVIEWS EVIDENCE TABLES

Included systematic reviews on efficacy of opioids for chronic noncancer pain

Author, year, title	Key Question(s)	Purpose of study	Databases searched, date of last search	Number of studies	Types of studies included/ limitations of primary studies	Methods for rating methodological quality of primary studies	Methods for synthesizing results of primary studies	Number of patients (treatment and control)	Interventions	Results	Adverse events	Overall quality rating*
Martell, 2007[82] Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction	4 5	To determine the prevalence of opioid treatment, whether opioid medications are effective, and the prevalence of substance use disorders among patients receiving opioid medications for chronic low back pain.	MEDLINE (through February 2005), EMBASE (through February 2005), Cochrane Central Register of Controlled Clinical Trials (through 3rd quarter 2004), PsychInfo (through February 2005). Language: English	9 in meta-analysis 26 total	Studies of an adults using oral, topical or transdermal opioids for treatment of chronic back pain. Limitations: Retrieval and publication biases. Overall, poor study quality and heterogeneous designs. No trial evaluating efficacy was longer than 16 weeks. Only 2 studies diagnosed substance disorder using validation instrument. English language only.	Use of standardized instruments: Jahad (1996) and Downs (1998) cited.	Descriptive data provided for prevalence of opioid treatment, substance abuse disorders, and aberrant medication-taking behaviors. Meta-analysis of studies reporting efficacy and with a measure of effect size. Standardized effect size used. Opioid equianalgesic conversion charts used to compare medications across studies.	Not explicitly reported	Oral, topical or transdermal opioids	Prevalence of opioids for LBP treatment: varied by treatment setting, range 3%-66% Efficacy, opioid vs. placebo or nonopioid control: NS Weighted mean difference between groups, -0.199 composite standardized mean difference (95% CI, -0.49-0.11), p=0.136 (meta-analysis, 4 studies) Mean study duration 64 days (7 days to 6 weeks) Efficacy of different opioids: non-significant reduction in pain from baseline, weighted mean difference between groups -0.93; composite standardized mean difference (CI -1.89--0.03) p=0.055 (meta-analysis, 5 studies). Prevalence of lifetime substance abuse disorders: 36%-56% Estimates of prevalence of current substance abuse disorders: as high as 43% Aberrant medication-taking behaviors: 5%-24%.	Prevalence of lifetime substance abuse disorders: 36%-56% Estimates of prevalence of current substance abuse disorders: as high as 43% Aberrant medication-taking behaviors: 5%-24%.	6

* Detailed consensus quality ratings provided in Appendix 7

APPENDIX 6. SYSTEMATIC REVIEWS EVIDENCE TABLES

Included systematic reviews on efficacy of opioids for chronic noncancer pain

Author, year, title	Key Question(s)	Purpose of study	Databases searched, date of last search	Number of studies	Types of studies included/ limitations of primary studies	Methods for rating methodological quality of primary studies	Methods for synthesizing results of primary studies	Number of patients (treatment and control)	Interventions	Results	Adverse events	Overall quality rating*
Moore, 2005[83] Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomized trials of oral opioids	1a 1b 4 5 8	To examine the incidence of common adverse events of opioids in non-cancer pain; establish how much information is lost if analyses are limited to placebo-controlled trials; establish prevalence rates for oral opioid use in CNMP; investigate any major differences in opioid adverse events in chronic non-malignant pain of different etiology.	MEDLINE, EMBASE, Cochrane Library (all through July 2004). Language: report notes no restriction of language.	34	Double-blind trials of oral opioids with placebo or active control comparators used to treat CNC pain with ≥ 10 patients per arm. Limitations: Trials of short duration (only 2 lasted more than 4 weeks). Methods used to collect AEs varied. Many trials were small. Dose or titration not evaluated as a variable. Duration of opioid use or of AE not assessed.	Jadad scale	Qualitative analysis	5,546	Oral opioids used to treat chronic non-cancer pain	In Adverse Events column	Opioid vs. placebo, average event rate (95% CI) range Dry mouth: 25% (21-29) vs. 3.2% (0-6.7) Nausea: 21% (20-22) vs. 5.6% (3.9-7.2) Constipation: 15% (14-16) vs. 5.0% (3.3-6.7) Dizziness: 14% (13-15) vs. 4.5% (2.9-6.1) Drowsiness or somnolence: 14% (13-15) vs. 4.0% (2.3-5.6) Pruritus: 13% (11-18) vs. 2.1% (0.6-3.6) Vomiting: 10% (9.3-11) vs. 2.4% (1.1-3.8) Average percent of patients experiencing any adverse event (95% CI): 51% (49-53) vs. 30% (26-34)	2

* Detailed consensus quality ratings provided in Appendix 7

APPENDIX 6. SYSTEMATIC REVIEWS EVIDENCE TABLES

Included systematic reviews on efficacy of opioids for chronic noncancer pain

Author, year, title	Key Question(s)	Purpose of study	Databases searched, date of last search	Number of studies	Types of studies included/ limitations of primary studies	Methods for rating methodological quality of primary studies	Methods for synthesizing results of primary studies	Number of patients (treatment and control)	Interventions	Results	Adverse events	Overall quality rating*
Noble, 2008[84] Long-term opioid therapy for chronic noncancer pain: A systematic review and meta-analysis of efficacy and safety	4 5	To summarize evidence on efficacy and safety of long-term opioid therapy for CNCP	EMBASE, PubMed (through August 8, 2006), all Cochrane databases and registries (through Issue 3, 2006) Language: English	17 (7 oral treatment groups, 3 transdermal treatment groups)	Open-label uncontrolled time-series studies on patients treated with opioids for CNCP for > 6 months. Limitations: Low quality evidence, high drop-out rates with few scores from original randomized population available for analysis. Variability in thresholds in reporting adverse events, failure to report absence of unobserved but potential AEs, inconsistent reporting of AEs. Absence of control groups. Only 7/17 studies specifically reported opioid addiction.	14 item instrument developed by ECRI (available from author)	Pooling for meta-analysis when > 3 studies per mode of administration addressed outcome of interest and data robust after sensitivity analysis. Fixed effects analysis when no significant heterogeneity; otherwise, random effects. Publication bias assessed in homogenous evidence bases using trim and fill method. SMD calculated for continuous data. Treatment effect estimated when data for computation not available.	Total: 3079 Oral: 1504 Tansdermal: 1391 Intrathecal not reported here	Oral, transdermal or interthecal opioids for treating moderate to severe pain at baseline due to nociceoptive or neuropathic pain or both.	Only oral and transdermal treatment results reported here, except for addiction outcome. Addiction: 7 of 17 (oral, intrathecal or transdermal) studies (with 2,042 patients) "specifically mentioned" opioid addiction. 1/2042 was reported as having possibly experienced addiction. Presumed addicition rate=0.042% Withdrawal due to insufficient pain relief: oral opioids (6-18 months): 13.1% (95%CI, 11.7-15.5%), I2=91.04% transdermal (12-48 months): 5.8% (95%CI, 4.2-7.9%), I2=52.2% Pain: oral opioids (16-18 months): SMD=1.99 (95%CI, 1.17-2.80), I2=86.6% transdermal: insufficient data	Withdrawal due to adverse events: Oral opioids: 30.4%(95% CI, 19.9%-43.4%), follow-up time range 6-18 months Transdermal: 17.6%(95% CI, 6.6%-39.2%), follow-up time range 12-48 months Substantial heterogeneity in both oral (I2=94.9%) and transdermal trials (I2=98.2%) Most commonly reported adverse events (data not provided): gastrointestinal (constipation, nausea, dyspepsia), headache, fatigue/lethargy/somnolence,urinary (retention, hestitancy, "disturbance".	7

* Detailed consensus quality ratings provided in Appendix 7

APPENDIX 6. SYSTEMATIC REVIEWS EVIDENCE TABLES

Included systematic reviews on efficacy of opioids for chronic noncancer pain

Author, year, title	Key Question(s)	Purpose of study	Databases searched, date of last search	Number of studies	Types of studies included/ limitations of primary studies	Methods for rating methodological quality of primary studies	Methods for synthesizing results of primary studies	Number of patients (treatment and control)	Interventions	Results	Adverse events	Overall quality rating*
Sandoval, 2005[85] Oral methadone for chronic non-cancer pain: a systematic literature review of reasons for administration, prescription patterns, effectiveness and side effects	4 5	To assess the indications, prescription patterns, effectiveness, and side effects of oral methadone for treatment of chronic noncancer pain.	MEDLINE (through May 2003), EMBASE (through July 2002) Language: English, French, Spanish and Portuguese. Otherwise, other languages only if English abstract had enough information about population, doses, results, and/or side effects.	21	21 studies of any design in which oral methadone was given for relief of chronic pain of non-cancer origin and a pain outcome was reported. 13 caser reports (31 patients), 7 case series (495 patients), 1 RCT (19 patients). Limitations: Only 1 trial (cross-over), possibility of publication bias. In half of patients, no specific diagnosis reported. Pain relief categories were broad in included studies (E.g.: 30%-50% relief labeled as "non-meaningful" results). Included study quality uneven, and Sandoval et al suspect effectiveness was overrated.	Quality of uncontrolled studies not measured. Jahad scale used for the one trial included.	For uncontrolled studies, effectiveness of pain relief calculated by: "number of patients who experienced 'meaningful' pain relief divided by the total number of patients using methadone. "Meaningful" was operationalized: significant change in quantitatively measured outcome or satisfactory or acceptable pain relief in well-defined categorical outcomes or worthwhile relief as judged by 3 reviewers of narratives. "Non-meaningful": relief < 30% of pain reduction; or mild or no relief of the original pain. "Unclassifiable relief": outcomes in which degree of relief was not defined.	545	Oral methadone	Pain outcomes: methadone (20 mg/day) significant improvement vs. placebo (placebo-controlled cross-over trial, 18 patients, 20 day duration) "meaningful" in 59% (308) of patients (uncontrolled studies), "nonmeaningful" in 40% (212), "unclassifiable" in 1% (6) (uncontrolled studies) Starting dose: 0.2-80 mg/day. Maximum dose: 20-930 mg/day 3 common reasons for methadone administration (uncontrolled studies that stated reasons): 1. opioid rotation, ineffectiveness of previous treatment (344 patients); ineffectiveness, side effects or 1st choice (155 patients); no detail (4 patients) 2. first choice (34 patients) 3. pain syndrome in person with addiction already receiving methadone (3 patients) No prescription pattern identified	In small (18 patients randomized), placebo-controlled cross-over trial of 20 days duration, most common side effects for 10 mg/day vs. 20 mg/day vs. placebo: nausea: 7 patients vs. 8 vs. 4 vomiting: 4 vs. 1 vs. 1 headache: 5 vs. 0 vs. 2 somnolence: 2 vs. 3 vs. 2 dizziness: 6 vs. 3 vs. 0 constipation: 2 vs.3 vs.1 pruritus: 2 vs. 2 vs. 0 diarrhea: 2 vs. 2 vs. 0 sweating: 2 vs. 3 vs. 0 1 patient withdrew from Phase I due to side effects and 6 from Phase II due to serious nausea. 10 of 20 non-controlled studies (225 patients) reported side effects or complications. Nausea and/or vomiting: in 23.6% (53) of patients, sedation 18.5% (41), itching and/or rash 13% (29), constipation 11.7% (26).	2

* Detailed consensus quality ratings provided in Appendix 7

APPENDIX 7. SYSTEMATIC REVIEWS EVIDENCE TABLES

Detailed consensus quality ratings of included systematic reviews on efficacy of opioids for chronic noncancer pain

Author, year, title	Search methods?	Comprehensive?	Inclusion criteria?	Bias avoided?	Validity criteria?	Validity assessed?	Methods for combining studies?	Appropriately combined?	Conclusions supported?	Overall quality
Cepeda, 2006[74]	YES	YES	YES	YES	YES	YES	YES	YES	YES	7
Chou, 2003[53]	YES	YES	YES	YES	YES	YES	YES	YES	YES	6
Clark, 2004[75]	PARTIAL	PARTIAL one database and company database	YES	CAN'T TELL	NO	NO	YES	NO pooled across RCTs and non-RCTs	CAN'T TELL	2
Deshpande, 2007[76]	YES	YES	YES	YES	YES	YES	YES	YES	YES	7
Devulder, 2005[77]	YES	YES	YES	PARTIAL	YES	PARTIAL accessed, but not analyzed	NO	NO	NO	2
Eisenberg, 2005[78]	YES	YES	YES	YES	YES	YES	YES	YES	YES	7
Fishbain, 2002[86]	YES	YES	PARTIAL	CAN'T TELL	NO	NO	YES	PARTIAL	PARTIAL	3
Fishbain, 2003[87]	YES	YES	PARTIAL	CAN'T TELL	NO	NO	YES	PARTIAL	PARTIAL	3
Furlan, 2006[79]	YES	YES	YES	YES	YES	YES	YES	YES	YES	7
Hollingshead, 2006[80]	YES	YES	YES	CAN'T TELL	YES	YES	YES	PARTIAL	YES	5
Kalso, 2004[81]	YES	YES	YES	YES	YES	YES	YES	YES	YES	7
Martell, 2007[82]	PARTIAL	YES	YES	CAN'T TELL	YES	YES	YES	YES	YES	6
Moore, 2005[83]	YES	YES	YES	PARTIAL	PARTIAL	NA Only one trial included	NO	CAN'T TELL	CAN'T TELL	2
Noble, 2008[84]	YES	YES	YES	YES	YES	YES	YES	YES	YES	7
Sandoval, 2005[85]	YES	YES	YES	PARTIAL	PARTIAL none for observational studies	NA only one trial included	NO no rationale for combining observational studies	CAN'T TELL pooled observational studies	CAN'T TELL	2

APPENDIX 8. SYSTEMATIC REVIEWS EVIDENCE TABLES

Excluded systematic reviews

Author, year, title	Reason for exclusion
Angst, 2006[174] Opioid-induced hyperalgesia: a qualitative systematic review	120 animal studies, 37 human studies. The only possible relevant studies are of former addicts now on methadone.
Brown, 1996[324] Chronic opioid analgesic therapy for chronic low back pain	Care series only
Challapalli, 2006[325] Systemic administration of local anesthetic agents to relieve neuropathic pain	Not opioid
Curatolo, 2002[326] Drug combinations in pain treatment: A review of the published evidence and a method for finding the optimal combination	No relevant data for our population
Dunlop, 2006[327] Pain management for sickle cell disease	No studies on chronic pain in SS
Fine, 2004[328] Opioid insights: Opioid-induced hyperalgesia and opioid rotation	Wrong population
Halbert, 2006[329] Evidence for the optimal management of acute and chronic phantom pain: a systematic review	Not opioid
Handoll, 2002[330] Anaesthesia for treating distal radial fracture in adults	Not opioid
Moore, 2006[331] Single-patient data meta-analysis of 3453 postoperative patients: oral tramadol versus placebo, codeine and combination analgesics	Post-surgery
Quigley, 2002[332] Hydromorphone for acute and chronic pain	Cancer and / or acute
Quigley, 2003[333] A systematic review of hydromorphone in acute and chronic pain	Cancer and / or acute
Saarto, 2006[334] Antidepressants for neuropathic pain	Not opioid
Savoia, 2000[335] Systemic review of trials on the use of tramadol in the treatment of acute and chronic pain	Not English
Stones, 2005[336] Interventions for treating chronic pelvic pain in women	Not opioid

APPENDIX 8. SYSTEMATIC REVIEWS EVIDENCE TABLES

Excluded systematic reviews

Author, year, title	Reason for exclusion
Umbricht, 2003[337] Opioid detoxification with buprenorphine, clonidine, or methadone in hospitalized heroin-dependent patients with HIV infection	Not pain specific
Weinbroum, 2000[338] The role of dextromethorphan in pain control	No reference included
Wiffen, 2006[339] Carbamazepine for acute and chronic pain	No opioid comparison
Wiffen, 2006[340] Anticonvulsant drugs for acute and chronic pain	No opioid comparison
Yee, 1992[341] Transdermal fentanyl	Wrong population

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Adler, 2002[90]

A comparison of once-daily tramadol with normal release tramadol in the treatment of pain in osteoarthritis

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
7	To evaluate efficacy of extended-release (once-daily) tramadol versus immediate-release tramadol for osteoarthritis	Randomized parallel-group trial	Adult patients, radiographic evidence of osteoarthritis of the spine, hip, and/or knee, no analgesics or moderate/severe pain despite medication	Any chronic painful condition other than osteoarthritis likely to warrant persistent rescue analgesics, due for hip/knee replacement during the study, monoamine oxidase inhibitors within the previous 2 weeks or NSAIDs within the last week, or known sensitivity to paracetamol or opioids, any medical condition or concomitant medication placing patient at increased risk from opioid, pregnant, lactating, or inadequately protected against conception	Number approached and eligible not reported 279 enrolled (188 extended-release, 91 immediate release)	Mean age: 62 vs. 63 yearsFemale gender: 54% vs. 63%Race, disease duration, disease site: 'balanced' (data not reported)	UK Multicenter	Napp Pharma-ceuticals, Ltd.

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
VAS Pain score (0 to 100) Escape medication use Frequency of sleep disturbance due to pain	A: Tramadol extended release 100 mg once a day initially, titrated to 400 mg once a day B: Tramadol immediate release 50 mg three times a day initially, titrated to 100 mg four times a day	Pracetamol	Tramadol extended-release (once daily) versus tramadol immediate-release. Pain score in morning (0 to 100), adjusted mean difference at end of treatment: -7.2 (NS) (favors immediate-release). Pain score in evening (0 to 100), adjusted mean difference at end of treatment: -0.3 (NS). Mean use of escape medications: No differenceWaking with pain on last night: 60% Overall Patient global assessment good to excellent: 65% Overall (no differences)Withdrawal due to lack of efficacy: 9% (16/188) vs. 9% (8/91)	21 days	139/279 (50%) withdrew	Not reported	6/11 4/5	Tramadol extended-release (once daily) versus tramadol immediate-release Withdrawal due to adverse events: 37% (69/188) vs. 35% (32/91) Withdrawal due to adverse events and lack of efficacy:2.7% (5/188) vs. 4.4% (4/91) Serious adverse events: 2 Overall Nausea: 36 % vs. 36% Constipation: 23% vs. 31% Drowsiness: 15% vs. 24% Dizziness: 20% vs. 17% Vomiting: 19% vs. 18% Headache: 18% vs. 15% Confusion: More frequent with extended-release (p=0.04, data not reported) Depression: More frequent with extended-release (p=0.04, data not reported)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Allan, 2005[124]
Transdermal fentanyl versus sustained release oral morphine in strong-opioid naïve patients with chronic low back pain

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
1a 7	Evaluate efficacy and safety of titrated transdermal fentanyl versus oral sustained-release morphine in patients with chronic low back pain not recently on regular strong opioids	Parallel-group RCT	Adults with chronic low back pain requiring regular strong opioids	Receipt of more than 4 doses of strong opioids in a week in the 4 weeks before the study, high risk of ventilatory depression or intolerance to study drugs, prior alcohol or substance abuse, presence of other chronic pain disorders, or life-limiting illness	Number approached and eligible not reported 683 randomized (338 to transdermal fentanyl and 342 to sustained-release morphine, 3 group assignment not reported)	Avg. 54.0 years, 61% female Race: not reported, Prior opioid use not reported 35% nociceptive, 4% neuropathic, 46% nociceptive and neuropathic, 3% nociceptive with psychologic factors, 4% neuropathic with psychologic factors, 83% mechanical low back pain, 8% inflammatory 39% trauma/surgery, 1% metabolic, 3% other Pain duration average 124.7 months	Europe Multicenter (number of sites not clear) Clinic setting not described	Janssen Pharma-ceutica One author employed by Janssen

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medi-cations	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain relief VAS (0-100) assessed at baseline and every week. Bowel function PAC-SYM baseline, day 15, day 29, and monthly. Quality of Life (SF-36) baseline, day 29, then monthly or 3-monthly. Back pain at rest, on movement, during day, and at night scale not specified. Global assessment investigator assessment on 3-point scale (deteriorated, un-changed, improved) Rescue medication use. Work status number of days lost to work	A: Transdermal fentanyl (titrated from 25 mcg/hr) (Mean dose 57 mcg/h) B: Sustained-release morphine (titrated from 30 mg q 12 hrs) (Mean dose: 140 mg) 13 months	Permitted, dose and drug not specified	Transdermal fentanyl (A) vs. sustained-release morphine (B): Pain score (mean, 0-100 VAS) at 56 weeks (N=608): 56.0 (A) vs. 55.8 (B) Severe pain at rest (per protocol analyses, N=248 and 162)\: 22/248 (9%) (A) vs. 20/162 (12%) (B), p=0.030 (no significant differences in ITT analysis, but data not provided). Severe pain on movement (per protocol): 70/248 (28%) (A) vs. 43/162 (27%) (B), p=0.61. Severe pain during the day (per protocol): 48/248 (19%) (A) vs. 40/162 (25%) (B), p=0.385. Severe pain at night (per protocol): 25/248 (10%) (A) vs. 26/162 (16%) (B), p=0.003 (no significant differences in ITT analysis, but data not provided) Rescue strong opioids use: 154/296 (52%) (A) vs. 154/291 (53%) (B). Quality of life (SF-36): No differences between interventions. Loss of working days: No differences between interventions. Withdrawal due to lack of efficacy: 18/335 (5%) vs.15/342 (4%)	13 months	48% in transderm-al fentanyl vs. 53% in oral sustained-release morphine arms did not complete trial	Terminated from trial due to non-compliance: 3/338 (<1%) vs. 6/342 (2%)	4/11 2/5	Transdermal fentanyl (N=338) vs. sustained-release oral morphine (N=342) Any adverse event: 87% vs. 91% Constipation (ITT): 176/338 (52%) vs. 220/338 (65%) (p<0.05) Nausea: 54% vs. 50% Vomiting: 29% vs. 26% Somnolence: 17% vs. 30% Dizziness: 25% vs. 24% Fatigue: 17% vs. 14% Pruritus: 15% vs. 20% Application site reactions: 9% in transdermal fentanyl group. Deaths: None; Addiction: None reported. Use of laxatives: 177/336 (53%) vs. 221/336 (66%) (p<0.001) Use of antiemetics/anticholingergics:38% vs. 36% Use of antihistamines: 21% vs. 12% (p=0.002) Withdrawal (Overall): 52% (177/338) vs. 47% (162/342). Withdrawal (adverse events):125/335 (37%) vs. 104/337 (31%) (p=0.098)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Beaulieu, 2007[197]
A randomized, double-blind, 8-week crossover study of once-daily controlled-release tramadol versus immediate-release tramadol taken as needed for chronic noncancer pain

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
7 12	To evaluate efficacy of extended-release (once-daily) tramadol versus sustained-release (once-daily) diclofenac for osteoarthritis of the hips or knees	Parallel-group RCT	35 to 75 years old, primary osteoarthritis (pain at least moderate severity, stiffness, disability, bony crepitus), use of NSAIDs acetaminophen, or opioids for at least 3 months prior to study entry, radiographic evidence of arthritis	Intolerance to any opioid or NSAID, history of drug or alcohol abuse, renal or hepatic impairment, secondary osteoarthritis, significant pain of alternate etiology, shortened gastrointestinal transit time, peptic ulcer disease, inflammatory bowel disease, history or seizures or risk of seizures, use of corticosteroids, viscosupplementation, monoamine oxidase inhibitors, carbamazepine, quinidine, antidepressants, neuroleptics, cyclobenzaprine, or promethazine	Number approached reported as 130 Number eligible 129 128 randomized (62 to tramadol and 66 to diclofenac)	Mean age: 59 vs. 65 years Female: 68% vs. 67% Non-white: Not reported Duration of osteoarthritis: 9.3 vs. 12 years Baseline pain intensity (0 to 100): 58 vs. 57 (estimated from graph)	Canada (unclear if also in U.S.) Number of clinics not described Clinic setting not described	Purdue Pharma

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Overall pain intensity: VAS 0 to 100 Pain in last 24 hours: VAS 0 to 100 WOMAC pain subscale Pain and Sleep Questionnaire: 0 to 500 Patient Global Assessment: 7-point scale (markedly improved to markedly worse) Drug Liking Index: 1 (dislike very much) to 9 (like very much)	A: Extended-release tramadol 200 mg once daily, titrated up to 400 mg once daily B: Sustained-release diclofenac 75 mg once daily, titrated up to 150 mg once daily	Acetaminophen	Extended-release tramadol 200 to 400 mg once daily versus sustained-release diclofenac 75 to 150 mg once daily WOMAC pain, mean change from baseline (0 to 500): 73 vs. 80 (NS) VAS pain, mean change from baseline (0 to 100: 17 vs. 16 (NS) WOMAC physical function, mean score at week 6 (0 to 1700): 634 vs. 607 WOMAC stiffness, mean score at week 6 (0 to 200: 90 vs. 79) Pain and sleep index score, mean scores at weeks 5 and 6: 117 vs. 140 Patient global assessment "moderate" to "marked" improvement: 67% vs. 54% (p=0.66)	6 weeks	31/128 (24%) did not complete trial 97/128 (76%) analyzed for efficacy	2/128 (2%) protocol violation	5/11 3/5	Extended-release tramadol 200 to 400 mg once daily versus sustained-release diclofenac 75 to 150 mg once daily Any adverse event: 78% vs. 59% Withdrawal due to adverse events: 16% vs. 15% Dizziness: 24% vs. 18% Nausea: 24% vs. 11% Constipation: 21% vs. 15% Somnolence: 18% vs. 8% Vomiting: 14% vs. 4% Headache: 11% vs. 2% Sweating: 14% vs. 0% Abdominal pain: 3% vs. 9% Serious adverse events: 0% vs. 2/66 (1 gastrointestinal bleed and 1 pancreatitis)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for non-cancer pain

Bodalia, 2003[118]

A comparison of the pharmacokinetics, clinical efficacy, and tolerability of once-daily tramadol tablets with normal release tramadol capsules

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
7	To evaluate efficacy and tolerability of extended-release (once-daily) tramadol with immediate-release tramadol for osteoarthritis	Randomized crossover trial	Moderate pain caused by osteoarthritis of the spine, hip, and/or knee, confirmed by radiographic findings	Painful conditions other than osteoarthritis likely to warrant rescue analgesics, imminent hip/knee replacement surgery, monoamine oxidase inhibitors within the previous two weeks, long-acting NSAIDs within the last week, known sensitivity to opioids, any medical conditions placing patients at increased risk from opioids, pregnancy, lactation, inadequate protection against conception	Number approached and eligible not reported 134 enrolled (20-24 patients allocated to one of six different treatment orders)	Demographics not reported by initial randomization groups Mean age: 61 years Duration >1 year: 89% Primary site of pain back: 45% Baseline pain scores: 39.5 vs. 36.3 vs. 35.0	UK Multicenter	Napp Pharma-ceuticals Ltd.

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
VAS Pain score (0 to 100) Escape medication use	A: Tramadol extended release 150 mg once a day B: Tramadol extended release 200 mg once a day C: Tramadol immediate release 50 mg three times a day Five to eight days each intervention, followed by crossover (according to allocated crossover sequence)	Pracetamol	Tramadol extended-release 150 mg once daily versus tramadol extended-release 200 mg once daily versus tramadol immediate-release 50 mg three times daily (all results reported for first intervention due to carry-over effects) Median Pain score (0 to 100) prior to morning dose: 33.5 vs. 34.0 vs. 32.5 Median Pain score (0 to 100) following morning dose: 26.1 vs. 27.1 vs. 26.6 Median number of doses of escape medication (acetaminophen): 0.6 vs. 0.5 vs. 0.4 Awakenings from sleep: No differences	5-8 days each intervention	26/134 (19%) early discontinuation	26/134 (19%) early discontinuation	5/11 3/5	Not reported

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Burch, 2007[91]
A comparison of the analgesic efficacy of Tramadol Contramid OAD versus placebo in patients with pain due to osteoarthritis

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
4	Evaluate efficacy of extended- + immediate-release (once daily) tramadol (Tramadol Contramid OAD) for knee osteoarthritis	Parallel-group RCT	40-80 years old, pain due to osteoarthritis of the knee, taking NSAIDs or tramadol on a regular basis for osteoarthritis during the 30 days prior to enrollment, pain score at least 4 on a 0 to 10 scale after washout from usual analgesics with an increase of at least 2 points	Arthritis other than osteoarthritis, history of an injury or procedure that would interfere with assessment of pain in the knee, current or prior substance abuse or dependency, treatment with a drug that reduced seizure threshold in the last 3 weeks	Number approached not reported 1028 in open-label run-in period 646 enrolled in randomized trial (432 to Tramadol Contramid OAD and 214 to placebo)	Mean age: 62 vs. 62 years Female: 64% vs. 62% Non-white race: 12% vs. 14% Baseline pain (0 to 10 scale): 7.2 vs. 7.2 Duration of osteoarthritis: Not reported	Canada, France, Romania, U.S. Multicenter Clinic setting not reported	Not reported, but corresponding author is employed by Labopharm, Inc.

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain Intensity: 0 to 10 Numerical Rating Scale Patient and physician Global Impression of Change: 1 to 7 scale	A: Tramadol Contramid OAD 200 to 300 mg po qD B: Placebo	Short-acting medications for pain other than that due to osteoarthritis permitted; not specified	Tramadol Contramid OAD vs. placebo Pain Intensity (difference in absolute improvement on a 0 to 10 scale): -0.70, 95% CI -1.02 to -0.38 Improvement in pain score ≥1 point (0 to 10 scale): 94% vs. 89% (p=0.036) Improvement in pain score ≥2 points: 87% vs. 81% (p=0.035) Improvement in pain score ≥3 points: 75% vs. 64% (p=0.002) Improvement in pain score ≥4 points: 59% vs. 47% (p=0.005) Improvement in pain score ≥5 points: 45% vs. 30% (p<0.001) Patient Global Impression of Change "improved": 80% vs. 69% (p=0.0002) Physician Global Impression of Change "improved": 80% vs. 69% (p=0.0042)	12 weeks	155/646 (24%) did not complete trial Number analyzed: 589/646 for main outcome (mean improvement in pain score)	Not reported	6/11 1/5	Tramadol Contramid OAD vs. placebo Nausea: 15% vs. 6% Constipation: 14% vs. 4% Dizziness/vertigo: 10% vs. 4% Somnolence: 7% vs. 4% Withdrawal due to adverse events: 10% (44/432) vs. 5% (11/214) (22% or 225/1028 discontinued Tramadol Contramid OAD during open-label run-in period)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Carr, 2004[92]
Safety and efficacy of intranasal ketamine for the treatment of breakthrough pain in patients with chronic pain: a randomized, double-blind, placebo-controlled, crossover study

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
14	Evaluate efficacy of intranasal ketamine for relief of breakthrough pain in opioid-treated patients with chronic pain	Randomized crossover trial	>18 years, stable pain for >2 weeks of 2-7 breakthrough pain episodes despite stable doses of analgesics, spontaneous breakthrough pain on the days of testing, able to use intranasal ketamine, on at least 60 mg/day of morphine (or equivalent)	Intolerance or allergy to ketamine, new analgesic within 2 weeks, use of potentially interfering medications, nasal/sinus anomalies or dysfunction, acute illness or other medical event that might alter pain ratings, cognitive impairment, pregnant, or women of childbearing potential and not using effective contraception, participant in trial within 1 month, history of cardiac, hepatic, lung, or psychiatric disorder, history of cardiac events, poorly controlled hypertension, history of cerebrovascular disease, weight <50 kg	Number approached and eligible not reported 22 randomized (12 to placebo/ketamine and 10 to ketamine/placebo)	Mean age: 53 vs. 44 years Female gender: 70% vs. 70% Non-white race: Not reported Duration of pain: Not reported Underlying condition: Not reported by group (4 history of cancer, remainder non-cancer) Baseline pain: 6.00 vs. 7.6	U. S. 3 centers Pain clinics	Tufts-New England Medical Center's General Clinical Research Center, funded by an NIH grant to Innovative Drug Delivery Systems, Richard Saltonstall Charitable Foundation

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Results	Duration of follow-up	Loss to follow up	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Numerical Pain Intensity Score (0 to 10)	A: Ketamine 10mg intranasal one spray for breakthrough pain, up to five sprays separated by 90 seconds B: Placebo	Intranasal ketamine vs. placebo Proportion with lower pain score after treatment for breakthrough pain episode: 65% (13/20) vs. 20% (4/20) Reduction in pain score (>40%): 45% (9/20) vs. 5% (1/20) (p=0.0078) Pain score <2.2 (0 to 10 scale): 55% (11/20) vs. 10% (2/10) Mean reduction in pain score (0 to 10): -2.65 vs. -0.81 (p<0.0001)	60 minutes following each break-through pain episode	2/22 randomized did not receive any study drug 20/22 analyzed	Not reported	9/11 5/5	Intranasal ketamine vs. placebo Withdrawn due to adverse event: 0% vs. 0% Serious adverse event: 0% vs. 0% Any SERSDA adverse event (Side Effect Rating Scale for Dissociative Anesthetics): 50% vs. 10%

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Cowan, 2005[93]

A randomized, double-blind, placebo-controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
33	Evaluate effects of abrupt cessation of opioids on pain intensity, markers for psychological dependence or drug craving, and withdrawal symptoms	RCT with crossover	>18 years, chronic non-cancer pain on sustained-release oral morphine for ≥30 days, willing to abstain from morphine, able to give regular blood samples	Pain not adequately controlled by immobilization and alternative medication, patient may require a sudden change in opioid dose, pregnant or lactating	33 approached 11 eligible 10 randomized	Mean age: 56 years Female gender: 40% Non-white race: Not reported Pain >5 years: 90% Duration of morphine use: mean 2.2 years Dose ≤60 mg/day: 90%	UK Single center Pain clinic	Janssen-Cilag Ltd., Napp Pharma-ceuticals

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Effects of cessation of opioids: Un-validated 19-item questionnaire Brief Pain Inventory Evaluation of physiologic parameters (heart rate, blood pressure, temperature, respiration, pupil size)	A: Continued sustained-release morphine for 60 hours B: Abrupt cessation of morphine for 60 hours	Not specified	Continued sustained-release morphine vs. abrupt cessation Brief Pain Inventory, average pain in last 24 hours (0 to 10): 3.2 vs. 5.3 (p<0.026) Pain interference with general activity in last 24 hours (0 to 10): 0.2 vs. 4.3 (p,0.027) Physiologic parameters: No differences	60 hours	No attrition, all patients enrolled were analyzed	Appears complete	6/11 4/5	Adverse events during cessation of opioids: 3/10 (30%) "Do you have any drug craving?": 0/10 after abrupt cessation of therapy

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Galer, 2005 (a)[94]
MorphiDex (morphine sulfate/dextromethorphan hydrobromide combination) in treatment of chronic pain: three multicenter, randomized, double-blind, controlled clinical trials fail to demonstrate enhanced opioid analgesia or reduction in tolerance (1:1, chronic pain, fixed dose)

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
21	Evaluate efficacy of morphine vs. morphine/dextromethorphan 1:1 for chronic pain using fixed doses after a titration period	Parallel-group randomized trial	Age ≥18 years, moderate to severe non-cancer, non-neuropathic pain with pain daily for at least 3 months and who required analgesic medication for at least one month prior to entry	Not specified	Number screened and eligible not reported 327 randomized (167 to morphine, 160 to morphine/ dextromethorphan 1:1)	Mean age: 49 vs. 49 years Female gender: 48% vs. 49% Non-white race: 6% vs. 6% Duration of pain: Not reported Underlying condition: 51% low back pain and 19% osteoarthritis and other arthritis (not reported by group) Baseline pain: 3.3 vs. 3.1	U.S. Number of settings and clinical setting not described	Not stated, though all authors employed by Endo Pharmaceuticals

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain Intensity: 0 to 10 Pain relief: 6 point scale Global satisfaction: 5 point scale Brief Pain Inventory Functional Measurements SF-36	A: Immediate-release morphine 15 mg tabs (dose based on morphine amount used during morphine/dextromethorphan titration) B: Immediate-release morphine/dextromethorphan 15/15 mg tabs (dose based on morphine/dextromethorphan titration) Average dose of morphine 125 mg (A) vs. 133 mg (B)	Not permitted	Immediate-release morphine versus immediate-release morphine/dextromethorphan (1:1)Difference in change in baseline pain intensity (0 to 10): 0.1 (95% -0.2 to 0.4) Withdrawal due to lack of efficacy: 32% (54/167) vs. 31% (50/160) Other outcomes: No differences (data not reported)	12 weeks	184/327 (56%) 314/327 (96%) analyzed	31/327 (9%) protocol violation	8/11 3/5	Immediate-release morphine vs. immediate-release morphine/dextromethorphan (1:1) Withdrawal (adverse events): 13/160 (8%) vs. 10/154 (6%) Any adverse event: 92% vs. 87%

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Gana, 2006[95]
Extended-release tramadol in the treatment of osteoarthritis: a multicenter, randomized, double-blind, placebo-controlled clinical trial

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
4 5	Evaluate efficacy of extended-release (once daily) tramadol for knee or hip osteoarthritis	Parallel-group RCT	Radiographically confirmed ACR Functional Class I-III osteoarthritis of the knee or hip; use of acetaminophen, an NSAID, or an opioid for at least 75 of the previous 90 days, baseline pain ≥40/100 after washout of prior analgesics	Any medical condition other than osteoarthritis poorly controlled, chronic pain syndrome or fibromyalgia, contraindication to tramadol, substance abuse in the previous 6 months, any condition likely to influence absorption, safety, or efficacy of tramadol	Number approached and eligible not reported 1020 randomized (205 to extended-release tramadol 400 mg, 300 mg to extended-release tramadol 300 mg, 203 to extended-release tramadol 200 mg, 203 to tramadol 100 mg, and 205 to placebo)	Mean age: 56 to 59 years Female gender: 58% to 69% Non-white race: 18% to 28% Duration of osteoarthritis: 7.7 to 80 years Baseline WOMAC pain score (0 to 500): 298 to 315	U.S. Multicenter Clinic setting not reported	Biovail Laboratories International SRL

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compli-ance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
WOMAC pain (0 to 500), stiffness (0 to 200), and function (0 to 1700) subscales Arthritis pain: 0 to 100 VAS Sleep related questions: 0 to 100 VAS for each of 5 questions SF-36	A: Extended-release tramadol 400 mg once daily B: Extended-release tramadol 300 mg once daily C: Extended-release tramadol 200 mg once daily D: Extended-release tramadol 100 mg once daily E: Placebo	Acetamino-phen up to 2 gm/day for up to 3 consecutive days	Extended-release tramadol 400 mg vs. 300 mg vs. 200 mg vs. 100 mg vs. placebo (change from baseline to week 12) WOMAC Pain (0 to 500): -108 vs. -104 vs. -112 vs. -107 vs. -74 (p<0.05 vs. placebo for all tramadol arms) WOMAC Physical Function (0 to 1700): -330 vs. -336 vs. -350 vs. -332 vs. -234 (p<0.05 vs. placebo for all tramadol arms) WOMAC Stiffness (0 to 200): -45 vs. -48 vs. -47 vs. -43 vs. -32 (p<0.05 vs. placebo for all tramadol arms). WOMAC Composite Index (0 to 2400): -479 vs. -486 vs. -510 vs. -482 vs. -340 (p<0.05 vs. placebo for all tramadol arms). Arthritis pain intensity, index joint (0 to 100: -28 vs. -30 vs. -30 vs. -28 vs. -20 (p<0.01 vs. placebo for all tramadol arms) Patient global assessment of disease activity (0 to 100): -21 vs. -24 vs. -22 vs. -21 vs. -16 (p<0.05 for tramadol 200 mg versus placebo, NS for other comparisons) SF-36. Physical component (0 to 100): +3.2 vs. +3.6 vs. +3.9 vs. +3.6 vs. +2.4 (NS for all comparisons) SF-36. Mental component (0 to 100): -0.5 vs. -0.7 vs. +0.6 vs. +1.1 vs. -0.3 (NS for all comparisons) Sleep measures: Sleep quality, awakened by pain at night, and trouble falling asleep statistically superior for all tramadol arms vs. placebo, tramadol 100 mg superior to placebo for need sleep medication; tramadol 100, 200, and 300 mg superior to placebo for awakened by pain in AM	12 weeks	453/1011 (45%) did not complete trial Number analyzed: 1011/1020	Not reported	7/11 4/5	Extended-release tramadol 400 mg vs. 300 mg vs. 200 mg vs. 100 mg vs. placebo Any adverse events: 84% vs. 76% vs. 73% vs. 71% vs. 56%. At least one serious adverse event: 3.0% vs. 1.5% vs. 2.0% vs. 1.5% vs. 1.0% Drug-withdrawal syndrome: total of 4/815 (0.5%) subjects on tramadol Constipation: 30% vs. 22% vs. 16% vs. 13% vs. 6% Dizziness: 28% vs. 20% vs. 18% vs. 17% vs. 6% Nausea: 26% vs. 24% vs. 23% vs. 15% vs. 7% Somnolence: 20% vs. 9% vs. 10% vs. 8% vs. 2% Headache: 16% vs. 10% vs. 15% vs. 14% vs. 8% Flushing: 16% vs. 10% vs. 10% vs. 9% vs. 5% Pruritus: 12% vs. 6% vs. 8% vs. 6% vs. 2% Insomnia: 11% vs. 8% vs. 6% vs. 8% vs. 3% Vomiting: 9% vs. 7% vs. 8% vs. 5% vs. 3% Dry mouth: 9% vs. 11% Vs. 6% vs. 5% vs. 1%x Fatigue: 6% vs. 6% vs. 6^ vs. 4% vs. 1% Anorexia: 6% vs. 6% vs. 2% vs. 2% vs. 0.5%

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Gilron, 2005[96]
Morphine, gabapentin, or their combination for neuropathic pain

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
21	Evaluate efficacy of morphine, gabapentin, or their combination for chronic neuropathic pain	Random-ized trial with multiple crossovers	Diabetic neuropathy or post herpetic neuralgia for three months of more, moderate pain, age 18 to 89	Hypersensitivity to study medications, another severe pain condition, serious mood disorder, history of serious drug or alcohol abuse, pregnancy, lactation, no primary care physician, significant comorbidities	86 screened Number eligible not clear 57 enrolled (16 initially to morphine, 13 to gabapentin, 14 to combination, and 14 to placebo)	Avg 60 (diabetic neuropathy) and 68 (PHN) years Female gender: 49% and 36% Non-white race: 3% and 0% Diabetic neuropathy 61% Post herpetic neuralgia: 39% Prior morphine or oxycodone: 9% and 5% Duration of pain: 4.5 and 4.6 years	Canada Single center Pain clinic	Canadian Institutes for Health Research provided funding; gabapentin provided by Pfizer and morphine by Aventis Pharma

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain intensity: 0 (none) to 10 (worst pain imaginable) scale Adverse events Pain: McGill Pain Questionnaire (0 to 45) Pain-related interference: Brief Pain Inventory (0 to 10) Mood: Beck Depression Inventory (0 to 63) Health status: SF-36 (0 to 100) Mental status: Mini-mental status examination (0 to 30) Global pain relief: 6 point scale (pain worse to complete relief Administered at baseline and during each treatment period when on maximal dose	A: Sustained-release morphine titrated up to 120 mg/day B: Gabapentin titrated up to 3200 mg/day C: Sustained-release morphine titrated up to 60 mg/day plus gabapentin titrated up to 2400 mg/day D: Lorazepam 1.6 mg/day(active placebo) Average dose of morphine 45.3 mg/day (A) and 34.4 mg/day (C) Average dose of gabapentin 2207 mg/day (B) and 1705 mg/day (C) 5 weeks initial intervention, followed by crossovers to each of the other three interventions	Non-opioid drugs other than gabapentin permitted	Sustained-release morphine (A) vs. gabapentin (B) vs. sustained-release morphine + gabapentin (C) vs. lorazepam (D) Mean pain intensity (baseline 5.72 +/- 0.23): 3.70 +/- 0.34 vs. 4.15 +/- 0.33 vs. 3.06 +/- 0.33 vs. 4.49 +/- 0.34 (C superior to A, B, and D) Brief Pain Inventory, general activity (baseline 4.7): 3.1 vs. 3.0 vs. 2.9 vs. 4.5 SF-36 Physical functioning (baseline 51.7): 57.8 vs. 61.1 vs. 62.4 vs. 56.0 Beck Depression Inventory (baseline 10.3): 6.7 vs. 6.4 vs. 6.0 vs. 8.5	5 weeks per intervention	16/57 (28%) with-drawals 54 analyzed	Not reported	7/11 4/5	Sustained-release morphine vs. gabapentin vs. sustained-release morphine + gabapentin vs. lorazepam Withdrawals (overall) during first intervention: 4/16 (25%) vs. 3/13 (23%) vs. 4/14 (29%) vs. 0/14 (0%) Constipation: 39% vs. 2% vs. 21% vs. 5% Sedation: 16% vs. 8% vs. 21% vs. 6% Dry mouth: 5% vs. 6% vs. 21% vs. 0% Cognitive dysfunction: 2% vs. 2% vs. 7% vs. 2% Nausea: 5% vs. 0% vs. 0% vs. 7%

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Hale 1997[119]

Efficacy of 12 hourly controlled-release codeine compared with as required dosing of acetaminophen plus codeine in patients with chronic low back pain

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
7	Evaluate efficacy of scheduled, sustained-release versus as needed, immediate-release oxycodone (each with acetaminophen)	Randomized controlled trial Parallel group	Patients with chronic low back pain deemed by investigators to be in need of opioid or fixed combination codeine analgesics for control of stable mild to moderately severe pain	18 years and older; no medical contraindication to the use of codeine or acetaminophen	Not reported Not reported 104	Avg. 52 years 54% female Race not reported Back pain due to Arthritis (33%) Mechanical injury (45%) Prior opioid use mentioned but not reported in detail. Pain duration not reported.	U.S. 1 or 2 Centers	Purdue Frederick sponsored study 1 author (corresponding) employed by Purdue

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain intensity recorded at baseline and four times a day (0-3 categorical, no pain-severe) Rescue medication use: number of doses used Acceptability: 0 (very poor) to 4 (excellent) categorical scale	A: Sustained-release codeine (scheduled) + acetaminophen (as needed) B: Immediate-release codeine/ acetaminophen (as needed) Mean dose opioid 200 mg/day (A) 71 mg/day (B) Mean dose acetaminophen 542 mg/day (A) 771 mg/day (B) 5 days	Acetaminophen 325 mg every four hours as needed (group A) or Acetaminophen 325 + codeine 30 mg every four hours as needed (group B)	Sustained-release codeine + acetaminophen (round-the-clock, A) vs. immediate-release codeine/acetaminophen (as needed, B) Pain intensity: Mean pain intensity, improvement from baseline to day 5 (0 to 3 scale): 0.8 (A) vs. 0.5 (B) (estimated from Fig. 1, p not reported) Number of fluctuations in pain intensity ratings: 6.1 (A) vs. 8.6 (B) (p=0.011) Rescue medication use: Night: 0.7 vs. 0.9 (p=NS) Day: 1.0 vs. 1.5 (p=0.018) Acceptability Overnight: 1.97 vs. 1.61 (p=0.13) Daytime: 2.12 vs. 1.84 (p=0.32)	5 days	23/104 (22%) 82/104 (79%)	Not reported	5/11 3/5	Sustained-release codeine + acetaminophen vs. immediate-release codeine/acetaminophen [rate of "serious" adverse events in brackets] Nausea: 16/52 (31%) [15%] vs. 9/51 (18%) [4%] Vomiting: 5/52 (10%) [8%] vs. 1/51 (2%) [2%] Constipation: 10/52 (19%) [2%] vs. 8/51 (16%) [0%] Dizziness: 9/52 (17%) [4%] vs. 2/51 (4%) [0%] Headache: 8/52 (15%) [0%] vs. 4/51 (8%) [4%] Somnolence: 5/52 (10%) [0%] vs. 2/51 (4%) [0%] Dyspepsia: 4/52 (8%) [4%] vs. 2/51 (4%) [2%] Dry mouth: 8/52 (15%) [0%] vs. 0/51 (0%) [0%] Pruritus: 3/52 (6%) [4%] vs. 2/51 (4%) [2%] Withdrawal due to adverse events: 13/53 (25%) vs. 4/51 (8%)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Hale, 2005[98]
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

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
7	Evaluate efficacy of sustained-release oxymorphone versus sustained-release oxycodone and placebo for low back pain	Parallel-group RCT	18 to 75 years of age, confirmed diagnosis of moderate to severe low back pain, pain present at least 15 days/month and several hours/day for the past 2 months, on stable doses of opioids for at least 3 days	Pregnant, lactating, fibromyalgia, reflex sympathetic dystrophy, acute spinal cord compression, cauda equina compression, diabetic amyotrophy, regional pain syndrome, meningitis, discitis, back pain because of secondary infection or tumor, pain caused by confirmed or suspected neoplasm, major organic psychiatric condition, serious or unstable undercurrent illness, medical conditions affecting drug absorption, history of uncontrolled seizure disorders, history of drug or alcohol dependence, hypersensitivity to opioids, surgical procedure within 2 months or nerve/plexus block within 4 weeks, active or pending litigation	420 screened360 eligible330 randomized to double blind dose titration phase (166 controlled release oxymorphone, 164 controlled-release oxycodone)235 randomized to stable intervention treatment phase (80 controlled release oxymorphone, 80 controlled-release oxycodone, 75 placebo)	Median age=46 years47% femaleRace not reportedMedian duration of low back pain 8 years"Most common" etiologies: degenerative disc disease, disc hernia ion, fracture, spondylosis, and spinal stenosis	U.S. Multicenter Number and type of clinic setting not described	Endo Pharma-ceuticals Inc and Penwest Pharma-ceuticals

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medi-cations	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain intensity on VAS (0 to 100) at baseline and at 18 days and by 4 point categorical scale (0=none to 3=severe)Pain relief on VAS (0=no relief to 100=complete relief)Brief pain inventoryGlobal evaluation on 5-point categorical scale (poor to excellent) Interference with normal activities on 100 point scale (0=no interference to 10=complete interference)	A: Sustained-release oxymorphone (titrated) (Mean dose 79.4 mg/ day) B: Sustained-release oxycodone (titrated) (Mean dose 155 mg/day) C: Placebo 18 days	Morphine 15 mg q4-6 hours during first 4 days of intervention phase, then maximum 30 mg/day	Sustained-release oxymorphone (N=71) (A) vs. sustained-release oxycodone (N=75) (B) vs. placebo (N=67) (C)Pain Intensity (100 point VAS) Compared to C differences were -18.21 and -18.55 for A and B (p=0.0001 for each comparison). Pain Intensity Categorical scale: Proportion rating pain intensity "none" or "mild" similar for A and B (around 14%) vs. C (45%)Pain Relief 56.8 vs. 54.1 vs. 39.1. Pain Interference A and B similar and superior to C for general activity, mood, normal work, relations with other people, and enjoyment of life (no difference for sleep and walking ability). Global Assessment "Good", "very good", or "excellent': 59% vs. 63% vs. 27%Discontinuation due to treatment failure (treatment phase) 20% vs. 16% vs. 57% Discontinuation due to treatment failure (dose titration phase) 7/166 (4.2%) vs. 4/164 (2.4%)Rescue medication use 13.8 vs. 14.7 mg/day after first 4 days .	18 days	96/235 (41%) 213 analyzed	Not reported	9/11 5/5	Sustained-release oxymorphone (A) vs. sustained-release oxycodone (B) vs. placebo (C) Constipation: 39/110 (35%) vs. 32/111 (29%) vs. 12/108 (11%). Sedation: 19/110 (17%) vs. 22/111 (20%) vs. 2/108 (2%). Any adverse events: 85% vs. 86% vs. NR "Serious" adverse events possibly or probably related to study medication: 2 vs. 1 vs. NR (sample sizes not clear). Withdrawal (Overall, titration phase): 53/166 (32%) vs. 42/164 (26%) Withdrawal (Overall, treatment phase): 22/80 (28%) vs. 21/80 (26%) vs. 53/75 (71%) Withdrawal (adverse events, titration phase): 25/166 (15%) vs. 26/164 (16%) Withdrawal (adverse events, treatment phase): 2/80 (2.5%) vs. 4/80 (5.0%) vs. 5/75 (6.7%)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Hale, 2007[97]
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

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
4	Evaluate efficacy of sustained-release oxymorphone versus placebo for chronic low back pain	Parallel-group RCT	≥18 years, moderate to severe chronic low back pain present for at least several hours each day for a minimum of 3 months, taking at least 60 mg/day of morphine (or equivalent) for the two weeks before screening	Not taking adequate contraception, pregnant, lactating, radiculopathy, fibromyalgia, reflex sympathetic dystrophy or causalgia, acute spinal cord compression, severe lower extremity weakness or numbness, bowel or bladder dysfunction secondary to cauda equina compression, diabetic amyotrophy, meningitis, discitis, back pain caused by secondary infection or tumor, surgical procedure for back pain within 6 months, pain due to cancer, dysphagia or difficulty swallowing tablets, previous exposure to oxymorphone, hypersensitivity to opioid analgesics, history of seizure, ileostomy or colostomy	Number screened not reported 251 eligible and 244 enrolled in open-label titration 143 randomized (70 to sustained-release oxymorphone and 73 to placebo)	Mean age: 48 vs. 46 years Female gender: 57% vs. 33% Non-white race: 16% vs. 11% Degenerative disc disease: 43% vs. 32% Osteoarthritis: 23% vs. 14% Baseline pain (0 to 100); 68 vs. 72	U.S. Multicenter Multidisciplinary pain centers	Endo Pharma-ceuticals, Inc.

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain: VAS (0 to 100) Patient and physician rating of satisfaction: 5 point scale (1 = poor to 5 = excellent)	A: Sustained-release oxymorphone q 12 hrs, dose based on stable doses achieved during open-label titration (average 81 mg) B: Placebo	Sustained-release oxymorphone 5 mg q 4 to 6 hours as needed for first four days, then no more than 2 tabs daily	Sustained-release oxymorphone vs. placebo Pain intensity, change from baseline: +8.7 vs. +31.6 (p<0.001) Patient global rating "very good" or "excellent": 58% vs. 22% (p<0.001) Discontinuation due to lack of efficacy: 11% (8/70) vs. 53% (39/73)	12 weeks	76/143 (53%) did not complete trial Number analyzed: 142/143	3/143 (2%) withdrawal due to protocol violation	8/11 3/5	Sustained-release oxymorphone vs. placebo Withdrawal due to adverse event: 10% (7/70) vs. 11% (8/72) Withdrawal due to opioid withdrawal symptoms: 0% (0/70) vs. 7% (5/72) At least one adverse event: 44% (31/70) vs. 38% (27/72) Nausea: 3% vs. 1% Constipation: 6% vs. 1% Headache: 3% vs. 0% Somnolence: 3% vs. 0% Vomiting: 0% vs. 1% Pruritus: 1% vs. 0%

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Hanna, 2008[99]

Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
22	Evaluate efficacy of sustained-release oxycodone in patients with persistent painful diabetic neuropathy on gabapentin	Parallel-group randomized trial	Painful diabetic neuropathy for >3 months based on Michigan Neuropathy Screening Instrument score of >2.5, on stable maximum tolerated dose of gabapentin for at least 1 month with moderate to severe pain (score >=5 on Short-Form Brief Pain Inventory question 6)	Hemoglobin a1c >11%, long-acting opioid in the previous month, previous oxycodone plus gabapentin use	406 screened 338 randomized (169 to sustained-release oxycodone and 169 to placebo)	Mean age: 60 vs. 61 years Female: 39% vs. 33% Non-white: 1% vs. 1% Baseline pain score: 6.4 vs. 6.5 Gabapentin dose <1200 mg/day: 48% vs. 43%	Europe and Australia Multicenter Clinic setting not reported	Mundipharma Research Ltd.

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain: 0 (none) to 10 (worst pain imaginable) scale Rescue medication use Sleep disturbance/ sleep quality Global assessment of pain Short-From Brief Pain Inventory Short-Form McGill Pain Questionnaire Euro-Qol EQ-5D	A: Sustained-release oxycodone 5 mg q 12 hrs and titrated as needed B: Placebo Proportion who received oxycodone 80 mg/day for at least one day: 34% (mean final dose not reported)	Paracetamol allowed	Sustained-release oxycodone vs. placebo (each added to chronic stable doses of gabapentin) Pain (0 to 10, mean treatment difference): 0.55 (95% CI 0.15 to 0.95) Escape medication use (mean treatment difference): -0.48 (95% CI -0.91 to -0.05) Global assessment of pain relief "good" or "very good": 56% vs. 41% (p=0.003)	Up to 12 weeks	249/338 (74%) did not complete study; 283/338 (84%) not analyzed for main outcome	Not reported	8/11 5/5	Sustained-release oxycodone vs. placebo (each added to chronic stable doses of gabapentin) Withdrawal due to adverse events: 16% (27/169) vs. 5% (9/169) Any adverse event: 88% vs. 71% Constipation: 27% vs. 6% Nausea: 26% vs. 11% vomiting: 10% vs. 4% Fatigue: 18% vs. 8% Dizziness: 15% vs. 4% Somnolence: 22% vs. 5%

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Jamison, 1998[207]
Opioid therapy for chronic noncancer back pain. A randomized prospective study

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
7 11 21	To compare efficacy and safety of long-acting morphine + short-acting oxycodone, short-acting oxycodone + NSAID, or NSAID alone for chronic back pain	Randomized controlled trial	Chronic back pain >6 months duration, age 25 to 65 years, average pain intensify >40 on scale of 0 to 100, unsuccessful response to traditional pain treatment	Cancer, acute osteomyelitis or acute bone disease, spinal stenosis and neurogenic claudication, non-ambulatory, significant psychiatric history, pregnancy, treatment for drug or alcohol abuse, clinically unstable systemic illness, acute herniated disc within 3 months	48 screened Not reported 36 enrolled	Avg. 43 years 57% female Race not reported 39% failed back syndrome 25% myofascial pain syndrome 19% degenerative spine disease 14% radiculopathy 3% discogenic back pain Prior opioid use not reported Average pain duration 79 months	U.S. Single center Pain clinic	Roxane Laboratories (maker of long-acting morphine and short-acting oxycodone). Not clear if authors employed by Roxane

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain Intensity: timing not specified, Comprehensive Pain Evaluation Questionnaire Functional status: baseline and at end of treatment (SF-36) Symptom checklist: baseline and at end of treatment (Symptom Checklist-90) Weekly activity record at baseline and once a month Medication diary weekly Overall helpfulness during titration and at end of study (categorical scale, 0= no help, 10=extremely helpful)	A: Long acting morphine + short-acting oxycodone (titrated doses) + Naproxen B: Short-acting oxycodone (set dose) + Naproxen C: Naproxen Mean dose A: 41.1 mg morphine equivalent/day. Mean dose B: Not reported, max 20 mg oxycodone/day. Mean dose C: Not reported In all groups, max 1000 mg/day of naproxen 16 weeks	Naproxen, maximum 1000 mg/day	Sustained-release morphine + short acting oxycodone + naproxen (maximum 200 mg/day morphine equivalent) vs. immediate-release oxycodone + naproxen (maximum 20 mg/day oxycodone) vs. naproxen Average pain (means, 0-100 VAS): 54.9 vs. 59.8 vs. 65.5 Current pain (means, 0-100 VAS): 51.3 vs. 55.3 vs. 62.7 Highest pain (means, 0-100 VAS): 71.4 vs. 75.5 vs. 78.9 Anxiety (means): 11.2 vs. 15.0 vs. 31.6 Depression (means): 10.8 vs. 16.4 vs. 26.9 Irritability (means): 17.7 vs. 20.5 vs. 33.7 Level of activity (means, 0-100 scale): 49.3 vs. 49.3 vs. 51.5 Hours of sleep (means): 5.9 vs. 5.9 vs. 6.1	16 weeks	NA	Not reported	3/11 2/5	Sustained-release oxycodone vs. immediate-release oxycodone Somnolence: 8/30 (27%) vs. 10/27 (37%) Nausea: 15/30 (50%) vs. 9/27 (33%) Vomiting: 6/30 (20%) vs. 1/27 (4%) Postural hypotension: 0% vs. 0% Constipation: 9/30 (30%) vs. 10/27 (37%) Pruritus: 9/30 (30%) vs. 7/27 (26%)Confusion: 1/30 (3%) vs. 0% Dry mouth: 0/30 (0%) vs. 3/27 (11%) Dizziness: 9/30 (30%) vs. 6/27 (22%) Nervousness: 0/30 (0%) vs. 2/27 (7%) Asthenia: 2/30 (7%) vs. 3/27 (11%) Headache: 4/30 (13%) vs. 7/27 (26%) Withdrawal due to adverse events: 6/30 (20%) vs. 2/27 (7%)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Jensen, 1994[100]
Tramadol versus dextropropoxyphene in the treatment of osteoarthritis: A short term double-blind study

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
7	Evaluate efficacy of tramadol versus dextropropoxy-phene for osteoarthritis	Parallel-group RCT	Moderate to severe pain due to radiologically confirmed osteoarthritis of the hip and/or knee	Pregnancy, lactation, seizure disorder, organ impairment likely to prohibit the use of tramadol or dextropropoxyphene, other medical treatment for osteoarthritis or pain, allergy to opioids, simultaneous use of monoamine oxide inhibitors, and alcohol or substance abuse	Number approached and eligible not reported 264 randomized (135 to tramadol and 129 to dextropropoxyphene)	Mean age: 67 vs. 68 years Female gender: 76% vs. 82% Non-white race: Not reported Duration of osteoarthritis: 5.5 vs. 6.4 years Pain moderate of severe during daily activities: 92% vs. 84%	Belgium & Denmark Multicenter Clinic setting not described	Funding source not reported

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain VAS 0 to 100 Pain during daily activities and on walking (none, mild, moderate, severe) Pain during sleep (normal sleep, some interruption of sleep, moderate interruption of sleep, or no sleep) Functional impairment (no difficulty, moderate difficulty, great difficulty, or impossible)	A: Tramadol 100 mg tid B: Dextropropoxyphene 100 mg tid	Not specified	Tramadol versus detxropropoxyphene Mean pain relief (0 to 100): 41 vs. 36 (p=0.12) No intention-to-treat results for other outcomes	2 weeks	74/264 (28%) 264 (for ITT analysis)	74/264 (28%) 264 (for ITT analysis)	6/11 3/5	Tramadol versus dextropropoxyphene Any adverse event: 55.6% vs. 31.8% Nausea: 25.9% vs. 10.1% Vomiting: 17.0% vs. 2.3% Dizziness: 17.0% vs. 4.7% Constipation: 8.1% vs. 8.5% Withdrawal (Overall): 40% (54/135) vs.16% (20/129) Withdrawal (adverse event): 36% (48/135) vs. 11% (14/129)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Katz, 2000 (a)[101]
MorphiDex (MS:DM) double-blind, multiple-dose studies in chronic pain patients (RCT crossover)

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
21	Evaluate efficacy of morphine vs. morphine/dextromethorphan 1:1 for chronic pain using titrated doses	Randomized crossover trial	Moderate to severe chronic pain, other inclusion criteria not specified	Not specified	Number screened and eligible not reported 89 randomized (number randomized to initial therapy groups not reported)	Mean age: 49 years Female gender: 48% Non-white race: Not reported Underlying condition: 83% non-cancer, 17% cancer Baseline pain: Not reported	USA Multicenter Clinical setting not described	Not stated

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Daily morphine use (mg) Proportion of days with satisfactory pain relief	A: Immediate-release morphine 30 mg tabs (titrated) B: Immediate-release morphine/dextro-methoraphan 15:15 mg tabs (titrated) Average dose of morphine 161 mg (a) vs. 80 mg (b)	Not specified	Immediate-release morphine versus immediate-release morphine/dextromethorphan (1:1) Mean proportion of days with satisfactory pain relief: 79% vs. 78% (NS) Change from baseline in average daily morphine dose (mg), during first intervention phase: +20 mg vs. -50 mg (p<0.001)	2 weeks each intervention	Withdrawals not reported Number analyzed unclear except for one post-hoc analysis that reported results for all patients enrolled	Not reported	8/11 4/5	Pooled data from Katz 2000 (a) (first intervention phase) and Katz 2000 (b) Immediate-release morphine vs. immediate-release morphine/dextromehtorphan Withdrawal (adverse event): Not reported Any adverse event: Not reported Constipation: 18% vs. 8% Nausea: 12% vs. 17% Headache: 10% vs. 6% Vomiting: 9% vs. 12% Somnolence: 9% vs. 11% Asthenia: 8% vs. 6% Pruritus: 7% vs. 4% Dizziness: 4% vs. 12% Confusion: 3% vs. 6%

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Katz, 2007[102]

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.

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
4 5	Evaluate efficacy of sustained-release oxymorphone versus placebo for chronic low back pain	Parallel-group RCT	≥18 years, opioid-naïve (<5 mg oxycodone or equivalent for 14 days prior to screening), initial pain intensity ≥50 on 100 point VAS, moderate to severe chronic low back pain daily for at least several hours per day for ≥3 months	Reflex sympathetic dystrophy or causalgia, acute spinal cord compression, cauda equina compression, acute nerve root compression, other exclusion criteria as listed for Hale 2005	Number screened not reported 326 eligible and 325 enrolled in open-label titration 205 randomized (105 to sustained-release oxymorphone and 100 to placebo)	Mean age: 51 vs. 48 years Female gender: 56% vs. 50% Non-white race: 11% vs. 9% Average pain intensity: 12.2. vs. 11.3 Degenerative disc disease: 32% vs. 28% Osteoarthritis: 25% vs. 29% Baseline pain (0 to 100): 71 vs. 68	USA Multicenter Clinic setting not reported	Endo Pharmaceuticals, Inc.

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain: VAS (0 to 100) Time to discontinuation due to lack of efficacy Patient and physician global rating Adjective Rating Scale for Withdrawal Clinical Opiate Withdrawal Scale	A: Sustained-release oxymorphone 5 mg q 12 hours for 2 days followed by dose titration if necessary B: Placebo Mean dose 39 mg/day	NSAIDs and other stabilized analgesics (other than opioids or acetaminophen) allowed	Sustained-release oxymorphone vs. placebo Pain intensity, change from baseline: 26.9 vs. 10.0 (p<0.0001) Proportion with ≥30% decrease in pain intensity: 93% (66/71) vs. 72% (34/47) (p=0.002) Proportion with ≥50% decrease in pain intensity: 86% (61/71) vs. 55% (26/47) Patient global rating good, very good, or excellent: 82% vs. 42% vs2% (p<0.0001) Discontinuation due to lack of efficacy: 11% (12/105) VS. 35% (35/100)	12 weeks	87/205 (42%) did not complete trial 205/205 (100%) analyzed for main outcome; 68% analyzed for other outcomes	6/205 (3%) withdrawal due to protocol violation	8/11 4/5	Sustained-release oxymorphone vs. placebo Withdrawal due to adverse event: 9% (9/105) vs. 8% (8/100) Withdrawal due to opioid withdrawal symptoms: 1% (1/105) vs. 2% (2/100) At least one adverse event: 58% (61/105) vs., 44% (44/100) At least one serious adverse event: 2% (2/105) vs. 3% (3/100) Constipation: 7% vs. 1% Somnolence: 2% vs. 0% Nausea: 11% vs. 9% Dizziness: 5% vs. 3% Headache: 4% vs. 2% Pruritus: 3% vs. 1% Vomiting: 8% vs. 1% Diarrhea: 6% vs. 6%

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Khoromi, 2007[120]
Morphine, nortriptyline, and their combination vs. placebo in patients with chronic lumbar root pain

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
4 22	Evaluate efficacy of morphine, nortriptyline, or the combination of morphine plus nortriptyline for chronic radicular pain	Multi-crossover RCT	Evidence of lumbar radiculopathy including pain in one or both buttocks or legs for 3 months or greater for at least 5 days a week and meeting additional clinical, physical exam, or diagnostic testing criteria; average pain at least 4/10 for the past month, age 18 to 65	Serious medical illnesses, pregnancy or lactation, history of depression requiring antidepressants or score >20 on Beck Depression Inventory, history or opioid or alcohol abuse, narrow angle glaucoma, seizure disorder, fibromyalgia, pain of greater intensity in any other location than the low back or leg, polyneuropathy and peripheral vascular disease associated with symptoms of numbness or burning pain in the lower extremities, allergy to any study drug, somatoform disorder, unwilling to be tapered off of opioids prior to randomization	61 screened Number eligible not reported 55 randomized (15 to sustained-release morphine, 13 to nortriptyline, 13 to sustained-release morphine + nortriptyline, 14 to benztropine)	Median age: 53 years Female: 45% Non-white race: Not reported Median duration of pain: 5 years L5/S1 radiculopathy: 73% Prior opioids: 33% Baseline leg pain: 4.9	USA One center Clinic setting not reported	National Institute of Dental and Craniofacial Research

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain: VAS (0 to 100) Time to discontinuation due to lack of efficacy Patient and physician global rating Adjective Rating Scale for Withdrawal Clinical Opiate Withdrawal Scale	A: Sustained-release oxymorphone 5 mg q 12 hours for 2 days followed by dose titration if necessary B: Placebo Mean dose 39 mg/day	NSAIDs and other stabilized analgesics (other than opioids or acetaminophen) allowed	Sustained-release oxymorphone vs. placebo Pain intensity, change from baseline: 26.9 vs. 10.0 (p<0.0001) Proportion with ≥30% decrease in pain intensity: 93% (66/71) vs. 72% (34/47) (p=0.002) Proportion with ≥50% decrease in pain intensity: 86% (61/71) vs. 55% (26/47) Patient global rating good, very good, or excellent: 82% vs. 42% vs2% (p<0.0001) Discontinuation due to lack of efficacy: 11% (12/105) VS. 35% (35/100)	12 weeks	87/205 (42%) did not complete trial 205/205 (100%) analyzed for main outcome; 68% analyzed for other outcomes	6/205 (3%) withdrawal due to protocol violation	5/11 1/5	Sustained-release oxymorphone vs. placebo Withdrawal due to adverse event: 9% (9/105) vs. 8% (8/100) Withdrawal due to opioid withdrawal symptoms: 1% (1/105) vs. 2% (2/100) At least one adverse event: 58% (61/105) vs., 44% (44/100) At least one serious adverse event: 2% (2/105) vs. 3% (3/100) Constipation: 7% vs. 1% Somnolence: 2% vs. 0% Nausea: 11% vs. 9% Dizziness: 5% vs. 3% Headache: 4% vs. 2% Pruritus: 3% vs. 1% Vomiting: 8% vs. 1% Diarrhea: 6% vs. 6%

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Kivitz, 2006[103]

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.

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
4 5	Evaluate efficacy of sustained-release oxymorphone versus placebo for osteoarthritis	Parallel-group RCT	≥18 years, osteoarthritis (based on specific diagnostic criteria including radiographic evidence), regularly took acetaminophen, NSAIDs, or opioid analgesics for 90 days before screening with suboptimal response, on birth control or sexually abstinent if a premenopausal woman	Concomitant bone/musculoskeletal disease, history of seizure, knee or hip arthroplasty within 2 months, difficulty swallowing medication, history of substance of alcohol abuse, investigational drug use within 1 month, corticosteroid therapy within 2 months, intraarticular visco-supplementation within past 3 to 6 months, intolerance to opioids	516 screened 408 eligible 370 randomized (95 to controlled release oxymorphone 10 mg bid, 93 to controlled release oxymorphone 40 mg bid, 91 to controlled release oxymorphone 50 mg bid, 91 to placebo)	Mean age: 63 vs. 62 vs. 62 vs. 60 years Female gender: 68% vs. 62% vs. 54% vs. 57% Non-white race: 14% vs. 6% vs 9% vs. 11% Duration or severity of baseline pain: Not reported 25-40% on weak opioids prior to trial entry	USA Multicenter Clinic setting not reported	Endo Pharma-ceuticals, Inc. and Penwest Pharma-ceuticals

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain: VAS (0 to 100) WOMAC (pain, stiffness, physical function subscales and composite index) SF-36 Chronic Pain Sleep Inventory (0 to 100)	A: Sustained-release oxymorphone 10 mg q 12 hours B: Sustained-release oxymorphone 20 mg q 12 hours x 1 week, then 40 mg q 12 hrs x 1 week C: Sustained-release oxymorphone 20 mg q 12 hours x 1 week, then 50 mg q 12 hrs x 1 week D: Placebo	Not allowed	Sustained-release oxycodone 10 mg vs. 40 mg vs. 50 mg vs. placebo Pain (VAS, 0 to 100), change from baseline, least squares mean: -21 vs. -28 vs. -29 vs. -17 (p 0.012 and p=0.006 for 40 mg and 50 mg vs. placebo; no significant difference between 40 mg and 50 mg arms) WOMAC Composite Index (0 to 2400), change from baseline: -350 vs. -370 vs. -450 vs. -160 (estimated from graph; all oxycodone groups p<0.025 vs. placebo) WOMAC Physical Function score (0 to 1700): -230 vs. -260 vs. -320 vs. -110 (estimated from graph, p<0.025 for all oxycodone groups vs. placebo) SF-36 Physical Component Summary, change from baseline: +3.9 vs. +4.6 vs. +3.6 vs. -0.1 (p<0.001) Chronic Pain Sleep Inventory, change from baseline: -17 vs. -22 vs. -24 vs. -12 (p≤0.05 for 40 mg and 50 mg vs. placebo). Withdrawal due to lack of efficacy: 7% (7/95) vs. 5% (5/93) vs. 4% (4/91) vs. 16% (15/91)	2 weeks	172/370 (46%) did not complete trial Number analyzed: 357/370 (96%)	1 withdrawal due to protocol violation	9/11 5/5	Sustained-release oxycodone 10 mg vs. 40 mg vs. 50 mg vs. placebo Withdrawal due to adverse events: 25% (24/95) vs. 55% (51/93) vs. 52% (47/91) vs. 10% (9/91) Nausea: 23% vs. 41% vs. 55% vs. 9% Vomiting: 10% vs. 27% vs. 35% vs. 2% Dizziness: 16% vs. 22% vs. 31% vs. 6% Pruritus: 5% vs. 20% vs. 24% vs. 1% Constipation: 18% vs. 27% vs. 22% vs. 4% Somnolence: 10% vs. 23% vs. 21% vs. 3% Headache: 10% Vs. 15% vs. 19% vs. 10% Increasing sweating: 5% vs. 8% vs. 10% vs. 1%. Decreased appetite:1% vs. 4% vs. 9% vs. 1% Dry mouth: 6% vs. 11% vs. 9% vs. 0% Diarrhea: 0% vs. 3% Vs. 7% vs. 7% Fatigue: 5% vs. 12% vs. 3% vs. 1% Euphoric mood: 5% vs. 3% vs. 1% vs. 1%

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Langford, 2006[104]
Transdermal fentanyl for improvement of pain and functioning in osteoarthritis: a randomized, placebo-controlled trial.

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
4 5	Evaluate efficacy of transdermal fentanyl versus placebo for osteoarthritis	Parallel-group RCT	≥40 years, meet ACR criteria for hip or knee osteoarthritis, requiring joint replacement surgery, radiographic evidence of disease in affected joints, pain >3 months, >20 days each month, average pain >50 on 100 point scale	Receipt of strong opioid in last 4 weeks, recently started new therapy, deemed unsuitable for opioid	553 screenedNumber eligible not reported416 randomized (allocation only reported for 399, 202 to transdermal fentanyl and 197 to placebo)	Mean age: 66 vs. 66 yearsFemale gender: 65% vs. 68%Non-white race: Not reportedBaseline pain score (0 to 100 mm): 73 vs. 73Duration of pain: Not reportedKnee osteoarthritis: 52% vs. 54%88% on weak opioids prior to trial entry	Europe and Canada Multicenter Clinic setting not reported	Janseen-Cilag

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain: VAS (0 to 100)WOMAC (normalized to 0 to 10)SF-36Investigator assessed pain control, side effects, convenience of use, Overall impression of treatmentPatient-assessed questionnaire (10 items, each on a 5 point Likert scale)Short Opiate Withdrawal Scale: 10 items, each scored 0 to 3	A: Transdermal fentanyl 25 mcg/hr, titrated to maximum 100 mcg/hr B: Placebo1 week run-in period (no change in therapy), 6 week interventionMedian dose of transdermal fentanyl: 1.7 patches/day	Acetaminophen up to 4 gm/day	Transdermal fentanyl vs. placebo (changes from baseline)VAS pain score (0 to 100): -23.6 vs. -17.9 (p=0.025)WOMAC Overall score (normalized to 0 to 10): -3.9 vs. -2.5 (p=0.009)WOMAC Pain score (0 to 10): -1.5 vs. -0.8 (p=0.001)WOMAC Physical Functioning score (0 to 10): -1.1 vs. -0.7 (p=0.064)SF-36, Physical component: +3.4 vs. +2.4, p=0.171SF-36, Mental component: -0.9 vs. +1.1 , p=0.041SF-36, Pain index: +11.4 vs. +7.1 (p=0.047)Discontinuation due to lack of efficacy: 7% (15/202) vs. 32% (64/197)	6 weeks	217/416 (52%) did not complete trialNumber analyzed: 399/416	Not reported	9/11 5/5	Transdermal fentanyl vs. placeboWithdrawal due to adverse events: 26% (55/216) vs. 8% (15/200)At least one adverse event: 78% (169/216) vs. 51% (101/200)Nausea: 44% (94/216) vs. 19% (37/200)Vomiting: 28% (61/216) vs. 3% (5/200)Somnolence: 22% (48/216) vs. 4% (7/200)Dizziness: 12% (26/216) vs. 5% (10/200)Headache: 11% (23/216) vs. 12% (23/200)Application site reaction: 4% (9/216) vs. 11% (221/200)Constipation: 10% (22/216) vs. 2% (3/200)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Ma, 2007[161]
The efficacy of oxycodone for management of acute pain episodes in chronic neck pain patients

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
4 5 7	Evaluate efficacy of scheduled sustained-release oxycodone versus placebo for chronic neck pain with frequent acute pain episodes	Parallel-group RCT	Chronic neck pain for >6 months, MRI or CT suggesting degenerative disease process or neck injury followed by the development of posttraumatic ligament and muscular pain; acute pain flares more than three times per day with VAS pain score above 4 for 3 days, did not respond to non-opioids and NSAIDs, 40 to 70 years old, over 40 kg body weight	History of intolerable adverse effects from opioids, history of alcohol or drug abuse, severe liver and renal disease, use of opioids within the previous 2 weeks	Number screened not reported Data reported on 116 patients; number randomized not reported (trial lists withdrawal and change in oxycodone dose as "exclusions")	Mean age: 58 vs. 53 years Female: 31% vs. 45% Non-white: Not reported Duration of pain: 28 vs. 25 months Baseline pain: Not reported	China Single center Clinic setting not reported	Shanghai Sixth People's Hospital Clinical Research grant

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain: VAS (0 to 10) Quality of Sleep (good, average, bad) Adverse effects Withdrawal symptoms SF-36 Functional status: zero (no symptoms) to four (unable to care for himself/herself and confined to bed) Frequency of pain episodes Patient satisfaction scale: 0 (dissatisfied) to 10 (very satisfied)	A: Sustained-release oxycodone 5-10 mg q 12 hours B: Placebo Mean dose: Not reported	Not reported	Sustained-release oxycodone vs. placebo at 1 week Frequency of acute pain flares (>3 flares/day): 79% vs. 55% (p<0.05) Quality of sleep (bad): 9% vs. 53% (p<0.05) Pain (VAS 0 to 10): 3.24 vs. 5.01 (NS) Patient satisfaction scale (0 to 10): 4.74 vs. 4.06 (NS) Functional status (zero to four scale): 1.25 vs. 1.98 (NS)	1 to 4 weeks	58/116 (50%) did not complete 2 weeks of follow-up	Not reported	4/11 2/5	Sustained-release oxycodone vs. placebo at 1 week (insufficient data for longer follow-up) Nausea: 31% vs. 12% (p<0.05) Vomiting: 9% vs. 5% Constipation: 22% vs. 3% (p<0.01) Somnolence: 10% vs. 0% Dizziness: 28% vs. 0% (p<0.01) Pruritus: 19% vs. 2% (p<0.01) Agitated: 5% vs. 0%

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Markenson, 2005[105]
Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical trial.

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
4 5	Evaluate efficacy of sustained-release oxycodone for osteoarthritis	Parallel-group RCT	Meet ACR criteria for osteoarthritis, moderate to severe pain for at least 1 month, pain rated 5 or greater on 10 point scale, on NSAIDs or acetaminophen for at least 2 weeks (or NSAID-intolerant or high risk for adverse events) or on ≤60 mg oxycodone/day	Allergy to opioids, scheduled to have surgery, unstable coexisting disease or active dysfunction, active cancer, pregnant or nursing, past or present history of substance abuse, involved in litigation related to their pain, received intra-articular or intramuscular steroid injections involving the joint or site under evaluation within 6 weeks prior to baseline	Number approached and eligible not reported 109 randomized (56 oxycodone, 53 placebo)	Mean age: 62 vs. 64 years Female gender: 68% vs. 78% Non-white race: 7% vs. 6% Prior opioid use: 54% vs. 65% Baseline average pain intensity (Brief Pain Inventory): 6.9 vs. 6.3 Baseline composite score from WOMAC Osteoarthritis Index: 64.7 vs. 63.8. Knee osteoarthritis: 32% vs. 26%. Prior opioid use: 54% vs. 65%	USA Multicenter Clinic setting not reported	Purdue Pharma

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Brief Pain Inventory (0 to 10) WOMAC (pain, stiffness, physical function) (0 to 100) Patient Generated Index (PGI): 6 areas of function, each rated 0 to 100 Patient-reported satisfaction with medication (0 to 10) Patient-reported acceptability of medication (1 to 6)	A: Sustained-release oxycodone 10 mg q 12 hours, titrated to maximum 60 mg q 12 hours B: Placebo Up to 90 days intervention	Could continue usual NSAID or acetaminophen	Sustained-release oxycodone vs. placebo (changes from baseline) Brief Pain Inventory (0 to 10), average pain intensity at day 90: -1.7 vs. -0.6 (p=0.024) WOMAC Pain (0 to 100) , at 60 days: -17.8 vs. -2.4 (p<0.05). WOMAC Physical Function (0 to 100), at 60 days: -17.1 vs. -3.8 (p<0.05). WOMAC Stiffness (0 to 100), at 60 days: -21.7 vs. +0.1 (p<0.001). WOMAC Composite Index (0 to 100), at 60 days: -18.9 vs. -2.1 (p<0.05). Proportion experienced ≥30% pain relief at 90 days: 38% vs. 17.6% (p=0.031). Proportion experiencing ≥50% pain relief at 90 days: 20% vs. 5.9% (p=0.045). Brief Pain Inventory, Function composite: -1.9 vs. -0.4 (p=0.001). Patient Generated Index, primary activity, at day 45: 51.2 vs. 39.7. Withdrawal due to inadequate pain control: 16% vs. 67% (p<0.001).	up to 90 days	73/109 (67%) did not complete trial Number analyzed: 107/109 (98%)	1 withdrawal due to protocol violation	9/11 5/5	Sustained-release oxycodone vs. placebo Withdrawal due to adverse events: 36% (20/56) vs. 4% (2/51) (p<0.001) Any adverse event: 93% (52/56) vs. 55% (28/51) "Serious" adverse event: 5% (3/56) vs. 0% (0/51) Deaths: None Constipation: 48% (27/56) vs. 9.8% (5/51) Nausea: 41% (23/56) vs. 14% (7/51) Somnolence: 32% (18/56) vs. 10% (5/51) Dizziness: 32% (18/56) vs. 6% (3/51) Pruritus: 21% (12/56) vs. 0% (0/51) Headache: 20% (11/56) vs. 20% (10/51) Diarrhea: 12% (7/56) vs. 8% (4/51) Vomiting: 12% (7/56) vs. 2% (1/51) Sweating: 11% (6/56) vs. 4% (2/51)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Matsumoto, 2005[106]
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

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
4 5 7	Evaluate efficacy of sustained-release oxymorphone versus sustained-release oxycodone for osteoarthritis	Parallel-group RCT	Typical knee or hip joint symptoms and signs and radiographic evidence of osteoarthritis, taking an analgesic for at least 75 of 90 days prior to screening visit with suboptimal visit, >40 years, adequate birth control or abstinence in women of child-bearing potential, negative serum pregnancy test	Inflammatory arthritis, gout, Paget's disease, chronic pain syndrome, fibromyalgia, requiring arthroplasty within 2 months, weight <100 pounds, difficulty swallowing capsules or tablets, prior history of substance or alcohol abuse, corticosteroid or investigational drug use within 1 month, prior history of intolerance to opioids	Number approached and eligible not reported 491 randomized (121 oxymorphone 40 mg bid, 121 oxymorphone 20 mg bid, 125 oxycodone 20 mg bid, 124 placebo)	Median age: 61 vs. 63 vs. 63 vs. 62 yrs. Female gender: 64% vs. 56% vs. 58% vs. 65%. Non-white race: 12% vs. 18% vs. 10% vs. 14%. Duration of osteoarthritis >5 years: 64% vs. 71% vs. 67% vs. 77%. Knee osteoarthritis: 78% vs. 77% vbs. 75% vs. 75%. Baseline pain: Not reported. Previous opioids: Not reported	USA Multicenter Clinic setting not described	Endo Pharma-ceuticals, Inc. and Penwest Pharma-ceuticals

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medi-cations	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain intensity VAS (0 to 100) WOMAC pain, stiffness, and physical function subscales SF-36 Global assessments of therapy (method not reported) Sleep assessment (method not reported)	A: Sustained-release oxymorphone 20 mg bid x 2 weeks, then 40 mg bid B: Sustained-release oxymorphone 20 mg bid C: Sustained-release oxycodone 10 mg bid x 2 weeks, then 20 mg bid D: Placebo 4 weeks	Not specified	Sustained-release oxymorphone 40 mg bid (N=114) vs. sustained-release oxymorphpone 20 mg bid (N=114) vs. sustained-release oxycodone 20 mg bid (N=120) vs. placebo (N=119). Pain Intensity (100 point VAS), mean improvement (estimated from Figure 1): -26 vs. -24 vs. -22 vs. -17 (p not reported). WOMAC Pain (0 to 500), mean improvement (estimated from Fig. 3): -118 vs. -102 vs. -88 vs. -60 (p<0.01 for A vs. D, p<0.05 for B vs. D). WOMAC Physical Function (0 to 1700): -315 vs. -300 vs. -220 vs. -190 (p<0.05 for A vs. D and B vs. D). WOMAC Stiffness (0 to 200): -36 vs. -44 vs. -34 vs. -28 (p<0.05 for B vs. D). WOMAC Composite Index (0 to 2400): -480 vs. -460 vs. -360 vs. -290 (p<0.05 for A vs. D and B vs. D). Patient's global assessment (VAS 0 to 100): -28.6 vs. -23.2 vs. -25.4 vs. -19.5 (p<0.05 for A vs. D). Overall quality of sleep (VAS 0 to 100): +18.2 vs. +13.8 vs. +15.3 vs. +7.7 (p<0.05 for A vs. D and C vs. D). SF-36 Physical component: +4.5 vs. +3.4 vs. +4.0 vs. +1.8 (p<0.05 for A vs. D and C vs. D). SF-36 Mental component: -0.4 vs. +1.5 vs. -0.8 vs. +2.2 (p<0.05 for C vs. D). Withdrawal due to lack of efficacy: 7% (9/121) vs. 4% (5/121) vs. 10% (13/125) vs. 27% (34/124).	4 weeks	222/491 (45%) 467 analyzed	1.4% (7/491)	8/11 5/5	Sustained-release oxymorphone 40 mg bid (N=114) vs. sustained-release oxymorphpone 20 mg bid (N=114) vs. sustained-release oxycodone 20 mg bid (N=120) vs. placebo (N=119). Constipation: 32% vs. 40% vs. 36% vs. 11%. Dry mouth: 12% vs. 12% Vs. 15% vs. 0.8%. Dizziness: 31% vs. 29% vs. 26% vs. 4%. Headache: 11% vs. 29% vs. 26% vs. 4%. Nausea: 60% vs. 61% vs. 43% vs. 10%. Pruritus: 20% vs. 19% vs. 8% vs. 2%. Somnolence: 31% vs. 30% vs. 27% vs. 5%. Vomiting: 34% vs. 23% vs. 10% vs. 2%. Withdrawal (Overall): 56% (68/121) vs. 48% (58/121) vs. 40% (50/125) vs. 37% (46/124). Withdrawal (adverse events): 47% (57/121) vs. 38% (46/121) vs. 25% (31/125) vs. 27% (34/124). Any adverse events: 91% vs. 95% vs. 88% vs. 57%.

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Mongin, 2004[107]
Efficacy and safety assessment of a novel once-daily tablet formulation of tramadol

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
7	To evaluate efficacy of once-daily versus twice-daily tramadol in patients with osteoarthritis of the knee	Randomized parallel-group trial	40 to 75 years old, moderate to moderately severe osteoarthritis of the knee according to American College of Rheumatology criteria, baseline score ≥150 on WOMAC pain subscale	Rheumatoid arthritis, secondary arthritis, body mass index ≥35 kg/m^2, major illness requiring hospitalization in last 3 months, seizure disorder, bowel disease causing malabsorption, pregnancy, lactation, significant liver or renal disease, failed or discontinued tramadol therapy due to adverse events, another investigational agent within 30 days, allergy or adverse reaction to drugs similar to tramadol, current substance abuse or dependence (other than alcohol), using antidepressants or antipsychotics	477 screened 431 randomized (215 to tramadol once-daily, 216 to tramadol twice-daily)	Mean age: 61 vs. 60 years Female gender: 81% vs. 84% Non-white race: Not reported Baseline pain (WOMAC 0 to 500): 285 vs. 297 Duration of symptoms: not reported	Europe Multicenter	Labopharm, Inc.

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
WOMAC Pain: 0 to 500 WOMAC Stiffness: 0 to 200 WOMAC Physical Function: 0 to 1700 WOMAC Composite Index: 0 to 2400 Pain: VAS 0 to 100 Global rating of pain: very effective, effective, somewhat effective, ineffective	A: Tramadol extended release 100-400 mg once daily (titrated) B: Tramadol sustained release 100-400 mg divided twice daily (titrated) 12 weeks intervention - median dose 200 mg in each arm	Not allowed	Tramadol extended-release (once daily) versus tramadol sustained-release (twice daily) (all results percent improvement from baseline to last visit, unless noted otherwise) WOMAC Pain score: 58% vs. 59% (NS) WOMAC Stiffness score: 49% vs. 49% WOMAC Physical Function score: 52% vs. 50% WOMAC Composite Index: 54% vs. 52% Current pain: 35% vs. 35% Patient global rating "effective" or "very effective": 83% vs. 83%	12 weeks	70/430 (16%) early discontinuation	7/430 took study medication incorrectly, no other details	9/11 4/5	Tramadol extended-release (once daily) versus tramadol sustained-release (twice daily) Withdrawal due to adverse events: 8.8% (19/215) vs. 10% (22/215) Any adverse event: 81% vs. 79% Dizziness/vertigo: 26% vs. 37% Vomiting;: 8% vs. 14% Headache: 13% vs. 18% Somnolence: 30% vs. 21% Serious adverse events: 1.4% (3/125) vs. 3.7% (8/215)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Mullican, 2001[108]

Tramadol/acetaminophen combination tablets and codeine/acetaminophen combination capsules for the management of chronic pain: a comparative trial

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
7	Evaluate efficacy of tramadol/acetaminophen versus codeine/acetaminophen for low back pain and/or osteoarthritis	Parallel-group RCT	Mild to moderate pain ≥6 months due to low back pain or osteoarthritis, >18 years, good health	Pregnancy or woman with child-bearing potential not using appropriate birth control; seizures, alcohol or drug abuse within the past year, suicidal tendencies, antidepressants or other drugs that could reduce seizure threshold, allergy, sensitivity or contraindication to any study medication	Number approached and eligible not reported 462 randomized (309 to tramadol/acetaminophen and 153 to codeine/ acetaminophen)	Mean age: 56 vs. 60 years Female gender: 62% vs. 61% Non-white race: Not reported Baseline pain moderate or severe: 76% vs. 77% Type of pain osteoarthritis: 35% vs. 35%	USA Multicenter Clinic setting not described	R. W. Johnson Pharma-ceutical Research Institute and Ortho-McNeil Pharma-ceutical, Inc.

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain relief: 0 (none) to 4 (complete) Pain intensity: 0 (none) to 3 (severe) Patient and investigator assessment of global efficacy: 1 (poor) to 5 (excellent)	A: Tramadol 37.5 mg/acetaminophen 325 mg 1-2 tablets q 4 to 6 hrs, maximum 10 tablets/day (maximum 8 tablets/day if >75 years old) B: Codeine 30 mg/acetaminophen 300 mg 1-2 capsules q 4 to 6 hrs, maximum 10 capsules/day (maximum 8 capsules/day if >75 years old) Mean doses 3.6 tablets/capsules per day	Ibuprofen 400 mg every 4 to 6 hours as needed	Tramadol/acetaminophen vs. codeine/acetaminophen Overall efficacy (1 to 5): 2.9 vs. 2.8 Maximum pain relief (0 to 4): 2.5 vs. 2.4	22 days	NA	93/462 (20%) 459 analyzed	7/11 4/5	Tramadol/acetaminophen versus codeine/acetaminophen Constipation: 11% vs. 21% (p<0.01) Somnolence: 17% vs. 24% (p=0.05) Possible allergic reaction: 8% vs. 8% Withdrawal (Overall): 20% (61/309) vs. 21% (21/153) Withdrawal (adverse events): 12% (37/309) vs. 14% (21/153)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Nicholson, 2006[195]
Randomized trial comparing polymer-coated extended-release morphine sulfate to controlled-release oxycodone HCl in moderate to severe nonmalignant pain

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
7	Evaluate efficacy of polymer-coated extended-release (once daily) morphine versus sustained-release oxycodone (twice daily)	Parallel-group RCT	18-85 years, moderate to severe non-cancer pain, continuous treatment with a sustained-release opioid indicated, pain predominantly non-neuropathic, baseline pain ≥4 on a 0 to 10 scale	Underlying cancer, hypersensitivity to opioids, conditions contraindicating treatment with morphine, impaired bowel motility or intractable vomiting caused or agitated by opioids, significant respiratory disease (including asthma) or respiratory distress likely to be worsened by opioids, clinically significant lab abnormalities that might affect safety, likely to require drugs not permitted by protocol, other conditions or findings judged to possibly affect results, pregnancy, lactating, not using effective contraception	Number approached and eligible not reported 112 randomized (53 to extended-release morphine and 59 to sustained-release oxycodone)	"Similar" for age (mean 51 years), non-white race (6%) Female gender: 63% vs. 41% (p<0.05) Back pain: 63% vs. 52% (p=0.31) Duration of symptoms (not reported) Baseline SF-36 Physical Component Summary scores: 26.4 vs. 31.1 (p <0.05) Baseline Pain scores: 7.2 vs. 7.4 Prior opioid use: "No difference"	USA Multicenter Clinic setting not described	Alpharma Branded Products Division

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain: 0 (no pain) to 10 (worst pain imaginable) categorical scale SF-36 Physical and Mental Component Summaries (0 to 100 each) Sleep Interference Scale of the Brief Pain Inventory: 0 (pain does not interfere with sleep) to 10 (completely interferes with sleep) Patient global assessment: -4 (completely dissatisfied) to +4 (completely satisfied) Clinician global assessment	A: Extended-release morphine (Kadian) initially dosed once daily according to previous analgesic dose and titrated (dose and frequency up to twice daily) (mean dose 79 mg/day) B: Sustained-release oxycodone initially dosed twice daily according to previous analgesic dose and titrated (dose and frequency up to three times daily) (mean dose 85 mg/day)	Immediate-release morphine (for morphine group) and immediate-release oxycodone (for oxycodone group)	Extended-release morphine (Kadian) once daily versus sustained-release oxycodone twice daily (mean improvement from baseline) SF-36 Physical Component Scale: +2.5 vs. +2.1 (NS). SF-36 Mental Component Scale: +0.8 vs. +4.2 (p for differences between groups not reported, but p<0.05 vs. baseline only for sustained-release oxycodone) Pain (0 to 10): -1.9 vs. -1.4 (NS) Sleep Interference Scale (0 to 10): -2.6 vs. -1.6 (p<0.05). Patient Global Assessment (-4 to +4): +2.6 vs. +1.7 (NS). Use of concomitant medications: 80% vs. 88% (NS). Withdrawal (lack of efficacy): 2% (1/53) vs. 7% (4/59)	24 weeks	52/112 (46%) 97/112 (87%) analyzed	5/112 (4%) dropped out due to non-compliance	4/11 2/5	Extended-release morphine (Kadian) once daily versus sustained-release oxycodone twice daily Any adverse event: Not reported Serious adverse events: 12 Overall Constipation: 26% vs. 10% (p=0.04). Nausea: 14% vs. 14% Somnolence: 10% vs. 7% Cognitive disorder: 4% vs. 2% Fatigue: 4% vs. 2% Headache: 4% vs. 0% Dizziness: 2% vs. 5% Edema: 0% vs. 3% Sedation: 0% vs. 5% Withdrawal (Overall): 57% (30/53) vs. 51% (30/59) Withdrawal (adverse events): 28% (15/53) vs. 22% (13/59)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Niemann, 2000[196]

Opioid treatment of painful chronic pancreatitis: Transdermal fentanyl versus sustained-release morphine

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
7	Evaluate efficacy of transdermal fentanyl versus sustained-release morphine for chronic pancreatitis	Randomized crossover trial	Patients with opioid treated painful chronic pancreatitis	Not specified	Not reported Not reported 18 enrolled	Median age=47 years 33.3% female Race not reported Median duration of chronic abdominal paiN=9 years Etiology of chronic pancreatitis Alcohol abuse=17(94.4%) Sjogren's syndrome=1(5.6%)	Denmark Multicenter Outpatient clinics	Janssen Research Foundation

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Preference recorded at end of study (assessment method not reported, categorical scale used) Global pain control assessment of last two weeks of trial periods compared to last month prior to study entry (assessment method not reported, categorical scale used) Quality of life assessed using SF-36 questionnaire at end of each 4-week period Side effects assessed using unspecified questionnaire at weeks 1, 2, and 4 of each trial period	A: Transdermal fentanyl (titrated) (Mean dose 55.6 mcg/hr) B: Sustained-release oral morphine (titrated) (Mean dose 128.3 mg/day) 4 weeks initial intervention followed by 4 week crossover	Immediate release morphine tablets of 10 mg (mean dose not reported)	Transdermal fentanyl (A) vs. sustained-release oral morphine (B) Patient Preference (N=17): "Preference" or "Strong Preference" 8(47%) A vs. 7(41.2%) B (NS) Pain Control "Good" or "Very Good"(N=18): 8(44.4%) (A) vs. 6(33.3%) (B) (NS) Quality of Life: A vs. B (NS) in physical functioning, general health, role physical, pain intensity, social functioning, mental health, and side effects summary median scores	4 weeks per interventions	1/18 (5.6%) 18 analyzed	Not reported	3/11 2/5	Transdermal fentanyl vs. sustained-release oral morphine Withdrawal due to adverse events: 6% (1/17) vs. 0% (0/17) Any adverse event: 12% (2/17) vs. 0% (0/17)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Paulson, 2005[109]
Alvimopan: an oral, peripherally acting, mu-opioid receptor antagonist for the treatment of opioid-induced bowel dysfunction--a 21-day treatment-randomized clinical trial

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
9	Evaluate efficacy of alvimopan for treating opioids-induced bowel dysfunction in patients with chronic non-cancer pain or opioid dependence	Parallel-group RCT	>18 years old, received opioid therapy for at least 1 month with a stable dose for at least 1 week, ≥10 mg morphine (or equivalent), opioid induced bowel dysfunction (preferably <3 bowel movements per week without aid of laxatives or enemas, and at least one associated symptom)	Soft or loose stools, unable to give informed consent, could not use electronic diary, known organic cause of bowel dysfunction or obstruction, used manual maneuvers for >25% of bowel movements, history of irritable bowel syndrome or intermittent loose stools, cancer-related pain, fecal incontinence, use of cathartic laxatives or enemas, exposure to vinca alkaloids within 6 months or history of vinca-associated gastrointestinal neurotoxicity (including paralytic ileus and intestinal pseudo-obstruction), use of illicit drugs or habitual alcohol	Number approached and eligible not reported 168 randomized (56 to alvimopan 1 mg, 58 to alvimopan 0.5 mg, 54 to placebo)	Mean age: 51 vs. 52 vs. 48 years Female gender: 61% vs. 50% vs. 65% Non-white race: 18% vs. 17% vs. 26% Duration of opioid use: 9.8 vs. 9.4 vs. 7.9 years Mean daily morphine equivalent dose: 102 vs. 120 vs. 85 mg Chronic non-cancer pain: 88% vs. 88% vs. 89% Source of pain back: 18% vs. 24% vs. 22%	USA Multicenter Clinic setting not described	Adolor Corporation

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Proportion of patients with a bowel movement within 8 hours after dosing	A: Alvimopan 1 mg once daily B: Alvimopan 0.5 mg once daily C: Placebo 3 weeks intervention	Not stated	Alvimopan 1 mg versus alvimopan 0.5 mg versus placebo Average proportion reporting a bowel movement within 8 hours of study drug administration: 54% (p<0.001 vs. placebo) vs. 43% (p<0.001 vs. placebo) vs. 29% Number of weekly bowel movements: 4.7 vs. 4.1 (p<0.01 vs. placebo) vs. 5.0 Proportion reporting "improved" during treatment: 70% (p=0.046 vs. placebo) vs. 58% (p=0.04 vs. placebo) vs. 50% Proportion reporting "improved" during follow-up: 11% vs. 18% vs. 22% (NS) Laxative use: No change Pain scores: No change	5 weeks	16/168 (10%) 168/168 (100%) analyzed	Not reported	10/11 4/5	Alvimopan 1 mg vs. alvimopan 0.5 mg vs. placebo Withdrawal (adverse events): 11% (6/56) vs. 3% (2/58) vs. 2% (1/54) Any adverse event: 48% vs. 37% vs. 33% Serious adverse events: 2% (1/56) vs. 2% (1/58) vs. 0% (0/54) Exacerbation of baseline pain: 4% (2/56) vs. 0% (1/58) vs. 0% (0/54) Abdominal cramping: 9% vs. 7% vs. 6% Nausea: 13% vs. 4% vs. 6% Diarrhea: 11% vs. 4% vs. 0% Flatulence: 4% vs. 4% vs. 4% Vomiting: 7% vs. 4% vs. 0% Abdominal pain: 2% vs. 4% vs. 4%

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Petrone, 1999[110]
Slowing the titration rate of tramadol HCl reduces the incidence of discontinuation due to nausea and/or vomiting: a double-blind randomized trial

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
11	Evaluate efficacy of different dose titration schedules (10, 13, or 16 days) of tramadol for discontinuations due to nausea or vomiting in patients who did not tolerate tramadol during faster titration	Randomized controlled trial Parallel group	18 years or older, chronic pain for at least 3 months, were receiving daily NSAIDs for at least 30 days prior to the study, and who required additional pain relief, did not tolerate tramadol titrated to 200 mg/day over 4 days	Trigeminal or post herpetic neuralgia, chronic painful conditions resulting from malignance, chronic painful conditions not appropriately treated, dysmenorrhea or recurrent headache, requirement for analgesic stronger than study drug, abnormal renal or hepatic function, contraindications to tramadol, investigational drug or device within 30 days, history of opioid or alcohol abuse within 12 months	931 enrolled in open-label titration phase 212 discontinued due to nausea or vomiting 169 randomized (54 to 10-day titration, 59 to 16-day titration, and 54 to 13-day titration; 2 post-randomization exclusions)	Mean age: 52 vs. 51 vs. 49 years Female gender: 83% vs. 85% vs. 83% Non-white race: 7% vs. 14% vs. 4% vs. 8% Duration of pain: 8.9 vs. 6.3 vs. 4.5 years Chronic low back pain: 20% vs. 30% vs. 33% Fibromyalgia: 22% vs. 15% vs. 7% Osteoarthritis: 26% vs. 34% vs. 24%	USA Multicenter Rheumatology clinics	Ortho-McNeil Pharma-ceuticals

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain intensity: 0 to 10 cm Nausea/vomiting/other adverse events Withdrawals due to adverse events	A: Tramadol 50 mg q am x 3 days, titrated to 50 mg qid on day 10 B: Tramadol 25 mg q am x 3 days, titrated to 50 mg qid on day 16 C: Tramadol 25 mg q am x 3 days, titrated to 50 mg tid on day 13	Not specified	Tramadol 10 days to 200 mg/day versus 16 days to 200 mg/day versus 13 days to 150 mg/day Pain intensity (improvement from baseline, 0 to 10 scale): -1.4 vs. -1.5 vs. -1.6 Patient rated study medication as very good or good: 63% vs. 67% vs. 61% Withdrawal (lack of efficacy): 2% (1/56) vs. 3% (2/59) vs. 0% (0/54)	28 days	74/169 (44%) 167/169 analyzed (99%)	Not reported	6/11 3/5	Tramadol 10 days to 200 mg/day versus 16 days to 200 mg/day versus 13 days to 150 mg/day Withdrawal due to adverse events: 29/54 (54%) vs. 20/59 (34%) vs. 16/54 (30%) ($p \leq 0.008$ for A or C vs. B) Withdrawal due to nausea and/or vomiting: 46% (25/54) vs. 22% (13/59) vs. 22% (12/54) Any adverse event: 76% vs. 70% vs. 61% Dizziness: 7% vs. 7% vs. 7% Headache: 18% vs. 15% vs. 13% Dry mouth: 0% vs. 2% vs. 6% Constipation: 7% vs. 3% vs. 11% Diarrhea: 7% vs. 5% vs. 2% Vomiting: 18% vs. 12% vs. 7% Nausea: 54% vs. 42% vs. 33% Somnolence: 9% vs. 7% vs. 0% Pruritus: 4% vs. 2% vs. 7%

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Portenoy, 2007[111]
Fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid-treated patients with chronic low back pain: a randomized, placebo-controlled study

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
14	Evaluate efficacy of fentanyl buccal tablet for relief of breakthrough pain in opioid-treated patients with chronic low back pain	Parallel-group randomized trial	18 to 80 years, chronic low back pain associated with osteoarthritis, degenerative disc disease, or spondylolisthesis resulting in functional disability for at least 3 months, receiving morphing ≥60 mg/day (or equivalent), average pain intensity ≤6 on a 0 to 10 scale in 24 hours prior to entry, duration of breakthrough pain less than 4 hours, use of an opioid to treat breakthrough pain described as at least somewhat effective	Uncontrolled or rapidly escalating pain, allergies or contraindications to study drug, cardiopulmonary disease that might affect safety, psychiatric or medical disease that might affect data collection, alcohol or substance abuse during the past 5 years, lactating, participated in an earlier fentanyl buccal tablet trial, or expected to have surgery during study	124 screened 105 enrolled in open-label dose titration 77 enrolled in randomized phase (randomized to one of 3 treatment sequences consisting of 6 fentanyl buccal tablets and 3 placebo tablets in different orders)	Not reported for randomization groups Mean age: 47 years Female gender: 55% Non-white race: 12% Baseline pain intensity: 5.1 (10 point scale) Primary etiology of low back pain degenerative disc disease: 68%	USA Multicenter Clinic setting not described	Cephalon, Inc.

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Results	Duration of follow-up	Loss to follow up	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain intensity: 0 to 10 scale Pain relief: 5-point scale (0 = none to 4 - complete) Onset time of "meaningful" pain relief	A: Buccal fentanyl 100 to 800 mcg for an episode of breakthrough pain B: Placebo Dose of buccal fentanyl: 800 mcg 56%; 600 mcg 24%; 400 mcg 15%; 200 mcg 5%	Buccal fentanyl vs. placebo Sum of the pain intensity differences from 5 through 60 minutes: 8.3 vs. 3.6 Proportion of breakthrough pain episodes with 'meaningful' pain reduction: 70% (289/413) vs. 30% (63/207) (p<0.0001) Proportion of breakthrough pain episodes with ≥33% reduction in pain intensity after 30 minutes: 42% (172/413) vs. 18% (18/207) (p≤0.0001) Proportion of breakthrough pain episodes with ≥50% reduction in pain intensity after 30 minutes: 30% (122/413) vs. 13% (27/207) (p≤0.0001) Proportion of breakthrough pain episodes with ≥33% reduction in pain intensity after 120 minutes: 65% (269/413) vs. 28% (57/207) (p≤0.0001) Proportion of breakthrough pain episodes with ≥50% reduction in pain intensity after 120 minutes: 48% (198/413) vs. 16% (33/207) (p≤0.0001)	120 minutes following each breakthrough pain episode	2/77 discontinued early	Not reported	9/11 5/5	All data reported only for buccal fentanyl Withdrawn due to adverse event: 1% (1/77) Serious adverse events: 3% (2/77) Nausea: 1% Dizziness: 4% Somnolence: 0% Dysgeusia: 8% Vomiting: 0% Dry mouth: 4%

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Raber, 1999[121]

Analgesic efficacy and tolerability of tramadol 100mg sustained-release capsules in patients with moderate to severe chronic low back pain

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
7	To evaluate efficacy of sustained-release (twice-daily) tramadol versus immediate-release tramadol for low back pain	Randomized parallel-group trial	Age 18 to 75 years, moderate to severe chronic low back pain >3 months due to chronic lumbar root irritation or compression or mechanical back pain	Metabolic bone disease, chronic inflammatory disease of the spinal column, arthritis related to enteropathies, patients with active cancer, clinical or radiological evidence of Paget's disease, acute nerve root compression or soft tissue damage, non-pharmacological therapy for low back pain, concomitant analgesics, cimeditine, carbamazepine, or monoamine oxidase inhibitors, pregnant or lactating	Number approached and eligible not reported 248 enrolled (125 sustained release, 122 immediate release) Duration of pain not reported Severity of baseline pain about 53 in both groups	Gender, age, race: Not reported ('well-matched') Duration of pain not reported Severity of baseline pain about 53 in both groups	Germany 22 centers	ASTA Medica AG, Frankfurt and Temmler Pharma GmbH, Marburg

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Visual Analogue Scale (VAS): 100 mm VAS Sleep questionnaire Functional capacity score: 4-point scale (good to poor) Patient's global assessment of efficacy Adverse events: reported spontaneously or elicited by investigator	A: Tramadol sustained release 100 mg twice a day B: Tramadol immediate release 50 mg four times a day 3 weeks intervention Additional tramadol sustained release 100 mg twice daily allowed if pain uncontrolled after 1 week	Not specified	Tramadol sustained-release versus tramadol immediate-release Pain relief, improvement in VAS (0 to 100): -25 vs. -25 for per-protocol analysis; ITT results stated as similar but data not reported Functional assessment 'without pain' or 'slight pain possible': >80% in both intervention groups for putting on jacket, putting on shoes, and climbing/descending stairs No awakenings due to low back pain: 41% vs. 47% Global assessment 'good' or 'moderately good': 80% (84/105) vs. 81% (80/99) Global assessment 'good': 47% (49/105) vs. 46% (45/99)	9 days	44/248 (18%) of enrolled patients withdrew or excluded from analysis due to protocol violations	SR: 1/125 withdrew due to lack of compliance 17 others (group not specified) did not comply	5/11 3/5	Tramadol sustained-release vs. tramadol immediate-release Withdrawal due to adverse events: 9.6% (12/125) vs. 8.2% (10/122) Headache: 18% vs. 29% (p=0.071) Nausea: 11% vs. 21% (p=0.038) Tolerability 'good' or 'moderately good': 78% vs. 70%

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Ralphs, 1994[310]
Opiate reduction in chronic pain patients: a comparison of patient-controlled reduction and staff controlled cocktail methods

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
33	Evaluate opiate reduction with goal for complete withdrawal using patient-controlled reduction versus cocktail reduction method	Prospective cohort	Patients referred to inpatient pain management, on opioids, chronic non-cancer pain, with any two of following: widespread disruption in activity due to pain, habitual over-activity leading to increased pain, regular use of analgesics and/or sedatives for >6 months, high affective distress, use of unnecessary aids, high levels of reported or observed pain behaviors, work reduced, impaired, or ceased owing to pain	Cannot use English, cannot climb stairs, current major psychiatric illness, unavailable for 4-week program, suitable for further physical treatments after medical examinations, pain of less than 1 year's duration, under 18 years old, currently using opioids for treatment of drug dependency	132 approached 108 enrolled (63 to patient-controlled method and 45 to cocktail method)	Mean age: 47 vs. 50 years Female gender: 49% vs. 71% Non-white race: Not reported Pain duration: 124 vs. 101 months Pain distress (0 to 100): 66 vs. 73 Mean opiate dose: 35.8 mg/day	UK Single center Inpatient setting	King Edwards Hospital Fund for London, Special Trustees of St. Thomas Hospital, and the South East Thames Regional Health Authority

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Sickness Impact Profile Pain intensity: 0 to 100 Pain-related distress: 0 to 100 Beck Depression Inventory Spielberger Anxiety Inventory Pain Self Efficacy Questionnaire (10 items, each rated 0 'not at all confident' to 6 'completely confident)	A: Patient-controlled reduction (patient discussed desired rate of reduction, aiming for abstinence by discharge, allowed to take longer if they wished, patients kept pills in room, plans adjusted as appropriate) B: Cocktail method (opioid mixed into a cocktail with dose gradually reduced, patient unaware of reduction schedule)	Allowed for patient-controlled reduction arm and recorded	Patient-controlled reduction versus cocktail method Abstinent at discharge: 68% vs. 89% ($p<0.05$) Abstinent 6 months after discharge: 54% (27/50) vs. 56% (18/32) Use of other drugs, pain, or psychological variables at 6 months: No differences between groups	6 months	24% (26/108)	Not reported	2/11 0/5	Not reported

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Rauck, 2006 and 2007[182]
A randomized, open-label, mulitcenter 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

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
7	Evaluate efficacy of extended-release (once daily) morphine (Avinza) versus sustained-release oxycodone for chronic low back pain	Paralleled-group RCT	30 to 70 years, persistent, moderate to severe chronic low back pain judged appropriate for chronic opioid therapy, suboptimal response to non-opioids, pain score >4 on a 0 to 10 scale	Treated with a sustained-release opioid, used a sustained-release opioid in last 6 months, previously unresponsive or intolerant to opioids, serious diagnosed medical condition that would interfere with ability to complete study, back surgery in the past 6 months, more than 2 surgeries for back pain, or back surgery or steroid injection expected during the first 12 to 13 weeks of the trial	Number approached and eligible not reported 392 randomized (203 to extended-release morphine and 189 to sustained-release oxycodone)	Median age: 50 vs. 50 Female gender: 64% vs. 58% Non-white race: 24% vs. 18% Duration of back pain: median 7 vs. 6 years Cause of back pain mechanical: 76% vs. 85% Baseline pain: 6.5 vs. 6.6	USA Multicenter Clinic setting not described	Ligand Pharma-ceuticals, Inc. and Organon Pharmaceuticals USA, Inc.

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Brief Pain Inventory: VAS (0 to 10) Ibuprofen rescue doses Pittsburgh Sleep Quality Index SF-12: 15-item ordinal scale Work Limitations Questionnaire	A: Extended-release morphine (Avinza) once daily (mean dose 64 mg) B: Sustained-release oxycodone (Oxycontin) twice daily (mean dose 53 mg)	Ibuprofen, up to 2400 mg/day	Extended-release morphine (Avinza) once daily versus sustained-release oxycodone (Oxycontin) twice daily Brief Pain Inventory score (0 to 10, mean improvement from baseline): -3.1 vs. -2.8 (p not reported) Proportion with >2 point improvement in BPI: 55% (73/132) vs. 44% (59/134) (p=0.03) Pittsburgh Sleep Quality Index (mean improvement from baseline): 33% vs. 17% (p=0.006) Rescue medication use: 2,595 vs. 3,154 doses (p<0.0001) SF-12 Physical Component Summary (mean improvement from baseline): 23% vs. 19% (NS) SF-12 Mental Component Summary (mean improvement from baseline): 23% vs. 16% (NS) Work Limitations Questionnaire (mean demands score, 0 to 100): 22.1 vs. 20.9 Withdrawal (lack of efficacy): 5% (10/203) vs. 3% (6/189)	8 weeks	220/392 (56%) did not complete trial 266/392 (68%) analyzed	3% (11/392)	4/11 2/5	Extended-release morphine (Avinza) once daily versus sustained-release oxycodone (Oxycontin) twice daily Serious adverse events: 3% (7/203) vs. 5% (9/189) Drug abuse or diversion: 0% (0/203) vs. 2% (4/189) Constipation: 92% vs. 90% Dizziness: 67% vs. 71% Drowsiness: 85% vs. 88% Dry mouth: 85% vs. 81% Itchiness: 67% vs. 62% Nausea: 60% vs. 56% Vomiting: 28% vs. 23% Withdrawal (overall): 46% (93/203) vs. 42% (79/189(Withdrawal (adverse events): 19% (38/203) vs. 14% (27/189)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Ruoff, 1999[112]

Slowing the initial titration rate of tramadol improves tolerability

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
11	Evaluate efficacy of different dose titration schedules (1, 4, or 10 days) of tramadol to achieve target doses of 200 mg/day	Randomized controlled trialParallel group	45 years or older, symptomatic chronic joint pain confirmed by radiograph, otherwise in good general health, stable dose of NSAID for at least 30 days, required additional pain relief	Rheumatoid arthritis, ankylosing spondylitis, active gout, intraarticular corticosteroids within 3 months, infection, major trauma, avascular necrosis of the joint, known contraindication to tramadol or NSAIDs, significant unstable medical disease or creatinin above 1.5 mg/dl, taking specific drugs or with known history of substance abuse	Number approached and eligible not reported465 randomized (132 to 1-day titration, 132 to 4-day titration, 132 to 10-day titration, 69 to placebo)	Mean age: 62 vs. 62 vs. 62 vs. 61 yearsFemale gender: 69% vs. 72% vs. 70% vs. 75%Non-white race: 10% vs. 11% vs. 11% vs. 3%Duration of arthritis: 9.6 vs. 8.3 vs. 8.3 vs. 8.1 yearsSite of osteoarthritis knee: 57% vs. 57 %vs. 48% vs. 57%	USA Multicenter Clinic setting not specified	Ortho-McNeil Pharma-ceutical Corporation

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Adverse events: mild, moderate, or marked	A: Tramadol 50 mg qid starting on day 1B: Tramadol 50 mg qD, titrated to 50 mg qid on day 4C: Tramadol 50 mg qD, titrated to 50 mg qid on day 10	Not specified	Tramadol 1 day to 200 mg/day versus 4 days to 200 mg/day versus 10 days to 200 mg/day versus placeboWithdrawal (lack of efficacy): 0.8% (1/130) vs. 1.6% (2/129) vs. 1.5% (2/132) vs. 0% (0/69)	14 days	106/465 (23%)459/465 (99%) analyzed	Not reported	8/11 5/5	Tramadol 1 day to 200 mg/day versus 4 days to 200 mg/day versus 10 days to 200 mg/day versus placeboWithdrawal due to adverse events: 31% (40/130) vs. 24% (31/129) vs. 15% (20/132) vs. 4% (3/68) (p<0.001 for trend)Withdrawal due to dizziness/vertigo: 10.8% vs. 10.1% vs. 1.5% vs. 0.0% (p=0.002 for trend)Withdrawal due to nausea/vomiting: 13.1% vs. 11.6% vs. 8.3% vs. 1.5% (p=0.04 for trend)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Salzman, 1999[209]

Can a controlled release oral dose form of oxycodone be used as readily as an immediate release form for the purpose of titrating to stable pain control?

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
11	Evaluate efficacy of sustained-release versus immediate-release oxycodone for dose titration	Random-ized controlled trial Parallel group	18 years or older, chronic stable moderate to severe back pain despite analgesic therapy with or without opioids	Contraindication to opioid history of substance abuse Unable to discontinue non-study narcotic Current oxycodone dose >80 mg/day Titration to 80 mg without achieving pain control	Treatment and Control not reported 57 enrolled	Avg. 56 years 54% Female 87% White 13% Hispanic Intervertebral disc disease, nerve root entrapment, spondylolisthesis, osteoarthritis, and other non-malignant conditions 84% (48/57) Pain duration not reported	USA Multicenter (5) Rheumatology clinics and others	Purdue Pharma sponsored study 2 authors employees of Purdue Role not otherwise reported.

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain Intensity: daily diary, categorical scale (0-3, none-severe) Study Medication Use: daily diary, amount used Rescue Drug Use: daily diary, amount used Achievement of Stable Pain Control: Stable pain control considered achieved if pain intensity rated as 1.5 or less for 48 hours with no more than 2 doses of rescue medication Time to Stable Pain Control: Days	A: Sustained-release Oxycodone (titrated) B: Immediate-release Oxycodone (titrated Titration comparison Mean dose A: 104 mg/day Mean dose B: 113 mg/day 10 days	Immediate-release oxycodone 5-10 mg/day every 4 hrs. as needed	Sustained-release oxycodone vs. immediate-release oxycodone Mean decrease in pain intensity (0 to 3 scale): 1.1 vs. 1.3 (NS) Proportion achieving stable analgesia: 87% (26/30) vs. 96% (26/27) (p = 0.36) Time to stable pain control: 2.7 vs. 3.0 days (p = 0.90). Mean number of dose adjustments: 1.1 vs. 1.7 adjustments (p = 0.58)	10 days	NA	Not reported	3/11 2/5	Tramadol 10 days to 200 mg/day versus 16 days to 200 mg/day versus 13 days to 150 mg/day Withdrawal due to adverse events: 29/54 (54%) vs. 20/59 (34%) vs. 16/54 (30%) ($p \leq 0.008$ for A or C vs. B) Withdrawal due to nausea and/or vomiting: 46% (25/54) vs. 22% (13/59) vs. 22% (12/54) Any adverse event: 76% vs. 70% vs. 61% Dizziness: 7% vs. 7% vs. 7% Headache: 18% vs. 15% vs. 13% Dry mouth: 0% vs. 2% vs. 6% Constipation: 7% vs. 3% vs. 11% Diarrhea: 7% vs. 5% vs. 2% Vomiting: 18% vs. 12% vs. 7% Nausea: 54% vs. 42% vs. 33% Somnolence: 9% vs. 7% vs. 0% Pruritus: 4% vs. 2% vs. 7%

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Simpson, 2007[113]
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

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
14	Evaluated efficacy of fentanyl buccal tablet for relief of breakthrough pain in opioid-treated patients with chronic neuropathic pain	Randomized crossover trial	18 to 80 years old, ≥3 months history of chronic neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, traumatic injury, or complex regional pain syndrome, on chronic opioids (at least 60 mg/day or morphine or equivalent), pain intensity <7 on a 0 to 10 scale, 1 to 4 daily episodes of breakthrough pain, use of opioid therapy for breakthrough pain described as at least partially effective; had to identify effective dose during dose-titration phase to be entered into randomized portion of trial	Unstable, uncontrolled, or rapidly escalating pain; allergies or other contraindications to study drug; alcohol or substance abuse in past 5 years; significant cardiopulmonary disease; significant medical or psychiatric disease; pregnancy or lactating	129 screened 103 enrolled in open-label dose titration 79 enrolled in randomized phase (randomized to one of 3 crossover treatment sequences consisting of 6 fentanyl buccal tablets and 3 placebo tablets)	Not reported for randomization groups	USA Multicenter Clinic setting not described	Cephalon, Inc.

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Results	Duration of follow-up	Loss to follow up	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain Intensity: 0 to 10 scale Sum of Pain Intensity differences from 5 through 60 minutes after administration of study drug	A: Buccal fentanyl 100 to 800 mcg for an episode of breakthrough pain B: Placebo Dose of buccal fentanyl: 800 mcg 54%; 600 mcg 19%; 400 mcg 18%; 200 mcg 5%, 100 mcg 5%	Buccal fentanyl vs. placebo Sum of the pain intensity differences from 5 through 60 minutes: 9.63 vs. 5.73 (p<0.001) Proportion of breakthrough pain episodes with 'meaningful' pain reduction: 69% vs. 36% (p<0.0001) Proportion of breakthrough pain episodes with ≥50% reduction in pain intensity after 15 minutes: 12% vs. 5% (p≤0.0001), p<0.0001 for each subsequent time point from 30 to 120 minutes Use of supplemental medication: 14% (59/432) vs. 36% (77/213) (OR=0.28, 95% CI 0.18 to 0.42)	120 minutes following each breakthrough pain episode over a 3 week period	2/79 discontinued early	1/79 withdrawn for non-compliance	9/11 5/5	All data reported only for buccal fentanyl: Withdrawn due to adverse event: 2.5% (2/79); 12% (12/103) withdrawn due to adverse events during open-label dose titration Nausea: 0% Dizziness: 1% Somnolence: 1% Vomiting: 0% Application site adverse event: 8% (8/103) during open-label dose titration

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Sorge, 1997[122]
Comparison of the analgesic efficacy and tolerability of tramadol 100 mg sustained-release tablets and tramadol 50 mg capsules for the treatment of chronic low back pain

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
7	To evaluate efficacy of sustained-release (twice-daily) tramadol versus immediate-release tramadol for low back pain	Randomized parallel-group trial	Moderate to severe low back pain of at least 3 months on unchanged non-pharmacological therapy for at least 3 weeks	Primary inflammatory etiology of low back pain, tumor or metastases, psychiatric disease, pension or disability claim, concomitant treatment with other analgesics or psychotropic drugs	Number approached and eligible not reported 205 enrolled (103 sustained release, 102 immediate release)	Female gender: 52% vs. 59% Mean age: 51 vs. 49 years Non-white race: Not reported Mean duration of pain: 9 years in both groups Baseline severity or underlying conditions: Not reported	Germany Multicenter Pain clinic	Grunenthal GmbH

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain intensity: 4-point verbal rating scale (1=none to 4=severe) Pain relief: 5-point verbal rating scale (none to complete) Adverse events: self-reported or elicited using non-leading questions	A: Tramadol sustained release 100 mg twice a day B: Tramadol immediate release 50 mg four times a day 3 weeks intervention Additional tramadol sustained release 100 mg twice daily allowed if pain uncontrolled after 1 week	2x 200mg SR/day as escape medication (open design)	Tramadol sustained-release versus tramadol immediate-release Pain relief 'complete', 'good', or 'satisfactory': 88% (52/59) vs. 86% (49/57; results only reported for persons who completed three-week course Pain relief 'complete': 8.5% (5/59) vs. 5.3% (3/57); results only reported for persons who completed three-week course	3 weeks	9 excluded due to 'protocol violations', another 80 did not complete 3-week course	Not reported	5/11 3/5	Tramadol sustained-release vs. tramadol immediate-release Any adverse event: 54% (56/103) vs. 53% (54/102) Withdrawal due to adverse event: 15% (15/103) vs. 19% (19/102) Headache: 4% vs. 8% (approximate, based on graph) Rates of nausea, dizziness, vomiting, constipation, tiredness, constipation, diaphoresis, dry mouth similar between groups

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Tennant, 1982[342] and 1983[343]
Outpatient treatment of prescription opioid dependence: comparison of two methods

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
33	Evaluate detoxification followed by psychotherapeutic counseling with detoxification followed by opioid maintenance if needed in patients dependent on prescription opioids	Non-randomized controlled clinical trial	Patients on opioids who volunteered for outpatient treatment for withdrawing opioids	Not reported	Number approached and eligible not reported 42 enrolled (21 to detoxification/counseling and 21 to detoxification/ maintenance)	Mean age: 33 vs. 44 years Female gender: 48% vs. 52% Non-white race: 19% vs. 14% Duration of opioid use: 7.2 vs. 9.2 years Proportion with chronic pain: 62% vs. 71% Back/spine disorder: 24% vs. 19% Use of codeine: 67% vs. 48%	US Single center Outpatient clinic	Not reported

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Proportion remaining in treatment past 3 weeks Proportion abstinent from opioids (as judged by history, negative urine test, and no further requests for opioids)	A: Detoxification/ counseling: Detoxification over 3 weeks with methadone, propoxyphene, clonidine, diphenoxylate, or sedative-hypnotics, followed by weekly psychotherapeutic counseling B: Detoxification/ maintenance: Detoxification as above, with maintenance on opioid if detoxification unsuccessful	Not specified	Detoxification/counseling vs. detoxification/maintenance Proportion remaining in treatment past 3 weeks: 24% (5/21) vs. 95% (20/21) Abstinent after 90 days: 10% (2/21) vs. 19% (4/21)	3 to 18 months	Not reported	Not reported	3/11 1/5	Not reported

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Thorne, 2008[123]
A randomized, double-blind, crossover comparison of the efficacy and safety of oral controlled-release tramadol and placebo in patients with painful osteoarthritis

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
4 5 7	Evaluate efficacy of extended-release (once daily) tramadol for hip or knee osteoarthritis	Cross-over RCT	Age >18 years, diagnosed with osteoarthritis (hip or knee symptoms , signs, and radiographic evidence of osteoarthritis), requiring use of acetaminophen, NSAIDs, or combination opioid and nonopioid analgesics for at least 3 months, pain at least 2 on acetaminophen or after washout in patients on any other analgesic (opioid or nonopioid)	Nursing or pregnant, intolerance to opioid, tramadol, or acetaminophen, using more than eight tablets/day of acetaminophen plus codeine (or equivalent), history of drug or alcohol abuse, other joint disease or joint replacement, renal or ehpatic impairment, shortened gastrointestinal transit time, peptic ulcer disease, inflammatory bowel disease, cardiac or respiratory conditions that put patient at risk for respiratory depression, history of seizures or risk for seizures, use of monoamine oxidase inhibitors, carbamazepine, quinidine, SSRIs or tricyclics, cyclobenzaprine, promethazine, neuroleptics, warfarin, or digoxin	Number approached and eligible not reported 100 randomized (50 to extended-release tramadol and 50 to placebo)	Baseline characteristics not reported by treatment group Mean age: 61 years Female: 55% Non-white: Not reported Duration of osteoarthritis pain: 8.3 years Baseline pain (0 to 100 VAS): 51	Canada Number of clinics unclear Clinic setting not reported	Purdue Pharma

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain Intensity: 0 (none) to 4 (excruciating) ordinal scale, 0 to 100 VAS WOMAC pain (0 to 500), stiffness (0 to 200), and physical function (0 to 1700) subscales Pain and Disability Index (0 to 70 overall score) Pain and Sleep Questionnaire: (0 to 500 composite score) SF-36 Overall effectiveness (patient and physician rated): not effective, slightly effective, moderately effective, highly effective	A: Extended release tramadol titrated up to 400 once daily B: Placebo Mean dose: 340 mg tramadol	Acetaminophen 325 to 650 mg up to every 4 to 6 hours	Extended-release tramadol titrated up to 400 mg once daily vs. placebo: Mean VAS pain score (0 to 100): 38.2 vs. 47.7 (p=0.0001). Mean ordinal pain score (0 to 4): 1.7 vs. 2.0 (p=0.001); WOMAC pain (0 to 500): 196 vs. 244 (p=0.0001). WOMAC physical function (0 to 1700): 656 vs. 773 (p=0.004). WOMAC stiffness (0 to 200): 23% vs. 20% improvement from baseline (difference NS). Pain and Disability Index (0 to 70): 22.8 vs. 27.2 (p=0.0004). Pain and Sleep Questionnaire (0 to 500): 105 vs. 141 (p=0.0008). SF-36: Tramadol superior to placebo on pain index, general health perception, vitality, and overall physical component score (by 2 to 3 pts on 100 pt scales); no differences on other scales. Patient overall assessment 'moderately' or 'highly' effective: 56% vs. 25%. Acetaminophen rescue medication use: 3.4 vs. 2.4 tablets/day. Discontinuation due to lack of efficacy: 2% (2/94) vs. 3% (3/88).	4 weeks, followed by crossover	25/100 (25%) did not complete trial Number analyzed: 77/100 (77%) for 'efficacy' analyses, unclear for intention-to-treat analyses	Not reported	5/11 4/5	Extended-release tramadol titrated up to 400 mg once daily vs. placebo Any adverse event: 80% vs. 66% Withdrawal due to adverse events: 13% (12/94) vs. 3% (3/88) Serious adverse event: none vs. 1 (atrial flutter) Nausea: 43% vs. 25% (p=0.03) Somnolence: 37% vs. 22% (p=0.08) Constipation: 23% vs. 6% (p=0.001) Anorexia: 6% vs. 1% (p=0.10) Vomiting: 6% vs. 1% (p=-.32) Dizziness: 5% vs. 3% (p=0.41)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Vorsanger, 2008[114]
Extended-release tramadol (tramadol ER) in the treatment of chronic low back pain

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
4 5 7	Evaluate efficacy of extended-release (once daily) tramadol for chronic low back pain	Parallel-group RCT	>6 months low back pain requiring daily treatment with an NSAID, acetaminophen, opioid, COX-2 selective inhibitor, and/or skeletal muscle relaxant for at least 60 of 90 days prior to enrollment; baseline pain intensity ≥40/100	Complex regional pain syndrome, significant inflammatory pain, fibromyalgia, history of lumbar spine surgery or chemonucleolysis, any medical condition not well controlled, undergoing transcutaneous electrical nerve stimulation or spinal manipulation, weight <100 lbs, dysphagia, intractable nausea and vomiting, history of intolerance to tramadol or known hypersensitivity to opioid analgesics, AST or ALT >2 times the upper limit or normal, creatinine >1.9, history of substance abuse within six months, diagnosis of cancer in the prior 3 years; recent monoamine oxidase inhibitor, TCA, corticosteroid use, or intra-articular visosupplementaion in the past 3 months	Number approached not reported 619 in open-label run-in period 386 randomized (128 to extended-release tramadol 300 mg/day, 129 to extended-release tramadol 200 mg/day, and 129 to placebo)	Mean age: 49 vs. 47 vs. 48 Female: 47% vs. 53% vs. 50% Non-white: 17% vs. 16% vs. 13% Duration of low back pain: Not reported Pretreatment pain intensity: 50 vs. 51 vs. 48	Canada Number of clinics unclear Clinic setting not reported	Purdue Pharma

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain Intensity: 0 (none) to 4 (excruciating) ordinal scale, 0 to 100 VAS WOMAC pain (0 to 500), stiffness (0 to 200), and physical function (0 to 1700) subscales Pain and Disability Index (0 to 70 overall score) Pain and Sleep Questionnaire: (0 to 500 composite score) SF-36 Overall effectiveness (patient and physician rated): not effective, slightly effective, moderately effective, highly effective	A: Extended release tramadol titrated up to 400 once daily B: Placebo Mean dose: 340 mg tramadol	Acetaminophen 325 to 650 mg up to every 4 to 6 hours	Extended-release tramadol titrated up to 400 mg once daily vs. placebo Mean VAS pain score (0 to 100): 38.2 vs. 47.7 (p=0.0001) Mean ordinal pain score (0 to 4): 1.7 vs. 2.0 (p=0.001) WOMAC pain (0 to 500): 196 vs. 244 (p=0.0001) WOMAC physical function (0 to 1700): 656 vs. 773 (p=0.004) WOMAC stiffness (0 to 200): 23% vs. 20% improvement from baseline (difference NS) Pain and Disability Index (0 to 70): 22.8 vs. 27.2 (p=0.0004) Pain and Sleep Questionnaire (0 to 500): 105 vs. 141 (p=0.0008) SF-36: Tramadol superior to placebo on pain index, general health perception, vitality, and overall physical component score (by 2 to 3 points on 100 point scales); no differences on other scales Patient overall assessment 'moderately' or 'highly' effective: 56% vs. 25% Acetaminophen rescue medication use: 3.4 vs. 2.4 tablets/day Discontinuation due to lack of efficacy: 2% (2/94) vs. 3% (3/88)	4 weeks, followed by crossover	25/100 (25%) did not complete trial Number analyzed: 77/100 (77%) for 'efficacy' analyses, unclear for intention-to-treat analyses	Not reported	7/11 4/5	Extended-release tramadol titrated up to 400 mg once daily vs. placebo Any adverse event: 80% vs. 66% Withdrawal due to adverse events: 13% (12/94) vs. 3% (3/88) Serious adverse event: none vs. 1 (atrial flutter) Nausea: 43% vs. 25% (p=0.03) Somnolence: 37% vs. 22% (p=0.08) Constipation: 23% vs. 6% (p=0.001) Anorexia: 6% vs. 1% (p=0.10) Vomiting: 6% vs. 1% (p=-.32) Dizziness: 5% vs. 3% (p=0.41)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Webster, 2006[115]
Oxytrex minimizes physical dependence while providing effective analgesia: A randomized controlled trial in low back pain

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
9	Evaluate efficacy of ultralow-dose naltrexone (in combination with oxycodone) for minimizing physical dependence and other opioid-associated adverse events	Parallel-group RCT	18 to 70 years old, persistent low back pain >6 months requiring daily analgesics, baseline pain intensity ≥5 at screening visit and over last 3 days of a washout period and after washout, at least 72 hours off opioids	Low back pain secondary to malignancy, automimmune disease, fibromyalgia, recent fracture, infection, urine drug screen positive for any illicit substance at baseline, history of substance abuse within 5 years, involvement in litigation involving low back condition, pregnancy, known hypersensitivity to study medications, significant co-morbid medical conditions; investigational drug use, corticosteroid therapy, intraspinal analgesic infusion or spinal cord stimulator, major surgery in last 3 months, percutaneous or open lumbosacral spine procedure in last 4 months, high doses of central nervous system depressants or phenothiazines	1061 approached 846 eligible 719 randomized (206 to oxycodone + ultralow-dose naltrexone qid, 206 to oxycodone + ultralow-dose naltrexone bid, 206 to oxycodone qid, and 101 to placebo)	Mean age: 48 vs. 48 vs. 48 vs. 49 Female: 62% vs. 62% vs. 61% vs. 61% Non-white race: Not reported Opioid use in last month: 41% vs. 43% vs. 48% vs. 43% ≥20 mg oxycodone/day (or equivalent): 7% vs. 6% vs. 5% vs.5% Baseline pain intensity: 7.3 vs. 7.6 vs. 7.6 vs. 7.7	USA Multi-center Clinic setting not described	Not reported Correspond-ing author employed by Pain Therapeutics, Inc.

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain Intensity: 0 to 10 scale Short-Form 12 Health Survey Oswestry Disabilty Index Quality of Analgesia (5 category scale, poor to excellent) Global Assessment of Study Drug (5 category scale, poor to excellent) Short Opiate Withdrawal Scale (0 to 30 scale) Constipation, somnolence, nausea, vomiting, dizziness, pruritis: Each rated on a 0 (none) to 3 (severe) scale	A: Oxycodone titrated to 20 mg + naltrexone 0.001 mg four times daily B: Oxycodone titrated to 40 mg and naltrexone 0.001 mg twice daily C: Oxycodone titrated to 20 mg four times daily D: Placebo 18 weeks intervention (6 weeks dose titration and 12 weeks intervention) followed by withdrawal	Not specified	Oxycodone 20 mg + naltrexone 0.001 mg qid vs. oxycodone 40 mg + naltrexone 0.001 mg bid vs. oxycodone 20 mg qid vs. placebo Pain intensity (improvement from baseline): -41% vs. -43% vs. -46% vs. -32% (all active treatments p<0.05 vs. placebo) Average oxycodone dose: 34.5 vs. 34.7 vs. 39.0 vs. 0 mg (p=0.03 for both naltrexone arms vs. oxycodone alone)	18 weeks intervention, 3 days follow-up after discontinuing study medication	54% (391/719) discontinued 50% (360/719) included in assess-ment of withdrawal symptoms	12/719 protocol violation	6/11 4/5	Oxycodone 20 mg + naltrexone 0.001 mg qid vs. oxycodone 40 mg + naltrexone 0.001 mg bid vs. oxycodone 20 mg qid vs. placebo. Withdrawal due to adverse events: 22% (45/206) vs 31% (63/206) vs. 24% (49/206) vs. 5% (5/101) Mean Short Opiate Withdrawal Scale (day 1): 2.3 vs. 1.2 vs. 2.7 vs. -0.1 (p<0.05 for naltrexone bid vs. oxycodone alone) Mean number of moderate to severe opioid-related adverse events during treatment: Constipation: 0.55 vs. 0.40 vs. 0.71 vs. 0.28 (p<0.05 for naltrexone bid vs. oxycodone alone). Dizziness: 0.32 vs. 0.35 vs. 0.37 vs. 0.13 (p>0.05 for all comparisons). Somnolence: 0.61 vs. 0.56 vs. 0.83 vs. 0.50 (p<0.05 for naltrexone bid vs. oxycodone alone) Pruritus: 0.28 vs. 0.25 vs. 0.51 vs. 0.05 (p<0.05 for naltrexone qid and naltrexone bid vs. oxycodone alone) Nausea: 0.53 vs. 0.52 vs. 0.60 vs. 0.21 (p>0.05 for all comparisons). Vomiting: 0.19 vs. 0.22 vs. 0.23 vs. 0.09 (p>0.05 for all comparisons)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Webster, 2008[116]
Alvimopan, a peripherally acting mu-opioid receptor (PAM-OR) antagonist for the treatment of opioid-induced bowel dysfunction: Results from a randomized, double-blind, placebo-controlled, dose-finding study in subjects taking opioids for chronic non-cancer pain

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
9	Evaluate efficacy of alvimopan for treating opioids-induced bowel dysfunction in patients with chronic non-cancer pain	Parallel-group RCT	>18 years old, bowel dysfunction resulting from chronic opioid treatment for chronic noncancer pain (fewer than 3 spontaneous bowel movements per week), on stable doses of opioids for >1 month	Pregnancy or lactation, use of opioids for cancer pain or addiction, use of mixed agonist/antagonist or partial agonist opioids, unwillingness to discontinue laxatives or manual maneuvers to facilitate defecation, severe constipation that had not been appropriately managed, GI or pelvic disorders that could affect bowel transit, bowel dysfunction not considered to be caused by opioid use	1108 screened 522 randomized (130 to alvimopan 0.5 mg bid, 133 1 mg qD, 130 to 1 mg bid, and 129 to placebo)	Mean age: 50 vs. 52 vs. 49 vs. 51 years Female: 59% vs. 63% vs. 68% vs. 65% Non-white: 96% vs. 89% vs. 89% vs. 93% Back pain: 62% vs. 55% vs. 56% vs. 60% Mean duration of current opioid use: 2.5 vs. 2.5 vs. 2.6 vs. 2.7 years	USA Multi-center Clinic setting not described	GlaxoSmith Kline

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Spontaneous bowel movements/week Opioid-induced bowel dysfunction global improvement (7-point scale) Laxative use Improvement in constipation symptoms Constipation-associated quality of life Satisfaction with treatment	A: Alvimopan 1 mg twice daily B: Alvimopan 1 mg once daily C: Alvimopan 0.5 mg twice daily D: Placebo 6 weeks intervention	Not stated	Alvimopan 1 mg bid vs. 1 mg qD vs. 0.5 mg bid vs. placebo Spontaneous bowel movements per week: 2.52 (95% CI 1.40-3.64) vs. 1.64 (95% CI 0.88 to 2.40) vs. 1.71 (95% CI 0.83 to 2.58) (p<0.05 for all doses versus placebo) Proportion with >3 spontaneous bowel movements per week: 68% vs. 63% vs. 63% vs. 39% (p<0.001 for all doses versus placebo) Opioid-induced bowel dysfunction global improvement (at least moderately improved): 42% vs. 40% vs. 39% vs. 14% (p<0.03 for all doses versus placebo) Rescue laxative use (tablets per week compared to placebo): -0.78 vs. -1.28 vs. -1.12 (p=0.01 for all doses)	6 weeks	17% (90/522) 100% (522/522) analyzed	1% (5/522) did not complete due to lack of compliance	7/11 4/5	Alvimopan 1 mg bid vs. 1 mg qD vs. 0.5 mg bid vs. placebo Deaths: None Serious adverse events: 4% vs. 8% vs. 5% vs. 3% Withdrawal due to adverse events: 13% vs. 11% vs. 5% vs. 9% Any adverse event: 67% vs. 65% vs. 71% vs. 66% Any GI-related adverse event: 43% vs. 38% vs. 30% vs. 36% Abdominal pain: 28% vs. 22% vs. 17% vs. 15% Diarrhea: 14% vs. 11% vs. 7% vs. 5%

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Wilder-Smith, 2001[198]

Treatment of severe pain from osteoarthritis with slow-release tramadol or dihydrocodein in combination with NSAID's: a randomised study comparing analgesia, antinociception and gastrointestinal effects

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
7	Evaluate efficacy of sustained-release tramadol versus sustained-release dextropropoxyphene for osteoarthritis in patients on NSAIDs	Parallel-group RCT	Osteoarthritis, awaiting hip or knee replacement surgery, mean pain score of 3 or more (on 0 to 4 scale) despite current NSAIDs,	Clinically relevant cardiopulmonary, hepatic, renal, or psychiatric co-morbidities, known allergies against study drugs, known drug abuse	95 approached Number eligible not reported 30 excluded because pain controlled on NSAIDs Number randomized not reported 57 evaluated in randomized arms (28 tramadol, 29 dihydrocodeine)	Mean age: 59 vs. 57 years Female gender: 29% vs. 31% Non-white race: 93% vs. 93% Osteoarthritis grade (ACR 1-4): 1.9 vs. 1.6 Joint involved knee or knee and hip: 68% vs. 72% Baseline pain (0 to 4 scale): 3 vs. 3	South Africa Single center Rheumatology clinic	Grunenthal AG and Grunenthal GmbH

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain intensity: 0 (none) to 4 (unbearable) at rest and during movement Bowel function (method not described) Overall satisfaction: 0 (unsatisfactory) to 2 (excellent) Sleep	A: Sustained-release tramadol 100 mg q 12 hours (titrated dose) B: Sustained-release dihydrocodeine 60 mg (titrated dose) Mean dose 203 mg/day (a) vs. 130 mg/day (b)	Immediate-release tramadol or dihydrocodeine at one-fifth of the 24-hour slow-release dose	Sustained-release tramadol versus sustained-release dihydrocodeine Pain intensity at rest at 4 weeks (median, 0 to 4 scale): 0 vs. 1 (p=0.04) Pain intensity with movement at 4 weeks (median, 0 to 4 scale): 1 vs. 1 (NS) Number of bowel movements: No changes Quality of sleep: Results poorly reported Global ratings: Median "excellent" for both drugs	1 month	8/95 (8%) of recruited patients dropped out, not clear what proportion of randomized patients dropped out	8/95 (8%) of recruited patients dropped out, not clear what proportion of randomized patients dropped out	3/11 1/5	Sustained-release tramadol versus sustained-release dihydrocodeine Sedation (0 to 4 scale): Median score 0 in both arms Insomnia: 4% vs. 0% Nausea/vomiting: 25% vs. 14% Dizziness: 21% vs. 14% Drowsiness: 54% vs. 28% Headache: 29% vs. 10% Withdrawal (Overall): Not reported Withdrawal (adverse event): Not reported

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 9. PRIMARY STUDIES EVIDENCE TABLES

Included randomized controlled trials of opioids for noncancer pain

Zautra, 2005[117]
Impact of controlled-release oxycodone on efficacy beliefs and coping efforts among osteoarthritis patients with moderate to severe pain.

Key Question(s)	Purpose of study	Study design	Inclusion criteria	Exclusion criteria	Number of Treatment & Control subjects (number approached, number eligible, number enrolled)	Subject age, gender, diagnosis	Country & setting	Sponsor
4	Evaluate efficacy of sustained-release oxycodone on pain relief and coping efforts in patients with moderate to severe pain	Parallel-group RCT	Osteoarthritis as defined by American College of Rheumatology guidelines, pain for at least 1 month with score >5 (>3 if on opioid)	>60 mg/day of oxycodone equivalent, allergic to opioids, scheduled for surgery, unstable coexisting disease or active severe organ dysfunction, active cancer, pregnant or breast-feeding, prior or present history of substance abuse, intra-articular or intramuscular steroid injections involving the joint under evaluation within 6 weeks	Number approached and eligible not reported 107 randomized (56 to sustained-release oxycodone, 51 to placebo)	Mean age: 63 vs. 64 years Female gender: 67% vs. 80% Non-white race: 6% vs. 7% Baseline pain score: 6.61 vs. 6.81 Duration of symptoms: Not reported	USA Multicenter Clinic setting not described	Supported in part by Purdue Pharma LP

Measures	Type of Intervention (experimental & control groups, dose, duration of treatment)	Rescue medications	Results	Duration of follow-up	Attrition Number analyzed	Compliance to treatment	Overall quality rating*	Adverse events & withdrawals due to AE's
Pain intensity 0 to 10 categorical scale) Positive and negative affect scales Coping effort: Vanderbilt Multidimensional Pain Coping Inventory Coping efficacy: 5 point scale Arthritis Helplessness Index: 5 items, each on a 6-point scale	A: Sustained-release oxycodone 10 mg q 12 hours, titrated up to 120 mg/day B: Placebo	Not permitted (stable regimens of non-opioids allowed)	Sustained-release oxycodone (A) vs. placebo (B) (all results at 2 weeks) 2 point or greater improvement in pain score (10-point scale): 40% (22/55) vs. 10% (5/49) (p<0.001) 24-hour pain (0 to 10): 4.96 vs. 6.34 (p<0.001) Positive affect: 2.95 vs. 2.79 (NS) Negative affect: 2.02 vs. 1.94 (NS) Active coping: 3.27 vs. 3.15 (NS) Coping efficacy: 3.39 vs. 3.11 (p=0.006) Arthritis Helplessness: 3.56 vs. 3.77 (p=0.05) Withdrawal due to lack of efficacy: 16% (9/56) vs. 67% (34/51)	3 months	71/107 (66%) 104/107 (97%) analyzed	Not reported	7/11 4/5	Sustained-release oxycodone vs. placebo Withdrawal (adverse events): 36% (20/55) vs. 4% (2/49)

* Detailed consensus quality ratings provided in Appendix 14

APPENDIX 10. PRIMARY STUDIES EVIDENCE TABLES

Included controlled studies of driving safety of patients on opioids for chronic noncancer pain

Author, year, title	Key Question(s)	Type of study, setting	Eligibility criteria	Exclusion criteria	Number screened Number eligible Number enrolled	Number withdrawn or loss to follow-up	Populations evaluated	Population characteristics	Method for assessing driving ability	Results	Applicability to target population	Funding source, role of funder
Byas-Smith, 2005[228] The effect of opioids on driving and psychomotor performance in patients with chronic pain	10	Cohort study USA	Age >21, no physical impairments, that might have an impact on driving ability, ability to pass a standard sobriety test on the day of examination, valid state drivers license, automobile insurance, access to an automobile, no use of benzodiazepine or barbiturate for at least a week prior to testing, chronic daily for at least 3 months and no change in analgesic dosage for at least 1 week prior to testing	See eligibility criteria	Number screened not reported 32/215 of eligible chronic pain patients enrolled 21 opioid users with chronic pain, 11 non-opioid users with chronic pain, 50 volunteers without pain	None	A: Chronic opioid use and chronic pain B: No opioid use and chronic pain C: No opioid use and no chronic pain	A vs. B vs. C Age: 48 vs. 46 vs. 43 years Female gender: 52% vs. 55% vs. 54% Pain intensity (0 to 100 VAS): 46 vs. 40 vs. 4.9 Daily morphine dose equivalent: 118 vs. 0 vs. 0 mg	Community drive, obstacle course, Test of Variables of A0ttention, Digit Symbol Substitution Test	A vs. B vs. C Community Drive Test, Obstacle Course, and Test of Variables of Attention: No differences Digit Symbol Substitution Test: C superior to A on Digit Symbol Substitution Test (59.66 vs. 48.13, $p<0.05$), but no difference between A and B (48.13 vs. 49.82)	Not clear how chronic pain patients identified. Small proportion of approached persons with chronic pain enrolled	Emory University Research Committee, role not described
Gaertner, 2006[344] Oral controlled-release oxycodone for the treatment of chronic pain. Data from 4196 patients	10	Cohort study Germany	>18 years, non-cancer pain responsive to opioids, treated with controlled-release oxycodone >4 weeks, no dose change in previous 12 days, valid driver's license, speak and write German	Receiving benzodiaz-epines or barbiturates >3 times per week, high dose antidepressant treatment (e.g. ≥75 mg of amitryptiline per day) or regular anti-histamines, physical disabilities, severe psychiatric or neurological diseases or visual disorders	Number screened and eligible not reported 30 patients with chronic pain and receiving opioids enrolled	None	A: Chronic controlled-release oxycodone use and chronic pain B: Randomly selected healthy volunteers	A vs. B Age: 55 vs. 55 years Female gender: 7% vs. 21% Non-white race: Not reported Duration of pain (group A): 65 months Current pain intensity (group A): 5 (on a 0 to 10 scale)	Test battery according to German national recommendations: Attention test; Test for reaction time under pressure, determination test; test for visual orientation; tachistoscopic perception, test for motor co-ordination (two-hand); vigilance test	A vs. B Number of passed tests (primary outcome, out of 5): 4.0 vs. 4.1 (p=0.18) Proportion passing all 5 tests: 37% vs. 56% (p=NS)	Not clear how chronic pain patients identified.	Not reported

APPENDIX 10. PRIMARY STUDIES EVIDENCE TABLES

Included controlled studies of driving safety of patients on opioids for chronic noncancer pain

Author, year, title	Key Question(s)	Type of study, setting	Eligibility criteria	Exclusion criteria	Number screened Number eligible Number enrolled	Number withdrawn or loss to follow-up	Populations evaluated	Population characteristics	Method for assessing driving ability	Results	Applicability to target population	Funding source, role of funder
Galski, 2000[230] Effects of opioids on driving ability	10	Cohort study USA	Chronic pain, no active involvement in pain management, absence of concomitant mental and/or neurological disorders, >6 months history of responding to opioids without complications, current use of a long-acting opioid, freedom from using other medications that might affect driving ability, adequate vision (minimum 20/50 visual acuity), possession of a valid driver's license	See eligibility criteria	Number screened : 128 Number eligible: Not clear Number enrolled: 16	None	A: Chronic opioid use and chronic pain B: No opioid use, cerebrally compromised patients who had undergone rehabilitation and evaluation for fitness to resume driving and passed C: No opioid use, cerebrally compromised patients who had undergone rehabilitation and evaluation for fitness to resume driving and failed	A vs. B vs. C Mean age: 48 vs. 46 vs. 46 years Gender and race: Not reported Pain intensity (group A): 3.48 (0 to 10 scale)	Cancellation Test, Trail Making Test, WAIS-R Digit Symbol Scaled Score, Rey Complex Figure Test, WAIS-R Block Design, Porteus Mazes, Raven Progressive Matrices, Driving simulator, Assessment of behaviors (distractibility, following directions, impulsivity, inattention, slowness in thinking)	A vs. B A superior to B on WAIS-R Digit Symbol Scaled Score, Rey Complex Figure Test-Time to Copy, Threat Recognition Braking % Valid, Following Directions. No other differences between A and B on Pre-driver evaluation, simulator evaluation, or behaviors.	Small proportion of patients with chronic pain enrolled	None reported

APPENDIX 10. PRIMARY STUDIES EVIDENCE TABLES

Included controlled studies of driving safety of patients on opioids for chronic noncancer pain

Author, year, title	Key Question(s)	Type of study, setting	Eligibility criteria	Exclusion criteria	Number screened Number eligible Number enrolled	Number withdrawn or loss to follow-up	Populations evaluated	Population characteristics	Method for assessing driving ability	Results	Applicability to target population	Funding source, role of funder
Menefee, 2004[232] The effects of transdermal fentanyl on driving, cognitive performance, and balance in patients with chronic nonmalignant pain conditions	10	Before-after study USA	Age 18 to 67, taking 15 mg oral oxycodone/day, valid driver's license, deemed appropriate for long-acting opiate therapy, and able to complete tests	Use of benzodiaz-epines, tizanidine, cyclobenz-aprine, carisoprodol, methocarb-amol, chlorzoxazone, metaxalone, >20 mg/day lioresal	Number screened not reported 27 eligible 26 started on transdermal fentanyl 23 completed study	3 patients who couldn't tolerate fentanyl did not complete study	A: Low-dose oxycodone use, chronic pain, switched to transdermal fentanyl and on stable dose for 1 month	Age: 47 years Female gender: 74% Race: Not reported Pain score (0 to 100 VAS): 53 (on fentanyl) Final fentanyl dose 75 mcg/hr in 17%	Driving simulator, Trail Making Test A & B, Rey Complex Figure Test and Recognition Trial, Weschler Memory Scale-III Spatial Span test, Test of Attention II, Conner's Continuous Performance Test II, Berg Balance Test	Comparison before and during treatment with transdermal Driving simulator: No differences Cognitive performance: Improved on some measures, no measures worsened. Balance: No differences	Not clear how chronic pain patients identified	Not reported
Mura, 2003[261] Comparison of the prevalence of alcohol, cannabis and other drugs between 900 injured drivers and 900 control subjects: results of a French collaborative study	22	Case-control study France	Drivers involved in a non-fatal road accident and admitted to an emergency room	See eligibility criteria	933 cases and 933 controls recruited; 33 excluded because of insufficient blood samples	See number screened and enrolled	Cases: Drivers in a non-fatal road accident Controls: Emergency room patients matched by sex and age	A vs. B: Mean age >50 years: 18% Female gender: 26% Non-white race: Not reported	Cases defined as drivers involved in a non-fatal motor vehicle accident	Odds ratios for presence in drivers involved in non-fatal road accidents Morphine (>20 ng/ml): 8.2 (2.5 to 27.3) Alcohol (>0.5 g/l): 3.8 (2.1 to6.8) Tetrahydro-cannabinol (>1 ng/ml): 2.5 (1.5 to 4.2) Benzodiaz-epines: 1.7 (1.2 to 2.4)	Unknown if morphine use prescribed or illicit and duration of morphine use	French Ministry of Health

APPENDIX 10. PRIMARY STUDIES EVIDENCE TABLES

Included controlled studies of driving safety of patients on opioids for chronic noncancer pain

Author, year, title	Key Question(s)	Type of study, setting	Eligibility criteria	Exclusion criteria	Number screened Number eligible Number enrolled	Number withdrawn or loss to follow-up	Populations evaluated	Population characteristics	Method for assessing driving ability	Results	Applicability to target population	Funding source, role of funder
Sabatowski, 2003[231] Driving ability under long-term treatment with transdermal fentanyl	10	Cohort study Germany	18 to 65 years, noncancer pain responsive to opioids, on transdermal fentanyl at least 4 weeks, no change in dose for 12 days, valid driver's license, ability to speak and write German	Receiving benzodiaze-pines or barbiturates >3 times per week, high dose antidepressant treatment (e.g. ≥75 mg of amitryptiline per day) or regular antihist-amines, physical disabilities, severe psychiatric or neurological diseases or visual disorders	Number screened and eligible not reported 30 patients with chronic pain and receiving opioids enrolled	None	A: Chronic transdermal fentanyl and chronic pain B: Randomly selected healthy volunteers	A vs. B Mean age: 50 vs. 50 Female gender: 40% vs. 37% Non-white race: Not reported Duration of pain (group A): 36 months Pain intensity (group A): 3 (0 to 10 scale)	Test battery according to German national recommend-ations: Attention test (COG); Test for reaction time under pressure, determination test (DT); test for visual orientation, tachistoscopic perception (TAVT); test for motor co-ordination (two-hand) (2-Hand); vigilance test (VIG)	A vs. B Sum score of Z-transformed COG, DT, and TAVT: 0.60 vs. -0.20, p=0.38 for non-inferiority test (0.19 for superiority test) Percentage of passed tests (60% vs. 74% (p=0.22)	Not clear how chronic pain patients identified	Deutsche Krebshilfe V. and Janssen-Cilag GmbH

APPENDIX 11. PRIMARY STUDIES EVIDENCE TABLES

Included studies on accuracy of screening instruments to identify aberrant drug-related behaviors in patients prescribed opioids

Author, year Instrument evaluated Method of administration	Number of patients Type of study	Definition of aberrant drug-related behaviors	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio	Other results	Quality*
Adams, 2004[280] Pain Medication Questionnaire (PMQ) Self-administered, 26 items	111 patients on opioids Cross-sectional	Physician Risk Assessment tool used to identify opioid misuse; based on a set of six dimensions, each rated on a 5-point Likert scale	Not calculable	Not calculable	Not calculable	Not calculable	Not calculable	Known opioid misuse (N=12) versus no known history of opioid misuse (matched sample) Mean PMQ score: 33.9 vs. 25.5 (p=0.045 based on 1-sided t-test)	6/9
Atluri, 2004[281] 6-item instrument Method of administration unclear, 6 items	107 cases, 103 controls Case-control	Inappropriate opioid use included inappropriate urine drug screen (not defined), intentional 'doctor shopping', alteration of opioid prescription to obtain more opioids, criminal activity involving prescription opioids (89% inappropriate urine drug screen)	0.77 (95% CI 0.68 to 0.84), for score ≥4	0.84 (95% CI 0.76 to 0.91) for score ≥4	4.93 (95% CI 3.11 to 7.83) for score ≥4	0.28 (95% CI 0.19 to 0.39) for score ≥4	17.8 (95% CI 8.93-35.6) for score ≥4	Risk of inappropriate opioid use Score ≥4 (out of 6) positive items (high risk) versus score <4 (low risk): OR 16.6 (95% CI 8.3 to 33)	2/9
Butler, 2007[282] Current Opioid Misuse Measure (COMM) Self-administered, 17 items	227 Cross-sectional (for assessing diagnostic accuracy)	Aberrant Drug Behavior Index positive if Patient Drug Use Questionnaire score >11 or urine toxicology screen positive (presence of illicit drug or non-prescribed opioid) and Prescription Opioid Therapy Questionnaire score ≥3	0.77 (95% CI 0.66 to 0.86) for COMM score ≥9 0.74 (95% CI 0.63 to 0.84) for COMM score ≥10	0.66 (95% CI 0.58 to 0.73) for COMM score ≥9 0.73 (95% CI 0.65 to 0.80) for COMM score ≥10	2.25 (95% CI 1.74 to 2.90) for COMM score ≥9 2.77 (95% CI 2.06 to 3.72) for COMM score ≥10	0.35 (95% CI 0.23 to 0.50) for COMM score ≥9 0.35 (95% CI 0.24 to 0.52) for COMM score ≥10	6.41 (95% CI 3.44 to 11.9) for COMM score ≥9 7.90 (95% CI 4.25 to 14.7) for COMM score ≥10	Area under receiver operating curve: 0.81 (95% CI 0.74 to 0.86)	5/9

APPENDIX 11. PRIMARY STUDIES EVIDENCE TABLES

Included studies on accuracy of screening instruments to identify aberrant drug-related behaviors in patients prescribed opioids

Author, year Instrument evaluated Method of administration	Number of patients Type of study	Definition of aberrant drug-related behaviors	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio	Other results	Quality*
Compton, 1998[283] Prescription Drug Use Questionnaire (PDUQ) Interviewer-administered, 40 items	52 Cross-sectional	American Society of Addiction Medicine criteria for substance abuse and substance dependence as evaluated by a single addiction medicine specialist	Not calculable	Not calculable	Not calculable	Not calculable	Not calculable	Score (range for number of positive items) on 40-item Prescription Drug Use Questionnaire ($p<0.0005$ on ANOVA) Nonaddicted: 6 to 15 Substance-abusing: 11 to 25 Substance-dependent: 15 to 28	7/9
Holmes, 2006[135] Pain Medication Questionnaire (PMQ) Self-administered, 26 items	271 Prospective cohort	Individuals with a known history of substance abuse (alcohol, prescription drugs, illicit drugs) based on self-admission, referring physician report, or initial psychologist evaluation; Physician Risk Assessment score; requests for early prescription refills	Not calculable	Not calculable	Not calculable	Not calculable	Not calculable	Known history of substance abuse (N=68) versus no known history of substance abuse (N=68) Pain Medication Questionnaire score (mean): 28.8 vs. 23.9 ($p=0.01$) High vs. low Pain Medication Questionnaire score Request for early refills: 61.5% vs. 33.3% ($p=0.02$); OR 3.2 (95% CI 1.21 to 8.44)	3/9

APPENDIX 11. PRIMARY STUDIES EVIDENCE TABLES

Included studies on accuracy of screening instruments to identify aberrant drug-related behaviors in patients prescribed opioids

Author, year Instrument evaluated Method of administration	Number of patients Type of study	Definition of aberrant drug-related behaviors	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio	Other results	Quality*
Manchikanti, 2004[284] Based on Atluri et al[281] Method of administration unclear, 4 items	150 Case-control	Controlled substance abuse defined as: Misuse of controlled substances in a clinical setting, including obtaining controlled substances from other physicians or other identifiable sources, dose escalations with inappropriate use, and/or violation of controlled substance agreement Illicit drug abuse not defined	0.49 (95% CI 0.37 to 0.60) **for score ≥2**	1.00 (95% CI 0.95 to 1.0) **for score ≥2**	69.2 (95% CI 4.33 to 1106) **for score ≥2**	0.52 (95% CI 0.42 to 0.64) **for score ≥2**	134 (95% CI 8.04 to 2241) **for score ≥2**	No controlled substance abuse/no illicit drug use vs. no controlled substance abuse/positive illicit drug use vs. positive controlled substance abuse/no illicit drug use vs. positive controlled substance abuse/positive illicit drug use Total score 0 or 1 out of 8 items: 100% vs. 94% vs. 20% vs. 23% (p values >0.05 for all comparisons) Total score ≥2 out of 8: 0% vs. 6% vs. 80% vs. 77% (p<0.05 for 6% vs. 0% and for 80% or 77% vs. 0% or 6%)	3/9

APPENDIX 11. PRIMARY STUDIES EVIDENCE TABLES

Included studies on accuracy of screening instruments to identify aberrant drug-related behaviors in patients prescribed opioids

Author, year Instrument evaluated Method of administration	Number of patients Type of study	Definition of aberrant drug-related behaviors	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio	Other results	Quality*
Michna, 2004[144] Abuse questions Items (3 questions) Interviewer-administered, 3 items	145 Cross-sectional	A: unanticipated positive results in urine toxicology tests B: episodes of lost or stolen prescription C: multiple unsanctioned escalations in dose D: frequent unscheduled pain center or emergency room visits E: concern expressed by a significant other about the patient's use of opioids F: excessive phone calls	2-3 positive responses A: 0.53 (95% CI 0.35 to 0.71) B: 0.47 (95% CI 0.29 to 0.65) C: 0.40 (95% CI 0.25 to 0.58) D: 0.40 (95% CI 0.19 to 0.64) E: 0.44 (95% CI 0.22 to 0.69) F: 0.36 (95% CI 0.11 to 0.69)	2-3 positive responses A: 0.75 (95% CI 0.66 to 0.83) B: 0.74 (95% CI 0.64 to 0.81) C: 0.72 (95% CI 0.63 to 0.80) D: 0.70 (95% CI 0.62 to 0.78) E: 0.71 (95% CI 0.62 to 0.79) F: 0.69 (95% CI 0.61 to 0.77)	2-3 positive responses A: 2.14 (95% CI 1.36 to 3.39) B: 1.77 (95% CI 1.09 to 2.85) C: 1.46 (95% CI 0.89 to 2.39) D: 1.35 (95% CI 0.74 to 2.46) E: 1.53 (95% CI 0.85 to 2.73) F: 1.19 (95% CI 0.52 to 2.70)	2-3 positive responses A: 0.62 (95% CI 0.42 to 0.92) B: 0.72 (95% CI 0.51 to 1.02) C: 0.82 (95% CI 0.62 to 1.10) D: 0.85 (95% CI 0.58 to 1.24) E: 0.78 (95% CI 0.51 to 1.20) F: 0.92 (95% CI 0.58 to 1.45)	2-3 positive responses A: 3.44 (95% CI 1.54 to 7.71) B: 2.44 (95% CI 1.10 to 5.44) C: 1.77 (95% CI 0.82 to 3.84) D: 1.59 (95% CI 0.61 to 4.11) E: 1.95 (95% CI 0.73 to 5.19) F: 1.30 (95% CI 0.38 to 4.41)	High risk (2-3 positive responses) versus low risk (0-1 positive responses) A: 38% vs. 15%, p<0.05 B: 33% vs. 17%, p<0.05 C: 33% vs. 22%, p>0.05 D: 18% vs. 12%, p>0.05 E: 18% vs. 10%, p>0.05 F: 9% vs. 7%, p>0.05	7/9
Wasan, 2007[285] Psychiatric items from the Prescription Drug Use Questionnaire (PDUQ) Interviewer-administered, 5 items	228 Prospective cohort	Drug Misuse Index: Misuse or abuse defined as positive scores on the self-reported Screener and Opioid Assessment for Pain Patients and the Current Medication Misuse Measure; or positive scores on the urine toxicology screen (presence of illicit substance or a non-prescribed opioid) and the Perception of Opioid Therapy Questionnaire	0.74 (95% CI 0.63 to 0.83) for ≥2 items on PDUQ	0.57 (95% CI 0.48 to 0.66) for ≥2 items on PDUQ	1.72 (95% CI 1.37 to 2.17) for ≥2 items on PDUQ	0.46 (95% CI 0.31 to 0.67) for ≥2 items on PDUQ	3.77 (95% CI 2.11 to 6.72) for ≥2 items on PDUQ	High psychiatric comorbidity (≥2 positive items out of 5 psychiatric items on the PDUQ) vs. low psychiatric comorbidity (<2 positive items) Drug Misuse Index positive: 52% vs. 22% (p<0.001)	6/9

APPENDIX 11. PRIMARY STUDIES EVIDENCE TABLES

Included studies on accuracy of screening instruments to identify aberrant drug-related behaviors in patients prescribed opioids

Author, year Instrument evaluated Method of administration	Number of patients Type of study	Definition of aberrant drug-related behaviors	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio	Other results	Quality*
Wu, 2006[286] Addiction Behaviors Checklist (ABC) Interviewer-administered, 20 items	136 Prospective cohort	Interviewer's global clinical judgment (yes or no to "Do you think patient is using medications appropriately?")	0.88 for ABC score ≥3 (confidence intervals not calculable)	0.86 for ABC score ≥3 (confidence intervals not calculable)	Not calculable	Not calculable	Not calculable	None	4/9

*See Appendix 14 for complete quality criteria scores

APPENDIX 12. PRIMARY STUDIES EVIDENCE TABLES

Included prospective studies of use of screening instruments to predict the risk of aberrant drug-related behaviors

Author, year Instrument evaluated Method of administration	Number of patients Duration of follow-up Opioid use at enrollment	Definition of aberrant drug-related behaviors	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio	Other results	Quality*
Akbik, 2006[149] Screener and Opioid Assessment for Patients with Pain (SOAPP) Version 1 Self-administered, 14 items	N=397 (155 had urine toxicology results) Duration unclear Patients not on opioids	Urine toxicology screen showing illicit substances and/or unprescribed opioids	0.68 (95% CI 0.52 to 0.81) for SOAPP Version 1 score ≥8	0.39 (95% CI 0.29 to 0.49) for SOAPP Version 1 score ≥8	1.11 (95% CI 0.86 to 1.43) for SOAPP Version 1 score ≥8	0.83 (95% CI 0.50 to 1.36) for SOAPP Version 1 score ≥8	1.34 (95% CI 0.64 to 2.84) for SOAPP Version 1 score ≥8	SOAPP Version 1 score ≥8 vs. ≤8 Urine toxicology screen available and abnormal: 30/89 (34%) vs. 14/51 (28%), p<0.05	5/9
Butler, 2004[150] Screener and Opioid Assessment for Patients with Pain (SOAPP) Version 1 Self-administered, 14 items	N=175 (95 completed 6 month follow-up) 6 months Mixed population	Prescription Drug Use Questionnaire score ≥11 (out of 42) and/or staff assessment of serious drug behavior by 2 or 3 staff members and/or urine toxicology sample with unexpected medications, absence of prescribed medications, and/or illicit substances	0.91 (95% CI 0.78 to 0.98) for SOAPP Version 1 score ≥7 0.86 (95% CI 0.73 to 0.95) for SOAPP Version 1 score ≥8	0.69 (95% CI 0.54 to 0.81) for SOAPP Version 1 score ≥7 0.72 (95% CI 0.58 to 0.84) for SOAPP Version 1 score ≥8	2.90 (95% CI 1.91 to 4.39) for SOAPP Version 1 score ≥7 3.15 (95% CI 1.98 to 4.99) for SOAPP Version 1 score ≥8	0.13 (95% CI 0.05 to 0.34) for SOAPP Version 1 score ≥7 0.19 (95% CI 0.09 to 0.40) for SOAPP Version 1 score ≥8	21.9 (95% CI 6.89 to 68.5) for SOAPP Version 1 score ≥7 16.7 (95% CI 5.91 to 47.2) for SOAPP Version 1 score ≥7	Area under receiver operating curve 0.88 (95% CI 0.81 to 0.95)	5/9

APPENDIX 12. PRIMARY STUDIES EVIDENCE TABLES

Included prospective studies of use of screening instruments to predict the risk of aberrant drug-related behaviors

Author, year Instrument evaluated Method of administration	Number of patients Duration of follow-up Opioid use at enrollment	Definition of aberrant drug-related behaviors	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio	Other results	Quality*
Butler, 2008[151] Revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R) Self-administered, 24 items	N=283 (223 completed 5 month follow-up) 5 months All patients on opioids	Positive result on the Aberrant Drug Behavior Index: Score on the 42-item Prescription Drug Use Questionnaire of >11, or 2 or more positive results on the 11-item Prescription Opioid Therapy Questionnaire plus an abnormal urine toxicology result (illicit drug or non-prescribed opioid)	0.80 (95% CI 0.70 to 0.89) for SOAPP-R score ≥17	0.68 (95% CI 0.60 to 0.75) for SOAPP-R score ≥17	2.50 (95% CI 1.93 to 3.24) for SOAPP-R score ≥17	0.29 (95% CI 0.18 to 0.46) for SOAPP-R score ≥17	8.71 (95% CI 4.51 to 16.8)	Area under receiver operating curve: 0.81 (95% CI 0.75 to 0.87)	6/9
Webster, 2005[152] Opioid Risk Tool (ORT) Self-administered, 10 items	N=185 12 months All patients on opioids	Not defined; 23 different aberrant behaviors reported. Methods for identifying behaviors also not reported.	Not applicable (not dichotomous)	Not applicable (not dichotomous)	High risk (score ≥8): 14.3 (95% CI 5.35 to 38.4) Moderate risk (score 4 to 7): 0.57 (95% CI 0.44 to 0.74) Low risk (score 0 to 3): 0.08 (95% CI 0.01 to 0.62)	Not applicable (not dichotomous)	Not applicable (not dichotomous)	Proportion with one or more aberrant behaviors, according to classification using ORT score: Low risk: 6% (1/18) Moderate risk: 28% (35/123) High risk: 91% (40/44)	4/9

*See Appendix 15 for complete quality criteria scores

APPENDIX 13. PRIMARY STUDIES EVIDENCE TABLES

Detailed consensus quality ratings of included primary studies of opioids for noncancer pain

	Cochrane scoring												Jadad scoring			
Author, year, title	Random-ization	Concealed Treatment Allocation	Baseline Group Similarity	Patient Blinded	Care provider Blinded	Outcome Assessor Blinded	Co-interventions Avoided or Similar	Compliance Acceptable in All Groups	Drop-out Rate Described and Acceptable	Timing of Outcome Assessment in All Groups Similar	Intention to Treat Analysis	Score	Random-ization	Blinding	Reporting of Withdrawals	Score
Adler 2002[90]	DK	DK	YES	YES	YES	YES	YES	DK	NO	YES	DK	6/11	1	2	1	4/5
Allan 2005[124]	DK	YES	YES	NO	NO	NO	YES	NO 158/680 protocol violation	NO	YES	NO	4/11	1	0	1	2/5
Beaulieu, 2007[197]	DK	DK	DK	YES	YES	DK	YES	YES	NO	YES	NO	5/11	1	1	1	3
Bodalia 2003[118]	DK	YES	DK	YES	YES	YES	YES	DK	NO	NO 5-8 days	DK	5/11	1	2	0	3/5
Burch, 2007[91]	DK	DK	YES	YES	YES	YES	DK	DK	NO 24%	YES	YES	6/11	1	2	1	4/5
Carr 2004[92]	YES	YES	YES	YES	YES	YES	DK	YES	YES	YES	NO	9/11	2	2	1	5/5
Cowan 2005[93]	YES	YES	DK	YES	YES	YES	DK	DK	NO	YES	DK	6/11	2	2	9	4/5
Galer 2005(a)[94]	DK	DK	YES	YES	YES	YES	YES	YES	NO	YES	YES	8/11	1	1	1	3/5
Gana 2006[95]	DK	YES	NO	YES	YES	YES	YES	DK	NO	YES	YES	7/11	1	2	1	4/5
Gilron 2005[96]	DK	YES	YES	YES	YES	YES	YES	DK	NO	YES	NO crossover	7/11	1	2	1	4/5
Hale 1997[119]	DK	DK	YES	YES	YES	YES	N different rescue meds	DK	NO	YES	NO	5/11	1	1	1	3/5
Hale 2005[98]	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	NO	9/11	2	2	1	5/5
Hale 2007[97]	DK	DK	YES	YES	YES	YES	YES	YS	NO	YES	YES	8/11	1	1	1	3/5
Hanna, 2008[99]	YES	YES	YES	YES	YES	YES	YES	DK	NO	YES	NO	8/11	2	2	1	5/5
Jamison 1998[207]	DK	DK	DK	NO	NO	NO	DK	DK	YES	YES	YES	3/11	1	0	1	2/5
Jensen 1994[100]	YES	DK	YES	YES	YES	YES	DK	DK	NO	YES	NO	6/11	1	2	0	3/5

APPENDIX 13. PRIMARY STUDIES EVIDENCE TABLES

Detailed consensus quality ratings of included primary studies of opioids for noncancer pain

	Cochrane scoring												Jadad scoring			
Author, year, title	Random-ization	Concealed Treatment Allocation	Baseline Group Similarity	Patient Blinded	Care provider Blinded	Outcome Assessor Blinded	Co-interventions Avoided or Similar	Compliance Acceptable in All Groups	Drop-out Rate Described and Acceptable	Timing of Outcome Assessment in All Groups Similar	Intention to Treat Analysis	Score	Random-ization	Blinding	Reporting of Withdrawals	Score
Katz 2000 (a)[101]	DK	DK	YES	YES	YES	YES	YES	YES	NO	YES	YES	8/11	1	2	1	4/5
Katz 2007[102]	DK	DK	YES	YES	YES	YES	YES	YES	NO	YES	YES	8/11	1	2	1	4/5
Khoromi, 2007[120]	DK	YES	DK crossover	YES	YES	YES	DK	DK	NO 49%	YES	NO 51%	5/11	1	2	1	4/5
Kivitz 2006[103]	YES	YES	DK insufficient info on pain	YES	YES	YES	YES	YS	NO	YES	YES	9/11	2	2	1	5/5
Langford 2006[104]	YES	YES	YES	YES	YES	YES	YES	DK	NO	YES	YES	9/11	2	2	1	5/5
Ma, 2007[161]	DK	DK	YES	YES	YES	DK	YES	DK	NO	NO	NO	4/11	1	1	0	2/5
Markenson 2005[105]	YES	DK	YES	YES	YES	YES	YES	YES	NO	YES	YES	9/11	2	2	1	5/5
Matsumoto 2005[106]	YES	DK	YES	YES	YES	YES	DK	YES	NO	YES	YES	8/11	2	2	1	5/5
Mongin 2004[107]	YES	DK	YES	YES	YES	YES	YES	YES	NO	YES	YES	9/11	1	2	1	4/5
Mullican 2001[108]	DK	DK	YES	YES	YES	YES	YES	YES	NO	YES	DK	7/11	1	2	1	4/5
Nicholson 2006[195]	YES	DK	NO	NO	NO	NO	YES	YES	NO	YES	NO	4/11	1	0	1	2/5
Niemann 2000[196]	DK	DK	DK	NO	NO	NO	DK	DK	YES	YES	YES	3/11	1	0	1	2/5
Paulson 2005[109]	DK	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	10/11	1	2	1	4/5
Petrone 1999[110]	YES	DK	YES	YES	YES	YES	DK	DK	NO	YES	YES	6/11	1	1	1	3/5
Portenoy 2007[111]	YES	YES	DK	YES	YES	YES	YES	DK	YES	YES	YES	9/11	2	2	1	5/5
Raber 1999[121]	DK	DK	DK	YES	YES	YES	DK	DK	YES	YES	NO	5/11	1	2	0	3/5
Ralphs 1994[310]	NO	NO	NO	NO	NO	NO	YES	DK	NO	YES	DK	2/11	0	0	0	0/5
Rauck 2006 and 2007[182]	DK	YES	NO	NO	NO	NO	YES	YES	NO	YES	NO	4/11	1	0	1	2/5

APPENDIX 13. PRIMARY STUDIES EVIDENCE TABLES

Detailed consensus quality ratings of included primary studies of opioids for noncancer pain

	Cochrane scoring												Jadad scoring			
Author, year, title	Random-ization	Concealed Treatment Allocation	Baseline Group Similarity	Patient Blinded	Care provider Blinded	Outcome Assessor Blinded	Co-interventions Avoided or Similar	Compliance Acceptable in All Groups	Drop-out Rate Described and Acceptable	Timing of Outcome Assessment in All Groups Similar	Intention to Treat Analysis	Score	Random-ization	Blinding	Reporting of Withdrawals	Score
Ruoff 1999[112]	YES	YES	YES	YES	YES	YES	DK	DK	NO	YES	YES	8/11	2	2	1	5/5
Salzman 1999[209]	DK	DK	YES	NO	NO	NO	YES	DK	NO	YES	NO	3/11	1	0	1	2/5
Simpson, 2007[113]	YES	DK	DK crossover	YES	YES	YES	YES measured as an outcome	YES	YES	YES	YES	9/11	2	2	1	5/5
Sorge 1997[122]	DK	DK	YES	YES	YES	YES	DK	DK	NO	YES	DK	5/11	1	2	0	3/5
Tennant 1982[342] **& 1983**[311]	NO	NO	NO	NO	NO	NO	DK	DK	YES	YES	YES	3/11	0	0	1	1/5
Thorne, 2008[123]	DK	DK	DK	YES	YES	YES	YES	DK	NO	YES	NO	5/11	1	2	1	4/5
Vorsanger, 2008[114]	YES	DK	YES	YES	YES	DK	YES	DK	NO	YES	YES	7/11	1	2	1	4/5
Webster, 2006[115]	DK	DK	YES	YES	YES	YES	DK	YES	NO >50%	YES	NO for main outcome	6/11	1	2	1	4/5
Webster, 2008[116]	DK	DK	YES	YES	YES	DK	YES	YES	NO	NO	NO	7/11	1	1	2	4/5
Wilder-Smith 2001[198]	YES	DK	YES	NO	NO	NO	DK	DK	NO	YES	DK	3/11	1	0	0	1/5
Zautra 2005[117]	DK	DK	YES	YES	YES	YES	YES	DK	NO	YES	YES	7/11	1	2	1	4/5

DK = Don't Know
Refer to Appendices 4 & 5 for details

APPENDIX 14. PRIMARY STUDIES EVIDENCE TABLES

Detailed consensus quality ratings of included studies on accuracy of screening instruments to identify aberrant drug-related behaviors in patients prescribed opioids

Author/year	Evaluates population other than the one used to derive the instrument	Consecutive series of patients or a random subset	Describes severity of symptoms, opioid dose/duration, and underlying conditions	Adequate description of screening instrument	Appropriate criteria included in screening instrument	Adequate description of method for identifying aberrant drug-related behaviors	Appropriate criteria used to identify aberrant drug-related behaviors	Aberrant drug-related behaviors assessed in all enrollees	Blinded assessment of aberrant drug-related behaviors	Score (max 9)
Adams, 2004[280]	NO	YES	NO	YES	YES	YES	YES	YES	DON'T KNOW	6/9
Atluri, 2004[281]	NO	NO	NO	YES	YES	NO	DON'T KNOW	DON'T KNOW	DON'T KNOW	2/9
Butler, 2007[282]	NO	YES	YES	YES	YES	YES	YES	DON'T KNOW	DON'T KNOW	5/9
Compton, 1998[283]	YES	YES	NO	YES	YES	YES	YES	YES	DON'T KNOW	7/9
Holmes, 2006[135]	YES	YES	NO	YES	YES	NO	NO	DON'T KNOW	DON'T KNOW	4/9
Manchikanti, 2004[284]	NO	YES	NO	NO	YES	NO	DON'T KNOW	YES	DON'T KNOW	3/9
Michna, 2004[144]	YES	YES	NO	YES	YES	YES	YES	YES	DON'T KNOW	7/9
Wasan, 2007[285]	YES	YES	NO	YES	YES	YES	YES	NO	DON'T KNOW	6/9
Wu, 2006[286]	NO	YES	NO	YES	YES	YES	NO	DON'T KNOW	DON'T KNOW	4/9

* Using nine criteria described in Methods section

APPENDIX 15. PRIMARY STUDIES EVIDENCE TABLES

Detailed consensus quality ratings of included prospective studies of use of screening instruments to predict the risk of aberrant drug-related behaviors

Author/year	Evaluates population other than the one used to derive the instrument	Consecutive series of patients or a random subset	Describes severity of symptoms, opioid dose/duration, and underlying conditions	Adequate description of screening instrument	Appropriate criteria included in screening instrument	Adequate description of method for identifying aberrant drug-related behaviors	Appropriate criteria used to identify aberrant drug-related behaviors	Aberrant drug-related behaviors assessed in all enrollees	Blinded assessment of aberrant drug-related behaviors	Score (max 9*)
Akbik, 2006[149]	YES	YES	NO	YES	YES	YES	NO	NO	DON'T KNOW	5/9
Butler, 2004[150]	NO	YES	NO	YES	YES	YES	YES	NO	DON'T KNOW	5/9
Butler, 2008[151]	NO	YES	YES	YES	YES	YES	YES	NO	DON'T KNOW	6/9
Webster, 2005[152]	YES	YES	NO	YES	YES	NO	DON'T KNOW	DON'T KNOW	DON'T KNOW	4/9

* Using nine criteria described in Methods section

APPENDIX 16. INCLUSION CRITERIA BY KEY QUESTION

Studies that met inclusion criteria for each Key Question

Topic area	Key question	Systematic reviews (number of randomized trials)	Randomized trials not included in systematic reviews	Prospective studies on risk prediction or studies of diagnostic accuracy	Case-control studies, cohort studies	Cross-sectional studies, other (secondary analyses of randomized trials, etc.)
Risk-benefit assessment	**1a**	3 (53 unique trials)	NA	0	NA	3
	1b	1 (35 trials)	NA	0	NA	0
	1c	0	NA	0	NA	0
	2	1	NA	4	NA	0
	3	0	0	NA	0	0
Benefits and harms of chronic opioid therapy (including high risk patients	**4**	12 (70 unique trials)	13	NA	0	0
	5	12 (70 unique trials)	11	NA	2	3
	6	0	1	NA	0	0
	7	1 (9 trials)	17	NA	3	0
	8	3 (53 unique trials)	0	NA	0	0
Prevention and treatment of opioid-related adverse effects	**9**	0	3	NA	0	0
Driving and work safety	**10**	2 (non randomized)	0	NA	4	0
Initiation and titration of chronic opioid therapy	**11**	0	4	NA	0	0
Selection of opioids and dosing methods	**12**	0	2	NA	0	0
	13	0	0	NA	0	0
Breakthrough pain	**14**	0	3	NA	0	0
Opioid rotation	**15**	0	0	NA	0	0
	16	0	NA	0	NA	NA

APPENDIX 16. INCLUSION CRITERIA BY KEY QUESTION

Studies that met inclusion criteria for each Key Question

Topic area	Key question	Systematic reviews (number of randomized trials)	Randomized trials not included in systematic reviews	Prospective studies on risk prediction or studies of diagnostic accuracy	Case-control studies, cohort studies	Cross-sectional studies, other (secondary analyses of randomized trials, etc.)
Dose escalations and high-dose opioid therapy	**17**	0	0	NA	0	0
	18	0	0	NA	0	0
	19	0	0	NA	0	0
	20	0	0	NA	1	0
Use of non-opioid therapies	**21**	0	0	NA	0	0
	22	0	9	NA	0	0
	23	0	0	NA	0	0
	24	0	0	NA	0	2
Methods for monitoring opioid use and detecting aberrant drug-related behaviors	**25**	0	0	NA	0	0
	26	0	NA	9	NA	0
	27a	0	NA	1	NA	0
	27b	0	NA	1	NA	0
	28	0	0	NA	1	0
	28	0	0	NA	0	0
	29	0	0	NA	1	0
	30	0	0	NA	0	0
	31	0	0	NA	0	0
	32	0	NA	0	NA	NA
	33	0	0	NA	0	0
Discontinuing opioids	**34**	0	0	NA	0	0
	35	0	1	NA	2 (non randomized trials)	0
Pregnancy	**36**	0	0	NA	0	0
Opioid prescribing policies	**37**	0	0	NA	0	0