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Research Gaps on Use of Opioids for Chronic Noncancer Pain: Findings From a Review of the Evidence for an American Pain Society and American Academy of Pain Medicine Clinical Practice Guideline

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Abstract: Chronic noncancer pain is common and use of opioids is increasing. Previously published guidelines on use of opioids for chronic noncancer pain have been based primarily on expert consensus due to lack of strong evidence. We conducted searches on Ovid MEDLINE and the Cochrane databases through July 2008 to identify studies that addressed one or more of 37 Key Questions that a multidisciplinary expert panel identified as important to be answered to generate evidence-based recommendations on the use of opioids for chronic noncancer pain. A total of 14 systematic reviews, 38 randomized trials not included in a previously published systematic review, and 13 other studies met inclusion criteria. Almost all of the randomized trials of opioids for chronic noncancer pain were short-term efficacy studies. Critical research gaps on use of opioids for chronic noncancer pain include: lack of effectiveness studies on long-term benefits and harms of opioids (including drug abuse, addiction, and diversion); insufficient evidence to draw strong conclusions about optimal approaches to risk stratification, monitoring, or initiation and titration of opioid therapy; and lack of evidence on the utility of informed consent and opioid management plans, the utility of opioid rotation, the benefits and harms specific to methadone or higher doses of opioids, and treatment of patients with chronic noncancer pain at higher risk for drug abuse or misuse.

Perspective: Currently, clinical decisions regarding the use of opioids for chronic noncancer pain need to be made based on weak evidence. Research funding priorities need to be set to address these critical research needs if the care of patients with chronic noncancer pain is to improve.

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Key words: Analgesics, opioid, pain, evidence-based medicine, risk assessment, drug monitoring, treatment outcomes, harms, research gaps, systematic review.

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Chronic noncancer pain (CNCP) is highly prevalent and can have significant negative effects on patients' functional capacity and quality of life.^{125,136} Prescriptions for opioids have risen steadily in the United States,^{21,100} in part due to their increased use in patients with CNCP. However, the prescription of opioids for CNCP remains controversial. Although opioids can decrease pain and improve function in some patients with CNCP,^{53,76} opioids are not always effective and are associated with important potential harms, including those related to drug misuse, abuse, and diversion.²³ In addition, uncertainty exists about long-term benefits and harms of opioids for CNCP.⁹⁹

Ideally, clinical decisions about the use of opioids for CNCP should be informed by high quality evidence. In reality, this principle is difficult to follow. Although a number of randomized trials are now available, they focus primarily on the evaluation of short-term benefits of opioids versus placebo in highly selected populations.^{53,76} In addition, evidence on a number of other areas relevant to opioid prescribing, such as risk assessment before initiation of a trial of opioids, methods for initiating and titrating opioids, monitoring of patients on chronic opioid therapy, use of high-dose opioids, and treatment of high-risk patients, is sparse. In fact, although several recently published guidelines recommend judicious use of opioids in appropriately selected patients with CNCP who have not responded to other treatments and analgesic medications, most were developed using a consensus process, in part due to a lack of strong evidence to guide most recommendations.^{16,57,74,75,128,132}

In 2006, the American Pain Society (APS) and the American Academy of Pain Medicine (AAPM) partnered to develop an evidence-based guideline on the use of opioids for CNCP. As part of this process, the APS/AAPM commissioned a systematic evidence review that addressed 37 Key Questions that a multidisciplinary expert panel believed to be critical to answer in order to develop evidence-based recommendations (Table 1).²⁸ The purpose of this article is to identify and summarize critical weaknesses (“research gaps”) in the literature on chronic opioid therapy for CNCP. We defined a research gap as an area in which the evidence base inadequately addressed a Key Question.

Materials and Methods

Data Sources and Searches

We conducted searches (through July 2008) that combined terms for opioids and chronic pain on Ovid MEDLINE, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials (Appendix 1 provides the detailed search strategies). Electronic searches were supplemented by reference lists and additional citations suggested by experts.

Evidence Selection

We included studies that met all of the following criteria:

- Evaluated adults (≥ 18 years old) with CNCP (defined as pain lasting 1 month longer than healing of lesion or pain that persisted for longer than 3 months)
- Was relevant to a Key Question
- Evaluated a risk assessment or monitoring instrument for use of opioids (including tramadol), a relevant diagnostic test, or benefits or harms of at least 1 opioid
- Either reported diagnostic accuracy of a risk assessment, monitoring instrument, or diagnostic test; or was a randomized trial, controlled observational study, or a systematic review.

We excluded studies of patients with cancer pain or end-of-life conditions as clinical and ethical considerations may be different compared with patients with

Research Gaps on Use of Opioids for Chronic Noncancer Pain CNCP. We also excluded non-English language studies, uncontrolled observational studies (eg, case series, case reports, pre-post studies), retrospective studies of risk prediction instruments, studies only published as conference abstracts, and unpublished studies.

Data Extraction and Quality Assessment

Two reviewers (R.C. and L.H.H.) independently rated the quality of each study. Discrepancies were resolved by discussion and a consensus process.

The quality of randomized trials, studies on diagnostic accuracy of risk assessment instruments, and systematic reviews was assessed using the criteria shown in Appendices 2, 3, and 4.^{52,62,71,80,103,134} For randomized trials and studies of risk prediction or diagnostic accuracy, studies were categorized as “higher-quality” if they met at least half of the predefined criteria.^{14,15,134} For systematic reviews, studies were categorized as “higher-quality” if they received a score of 5 or higher (maximum score 7).^{52,70,103}

Data Synthesis

The overall strength of each body of evidence that addressed a particular Key Question (or part of a Key Question) was assessed using methods adapted from the U.S. Preventive Services Task Force.⁶² To assign an overall strength of evidence (good, fair, or poor), the number, quality, and size of the studies; consistency of results between studies; and directness of the evidence were considered. Minimum criteria for fair and good quality ratings are shown in Appendix 5. Consistent results from a number of higher-quality studies across a broad range of populations support a high degree of certainty that the results of the studies are true (the entire body of evidence would be considered “good-quality”). For a “fair-quality” body of evidence, results could be due to true effects or to biases present across some or all of the studies. For a “poor-quality” body of evidence, any conclusion is uncertain due to serious methodological shortcomings, sparse data, or inconsistent results.

This report focuses on research areas identified by the Key Questions that are addressed by only poor quality evidence (“research gaps”). It does not focus on areas addressed by fair or good evidence (eg, short-term efficacy of opioids).^{53,76}

Results

Results of the Literature Search

The literature search yielded a total of 10,703 potentially relevant citations. Of these, we retrieved 186. After reviewing full-text articles, we judged 91 studies (including 15 systematic reviews and 38 randomized trials not included in previously published systematic reviews) to be relevant to one or more key questions and to meet inclusion criteria (Table 2). 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; noncontrolled observational study design; and lack of original data (eg, review article or editorial).

Table 1. Key Questions Used to Guide the Evidence Review*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 non-cancer 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 (eg, age, gender, race), specific underlying pain conditions, or comorbidities (eg, 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

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/d 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 with lower doses?

USE OF NONOPIOID THERAPIES

21. How effective are patient education methods or clinician advice for improving outcomes associated with chronic opioid therapy?
22. How effective is coprescription 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 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 OPIOID 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 screen 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?

Table 1. Continued

30. Is reevaluation 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?

Risk-Benefit Assessment

Evidence on risk stratification instruments to predict occurrence of aberrant drug-related behaviors is primarily limited to 4 prospective studies.^{3,17,19,141} The Opioid Risk Tool (ORT) and the Screener and Opioid Assessment of Patients with Pain (SOAPP) Version 1 and Revised SOAPP (SOAPP-R) instruments may be useful for predicting risk of future aberrant drug-related behaviors, but they require further study. Evidence is sparse for each instrument and characterized by presence of methodological shortcomings, such as high loss to follow-up, assessment of outcomes not blinded to results of the index test, and lack of external validation.²⁷ In addition, some instruments are associated with only modest likelihood ratios,^{17,19} and interpretation of available studies is a challenge because the definitions and methods used to identify aberrant drug-related behaviors were not standardized and did not differentiate between relatively less and more serious behaviors.

In addition to assessing risk of aberrant drug-related behaviors, a comprehensive assessment prior to initiating a trial of opioid therapy should also include assessments of potential benefits (eg, analgesia, return of function) and opioid-related adverse effects (eg, opioid-induced bowel dysfunction, nausea/vomiting, cognitive effects, and pruritus). There is insufficient evidence from small observational studies,^{7,39,69} secondary analyses of clinical trials,^{43,77} or indirect comparisons of placebo-controlled trials^{53,76,94} to reliably identify factors that predict benefits or adverse effects. There is also insufficient evidence to identify predictors of “opioid responsiveness,” or the balance of benefits achievable with tolerable adverse effects.^{81,91} No studies evaluated clinical outcomes associated with the use of different patient selection or risk stratification approaches.

Informed Consent and Opioid Management Plans

No studies were found that evaluated whether an explicit or detailed informed consent process before initiating chronic opioid therapy for CNCP is associated with improved clinical outcomes, adherence to the treat-

ment plan, or greater patient satisfaction, or how the consent process affects patients’ choices regarding use of opioids. No studies evaluated the effects of patient education methods, including different methods for providing or documenting informed consent, before initiating a trial of opioids.

Controlled data on the effects of opioid management plans on patient outcomes are limited to a single small (n = 20), retrospective, observational study that found no association between signing an opioid contract and a “successful outcome” (not defined) in patients with a history of substance abuse.⁴² No studies were found that evaluated how differences in the content of opioid management plans or use of written versus oral management plans affected clinical outcomes, either in average- or high-risk patients.

Initiation and Titration of Chronic Opioid Therapy

Two higher-quality trials found slower rates of dose titration of tramadol associated with fewer withdrawals due to adverse events compared to more rapid dose titration.^{106,115} However, tramadol is a relatively weak analgesic with both monoaminergic and opioidergic effects, and results of these trials may not be directly applicable to non-tramadol (particularly higher potency) opioids. There is insufficient evidence from two lower-quality trials to accurately judge benefits and harms of different methods for initiating and titrating non-tramadol opioids.^{72,118}

Benefits and Harms of Chronic Opioid Therapy

Over 70 randomized trials evaluated benefits or harms of opioids for CNCP, but nearly all were short-term (16 weeks or shorter) efficacy studies. Systematic reviews on efficacy of opioids for CNCP are summarized in Tables 3 and 4.^{25,30,40,41,44,53,67,76,83,94,99,119} In general, the trials excluded patients at higher risk for substance abuse or with significant medical or psychiatric comorbidities, and only 3 trials followed patients for more than 4 months.^{4,73,117} Long-term observational evidence is also sparse and characterized by substantial heterogeneity.⁹⁹

Table 2. Studies Meeting Inclusion Criteria for Each Key Question

TOPIC AREA	KEY QUESTION	SYSTEMATIC REVIEWS (NO. OF RANDOMIZED TRIALS)	RANDOMIZED TRIALS NOT INCLUDED IN SYSTEMATIC REVIEWS	PROSPECTIVE STUDIES	CASE-CONTROL STUDIES, COHORT STUDIES	CROSS-SECTIONAL STUDIES, OTHER (SECONDARY ANALYSES OF RANDOMIZED TRIALS, ETC)
				ON RISK PREDICTION OR STUDIES OF DIAGNOSTIC ACCURACY		
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	0	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)	10	NA	0	0
	5	12 (70 unique trials)	10	NA	2	3
	6	0	0	NA	0	0
	7	1 (9 trials)	14	NA	3	0
Prevention and treatment of opioid- related adverse effects	8	3 (53 unique trials)	0	NA	0	0
	9	0	3	NA	0	0
Driving and work safety	10	2 (nonrandomized)	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	1	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
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 nonopioid therapies	21	0	0	NA	0	0
	22	0	8	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 (nonrandomized trials)	0
Pregnancy	36	0	0	NA	0	0
Opioid prescribing policies	37	0	0	NA	0	0

Abbreviation: NA, not applicable.

Evidence on opioids specifically for low back pain, fibromyalgia, and daily headache is very limited or did not show a clear benefit.^{40,53,76,83,120}

Evidence on harms associated with chronic opioid therapy is of poorer quality than evidence on benefits, as most trials were designed to primarily assess efficacy. A great deal of variability exists between trials in estimates of common adverse effects (eg, nausea, constipation, or somnolence), due in part to differences in methods

for defining, assessing, or reporting adverse effects; differences in populations evaluated; and variable use of run-in periods.^{53,76,94} Few trials were designed with sufficient statistical power to identify serious but rare adverse effects or with sufficient duration to evaluate long-term harms, even though many patients in clinical practice are prescribed chronic opioid therapy indefinitely. Evidence on risk of aberrant drug-related behaviors is also limited.^{66,83} Trials excluded higher-risk

patients and did not perform active surveillance for signs of abuse or addiction. In addition, all of the studies used poorly standardized definitions or inadequate methods to identify aberrant drug-related behaviors.⁹⁹

Several cross-sectional studies of patients with CNCP reported a dose-related association between chronic sustained-release oral opioid use and hypogonadism in men and decreased levels of dehydroepiandrosterone sulfate (DHEAS) in men and women.³⁵⁻³⁷ Limitations of these studies include no adjustment for potential confounders and inability to establish causality because of their cross-sectional design. No evidence exists on endocrinologic effects of short-acting or intermittent opioids, and no randomized trials or controlled observational studies evaluated clinical outcomes associated with different approaches to monitoring or treating hypogonadism or DHEAS deficiency.

Observational studies showed an increased risk of fractures in older patients prescribed opioids but did not control well for potential confounders.¹²⁶ Several observational studies compared risks of adverse events between different opioids based on analyses of administrative databases, but are difficult to interpret because large baseline differences between groups prescribed different opioids were present, and the studies were limited in their ability to adjust or control for potential confounders.^{1,63,124}

Selection of Opioids and Dosing Methods

Evidence that compared the benefits and harms of around-the-clock versus as needed dosing of opioids for CNCP is limited to one lower-quality trial that showed no clear differences.⁶⁰ A number of head-to-head trials have compared benefits or harms of different sustained-release opioids or compared sustained- versus immediate-release opioids, but the studies had methodological shortcomings, such as use of an open-label design, lack of intention-to-treat analysis, or high loss to follow-up.²⁶ The studies also excluded patients at higher risk for addiction or abuse, only evaluated around-the-clock dosing strategies, and were not designed to evaluate rates of aberrant drug-related behaviors.^{4,26,61,84,97,98,113,114} Trials of patients with cancer pain suggest no advantages of intramuscular over oral administration of opioids and similar efficacy between oral and rectal routes of administration,^{8,10,11,38,90} but no randomized trials or comparative observational studies were found that directly compared regular intramuscular, subcutaneous, intranasal, buccal, or rectal versus oral or transdermal administration of opioids in patients with CNCP.

Methadone

Only one randomized trial evaluated methadone versus placebo for CNCP.⁹⁵ Its applicability to clinical practice is limited, as it randomized each patient to methadone or placebo every other day, with no treatment on alternate days. Evidence of serious harms (such as arrhythmias and deaths) associated with methadone for CNCP is limited to case series^{34,79} case-control studies with small

Research Gaps on Use of Opioids for Chronic Noncancer Pain number of patients with chronic pain,²⁹ or descriptive epidemiologic studies.^{22,24,101} These studies are difficult to interpret because they often did not distinguish between patients prescribed methadone for CNCP 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 rates of methadone usage.

Monitoring

Evidence on methods for monitoring patients prescribed chronic opioid therapy is limited to studies of diagnostic accuracy of various instruments to identify aberrant drug-related behaviors in patients prescribed opioids.^{2,6,18,31,68,82,92,137,144} Although one higher-quality derivation study found that the Current Opioid Misuse Measure identified aberrant drug-related behaviors with modest accuracy,¹⁸ studies of other instruments either found low accuracy^{92,137} or are of limited value because they did not evaluate standard measures of diagnostic accuracy^{2,31,68} or because they had serious methodological shortcomings, such as use of a retrospective design,^{6,82} assessment of outcomes not blinded to results of the index test,^{6,82,144} poorly standardized definitions for aberrant drug-related behaviors, and use of an inadequate reference standard.¹⁴⁴ No reliable evidence was found on the diagnostic accuracy of urine toxicology testing, pill counts, or prescription drug monitoring programs, or on clinical outcomes associated with implementation of different monitoring approaches.

High-Risk Patients

Nearly all randomized trials of opioids for CNCP excluded patients at higher risk for abuse or addiction.^{53,76} No controlled study evaluated different methods for selecting high-risk patients for a trial of opioid therapy or different strategies for initiating and titrating opioids and monitoring these patients.¹⁴³

Dose Escalations and High-Dose Opioid Therapy

Evidence on benefits and harms of high-dose opioids is very sparse. In randomized trials of opioids,^{53,76} the highest daily dose permitted was 240 mg/d of morphine,¹¹¹ and the highest average dose was 120 mg/d.⁶⁹ Evidence from observational studies on benefits and harms of high-dose opioid therapy is also sparse. No trial or controlled observational study evaluated outcomes associated with dose escalation above 200 mg/d of morphine (or equivalent) versus maintaining the current dose, switching to an alternative opioid, or discontinuing therapy in patients with inadequate symptom relief on lower doses. Evidence that high-dose opioids are associated with unique toxicities (such as arrhythmia, endocrinologic abnormalities, or hyperalgesia) is limited to small cross-sectional studies or case series that were not designed to evaluate causality or did not control for potential confounders.^{5,34-37,79}

Opioid Rotation

Evidence on effects of opioid rotation (switching from one opioid to a different opioid) in patients with CNCP is limited to 2 small prospective before-after studies^{50,51} and 3 retrospective studies^{64,110,130} with inconsistent results. No studies compared different methods of opioid rotation.

Discontinuation of Opioid Therapy

No randomized trials or controlled observational studies evaluated patient features or characteristics associated with improved outcomes with discontinuation of long-term opioid therapy versus continued treatment. There is insufficient evidence from 1 small (n = 10), higher-quality trial³³ to evaluate benefits and harms of continued opioid therapy versus abrupt cessation, and insufficient evidence from 2 lower-quality nonrandomized trials^{112,127} to evaluate benefits and harms of other methods for discontinuing opioids.

Prevention and Treatment of Opioid-Related Adverse Effects

Three published randomized trials evaluated the oral opioid antagonists alvimopan^{104,140} or low-dose naltrexone¹³⁹ for opioid-induced bowel dysfunction in patients with CNCP. The findings from the naltrexone trial are difficult to interpret because of high loss to follow-up and differential dosing frequencies, and alvimopan has not been approved by the U.S. Food and Drug Administration for use in patients with chronic pain, in part due to an increased rate of myocardial infarctions observed in an unpublished trial.⁵⁸ Other trials of opioid antagonists did not meet inclusion criteria because they enrolled healthy volunteers, persons undergoing surgery, or terminally ill patients.^{12,88} For example, trials of subcutaneous methylnaltrexone showed improvement in opioid-induced bowel dysfunction compared with placebo without opioid withdrawal and mild adverse effects, but only enrolled patients at end-of-life due to cancer or other advanced disease.^{109,129} Essentially all other evidence on prevention and treatment of opioid-related adverse effects in patients with CNCP is anecdotal.⁸⁷

Use of Nonopioid Therapies

No randomized trials directly evaluated the efficacy of behavioral therapy, multidisciplinary rehabilitation, or functional restoration versus or in addition to chronic opioid therapy in patients with CNCP. Two randomized trials of multidisciplinary rehabilitation and functional restoration evaluated opioid use as a secondary outcome and reported inconclusive results.^{32,105} Other evidence on the use of nonopioid therapies is almost entirely limited to trials of patients with chronic pain in general (not necessarily patients prescribed opioids).^{48,59,65,78,85,96,102,121,135} No study evaluated methods for identifying patients with CNCP more likely to benefit from nonopioid versus opioid therapy.

Driving and Work Safety

Evidence on driving and work safety is limited to epidemiologic studies and studies that evaluated the performance of patients on chronic opioid therapy on standardized driving tests.^{20,45,46,54,55,89,116} Limitations of the evidence include a reliance on cross-study comparisons to interpret epidemiologic studies (eg, comparing rates of opioid use in persons involved in motor vehicle accidents compared to estimates of opioid use in the general population), use of simulated and other controlled driving tests that may not completely reflect real-world driving conditions, and probable selection bias, as patients experiencing somnolence, impaired cognition, or other central nervous system opioid-related adverse effects are probably less likely to drive or to participate in studies that evaluate driving ability. No study evaluated the effects of opioid therapy on work safety.

Breakthrough Pain

Evidence on the use of short-acting opioids for treatment of breakthrough pain in patients on chronic opioid therapy for CNCP is restricted to two trials that evaluated transmucosal fentanyl for breakthrough pain.^{107,123} The usefulness of these trials is limited by their short duration of follow-up and by comparisons to placebo rather than to other opioids or nonopioid interventions for managing breakthrough pain.^{107,123}

Opioid Use During Pregnancy

Almost all of the literature on pregnancy and opioids has focused on women in methadone maintenance treatment, or women who used opioids for analgesia during labor, rather than pregnant women receiving chronic opioid therapy for CNCP. No randomized trials or controlled observational studies evaluated the effects of different strategies for managing CNCP with opioids (including tapering or discontinuation of opioids) during pregnancy.

Opioid Prescribing Policies

Although several studies found that the implementation of prescription monitoring programs for Schedule II opioids was associated with a decrease in prescription rates for Schedule II opioids,^{122,138} it is not possible to determine from these studies whether the changes were due to decreased inappropriate or unnecessary Schedule II opioid use, or if these changes resulted in subsequent under treatment of pain or had negative effects on other clinical outcomes. No study evaluated patient outcomes associated with implementation of a prescription monitoring program, formulary restrictions, or other policies related to opioid prescribing. Claims of positive effects of prescription monitoring programs on reducing diversions of efficacy from policy makers and law enforcement officials.¹³³ No studies evaluated how clinicians' knowledge of policy affects healthcare practice, patient care, or patient outcomes.

Discussion

Prescribing opioids for CNCP is far from straightforward. In addition to assessing patients and determining when a trial of opioids may be appropriate, clinicians must make choices regarding how to initiate, adjust, monitor, and in some cases discontinue chronic opioid therapy. Conventionally, it has been considered that clinical decisions such as these should be informed by well-conducted randomized controlled trials, controlled observational studies, or studies evaluating diagnostic test accuracy. However, for virtually every research question that an interdisciplinary expert panel assembled by the APS/AAPM thought was important to be asked to generate recommendations on use of chronic opioid therapy in patients CNCP, the findings from this systematic review identified important research gaps.

Available randomized trials of opioids are best described as efficacy⁵⁶ studies conducted in ideal settings and with selected populations, usually with short-term follow-up.^{53,76} Effectiveness trials and well-conducted prospective cohort studies (eg, registry studies¹⁰⁸) that assess long-term outcomes in less selected populations are needed to evaluate important benefits and harms (including those related to opioid misuse or abuse) relevant to clinical practice and to better understand why some patients continue chronic opioid therapy and others do not. More research is also needed to clarify optimal opioid dosing strategies. For example, although proposed advantages of using a long-acting opioid with around-the-clock dosing over as-needed and/or short-acting opioids include more consistent control of pain, improved adherence, and lower risk of addiction or abuse, no adequately conducted studies have demonstrated these possible benefits.^{16,57,74,75,128,132} Research is needed on the optimal approaches to initiate and titrate opioids and to treat breakthrough pain, on the utility of opioid rotation, and to determine if and how benefits or harms associated with methadone or other specific opioids differ.

Evidence on methods for performing risk assessment before starting opioids and for monitoring patients once on chronic opioid therapy is limited to a handful of diagnostic accuracy and prognosis studies that focused on prediction^{3,17,19,141} or identification^{2,6,18,31,68,82,92,137,144} of variably defined aberrant drug-related behaviors. All of these studies had at least some methodological shortcomings, including use of nonstandardized definitions for aberrant drug-related behaviors with uncertain clinical significance. No reliable evidence exists on the diagnostic accuracy of urine drug testing or on how use of screening instruments, urine drug testing, prescription monitoring programs, pill counts, or other risk assessment or monitoring approaches affects clinical decision-making or patient outcomes. Studies are needed to validate the diagnostic accuracy of risk assessment and monitoring instruments in a variety of settings using standardized definitions for clinically relevant aberrant-drug related behaviors and to determine whether using such instruments improves clinical outcomes. To help clinicians perform more balanced and comprehensive benefit-to-harm evaluations, future studies should develop and

Research Gaps on Use of Opioids for Chronic Noncancer Pain validate instruments that assess potential benefits and opioid-related adverse effects in conjunction with aberrant drug-related behaviors.¹³

Very little evidence exists on benefits and harms of higher doses of opioids, despite controversy regarding the appropriate role of higher dose therapy in persons who do not respond to lower doses.^{9,49} Studies are needed to quantify the risks associated with higher doses of opioids, to evaluate whether higher doses are associated with different or unique harms (such as endocrinologic dysfunction³⁵⁻³⁷ or hyperalgesia⁵) compared with lower doses, and to determine if there are patient characteristics that predict lack of response to higher doses of opioids. If a causal association between the use of higher doses of opioids and specific harms is found, additional research is needed to evaluate potential predictors of these harms, to determine their clinical impact, and to identify methods for minimizing their incidence and effects.

A number of other areas related to use of opioids for CNCP are also associated with important research gaps. For example, there is a lack of evidence on benefits and harms of opioid management plans and different methods for providing informed consent.⁴⁷ There is also insufficient evidence to reliably inform clinical decisions regarding driving and work-related risks in patients prescribed chronic opioid therapy, and essentially no evidence regarding benefits and harms of chronic opioid therapy for CNCP during pregnancy, or on how policies related to opioid prescribing affect clinical outcomes. Controlled observational studies that are designed to minimize bias, address potential confounders, and evaluate patient-centered outcomes could help fill a number of these research gaps, particularly when randomized controlled trials are not ethical or feasible (eg, chronic opioid therapy during pregnancy, driving safety, opioid-prescribing policies).

A potential limitation of our study is that non-English language studies, unpublished studies, uncontrolled observational studies of opioid interventions, and nonprospective studies of risk prediction were excluded. However, language restrictions do not necessarily lead to biased findings,⁹³ and we are not aware of non-English language or unpublished studies likely to change any of our main conclusions. In addition, the quality of unpublished studies is often difficult to assess due to incomplete reporting, and results can change between initial presentation and final journal publication.¹³¹ Observational studies were excluded if they lacked adequate safeguards against bias, did not include control subjects, or did not adequately demonstrate causality.

The presence of large and persistent evidence gaps on the use of chronic opioid therapy for CNCP represents a serious deficit in knowledge given the high prevalence of CNCP, increasing use of chronic opioid therapy for this indication, the need for complex and ongoing decision-making by clinicians to balance potential benefits against potentially serious harms, and the formulation of policies and regulations in the absence of evidence. Our study provides guidance for setting future research priorities. Until evidence gaps are adequately addressed, many clinical and policy decisions related to the use of

chronic opioid therapy for CNCP will need to be made without strong supportive evidence. At a minimum, this deficit will result in continued uncertainty regarding best practices, and at worst these deficiencies could contribute to unnecessary harms.

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Supplementary Data

Supplementary data accompanying this article is available online at www.jpain.org, www.sciencedirect.com, and at [doi:10.1016/j.jpain.2008.10.007](https://doi.org/10.1016/j.jpain.2008.10.007). The supplementary data include Appendices 1–5 and Tables 3 and 4.

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Appendix 1. Search Strategies

Cochrane Database of Systematic Reviews, Through 3rd Quarter 2008

1. opioid\$.mp.
2. narcotic\$.mp.
3. (alfentanil or α -prodine or β -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 piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp.
4. (((intract\$ or chronic\$ or severe\$ or unbearable\$) adj3 pain\$) or agony or agoniz\$).mp.
5. (or/1-3) and 4.

Cochrane Central Register of Controlled Trials and Ovid MEDLINE[®], 1950 to July Week 3 2008 (Includes Systematic Reviews and Primary Studies)

General Search

1. exp Narcotics/
2. exp Analgesics, Opioid/
3. narcotic\$.mp.
4. opioid\$.mp.
5. (alfentanil or α -prodine or β -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 piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp.
6. or/1-5.
7. (((intract\$ or chronic\$ or severe\$ or unbearable\$) adj3 pain\$) or agony or agoniz\$).mp.
8. 6 and 7.
9. limit 8 to humans.
10. limit 9 to English language.
11. limit 9 to abstracts.
12. 10 or 11.

Abuse

1. exp Narcotics/
2. exp Analgesics, Opioid/
3. narcotic\$.mp.

Research Gaps on Use of Opioids for Chronic Noncancer Pain

4. opioid\$.mp.
5. (alfentanil or α -prodine or β -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 piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp.
6. exp Patient Compliance/
7. exp Health Services Misuse/
8. exp "drug and narcotic control"/
9. (abuse\$ or abusing or misus\$ or diversion\$ or divert\$).mp.
10. exp Substance-Related Disorders/
11. or/1-5.
12. or/6-10.
13. 11 and 12.
14. (((intract\$ or chronic\$ or severe\$ or unbearable\$) adj3 pain\$) or agony or agoniz\$).mp.
15. 13 and 14.

Driving

1. exp Narcotics/
2. exp Analgesics, Opioid/
3. narcotic\$.mp.
4. opioid\$.mp.
5. (alfentanil or α -prodine or β -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 piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tramadol).mp.
6. or/1-5.
7. exp Automobile Driving/
8. exp Motor Vehicles/
9. exp Accidents, Traffic/
10. exp Accident Prevention/
11. (car or cars or truck\$ or automobil\$ or motor vehicle\$).mp.
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.
13. ((traffic\$ or drive or driver\$ or driving) adj7 (accident\$ or injur\$ or safe or safety or safer or safely)).mp.
14. or/7-13.
15. 6 and 14.

Drug Monitoring

1. exp Narcotics/
2. exp Analgesics, Opioid/
3. narcotic\$.mp.
4. opioid\$.mp.
5. (alfentanil or α -prodine or β -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.
6. or/1-5.
7. ((medication\$ or opioid\$ or pain\$) adj7 (contract\$ or agree\$)).mp.
8. exp Drug Monitoring/
9. (adher\$ adj5 monitor\$).mp.
10. ((pill or tablet\$ or dose or doses or prescript\$) adj7 (limit\$ or count\$ or ration\$ or monitor\$)).mp.
11. or/7-10.
12. 6 and 11.

Prognosis

1. exp Narcotics/
2. exp Analgesics, Opioid/
3. narcotic\$.mp.
4. opioid\$.mp.
5. (alfentanil or α -prodine or β -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.
6. or/1-5.
7. exp "Sensitivity and Specificity"/
8. Prognosis/
9. exp risk/
10. "outcome and process assessment (health care)"/ or "outcome assessment (health care)"/ or "process assessment (health care)"/

11. diagnostic accuracy.mp.
12. receiver operating characteristic.mp. or ROC Curve/
13. 6 and (or/7-12).
14. (((intract\$ or chronic\$ or severe\$ or unbearable\$) adj3 pain\$) or agony or agoniz\$).mp.
15. 13 and 14.

Pseudoaddiction

1. exp Narcotics/
2. exp Analgesics, Opioid/
3. narcotic\$.mp.
4. opioid\$.mp.
5. (alfentanil or α -prodine or β -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.
6. or/1-5.
7. pseudoaddict\$.mp.
8. ((fake\$ or faking or false\$ or mislead\$ or deceive\$) adj7 (addict\$ or depend\$)).mp.
9. 7 or 8.
10. 6 and 9.

Urine Testing

1. exp Narcotics/
2. exp Analgesics, Opioid/
3. narcotic\$.mp.
4. opioid\$.mp.
5. (alfentanil or α -prodine or β -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.
6. or/1-5.
7. exp Substance Abuse Detection/
8. (urine adj7 (screen\$ or test\$ or detect\$)).mp.
9. 6 and (7 or 8).

Appendix 2. Criteria for Grading Quality of Randomized Controlled Trials

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/Do Not 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/Do Not Know
C. Were the groups similar at baseline regarding the most important prognostic factors? "Yes", if similar: <ul style="list-style-type: none"> • Age and 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/Do Not 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":	Yes/No/Do Not Know
E. Was the care provider blinded to the intervention?	Use the author's statement on blinding, unless there is a differing statement/reason not to (no need for explicit information on blinding).	Yes/No/Do Not Know
F. Was the outcome assessor blinded to the intervention?	Cointerventions should either be avoided in the trial design or similar between the index and control groups.	Yes/No/Do Not Know
G. Were cointerventions avoided or similar?	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).	Yes/No/Do Not Know
H. Was the compliance acceptable in all groups?	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/Do Not Know
I. Was the dropout rate described and acceptable? ≤15% dropout rate is acceptable.	Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.	Yes/No/Do Not Know
J. Was the timing of the outcome assessment in all groups similar?	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/Do Not Know
K. Did the analysis include an intention-to-treat analysis? "Yes" if less than 5% of randomized patients excluded.		

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 the meta-analysis.

* Adapted from methods developed by the Cochrane Back Review Group.¹³⁴

Appendix 3. Criteria for Grading Quality of Studies Reporting Diagnostic Accuracy of Risk Stratification and Monitoring Instruments

1. Does the study evaluate diagnostic test performance in a population other than the one used to derive the instrument?
 2. Does the study evaluate a consecutive clinical series of patients or a random subset?
 3. Does the study adequately describe symptom severity, underlying condition, and duration and doses of opioids (if prescribed)?
 4. Does the study adequately describe the instrument evaluated?
 5. Does the study include appropriate criteria in the instrument (must include prior history of addiction or substance abuse and at least one other psychosocial item)?
 6. Does the study adequately describe the method used to identify aberrant drug-related behaviors?
 7. Does the study use appropriate criterion to identify aberrant drug-related behaviors (uses either a validated questionnaire or urine drug screen plus other corroborating data [such as a questionnaire, prescription drug monitoring program, pill counts, family interview, etc])
 8. Does the study evaluate outcomes or the reference standard in all patients enrolled (up to 10% loss considered acceptable)?
 9. Does the study evaluate outcomes blinded results of the screening instrument?
-

References: Harris et al,⁶² Lijmer et al,⁸⁰ Whiting et al¹⁴² McGinn et al.⁸⁶

Appendix 4. Criteria for Grading Quality of Systematic Reviews

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.

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.)

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.

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

- 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.
- For Question 8, if no 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).

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

* Operationalization of Oxman criteria,¹⁰³ adapted from Furlan et al.⁵²

Appendix 5. Methods for Grading the Overall Strength of a Body of Evidence

<i>GRADE</i>	<i>DEFINITION</i>
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (at least 2 consistent, higher-quality trials).
Fair	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 1 higher-quality trial of sufficient sample size; 2 or more higher-quality trials with some inconsistency; at least 2 consistent, lower-quality trials, or multiple consistent observational studies with no significant methodological flaws).
Poor	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality trials, important flaws in trial design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes

Adapted from methods developed by the U.S. Preventive Services Task Force.⁶²

Table 3. Included Systematic Reviews on Efficacy of Opioids for Chronic Noncancer Pain

AUTHOR, YEAR, TITLE	PURPOSE OF STUDY	DATABASES SEARCHED, DATE OF LAST SEARCH	NO. 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	NO. OF PATIENTS (TREATMENT AND CONTROL)	INTERVENTIONS	RESULTS	ADVERSE EVENTS	OVERALL QUALITY RATING*
Cepeda, 2006 ²⁵ Tramadol for osteoarthritis	1. To assess benefits and harms of tramadol for OA	Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and LILACS databases up to August 2005. No language restrictions	11	RCTs of tramadol (published and unpublished) Limitations: Average length of follow-up 35 days. High loss to follow-up. All but 1 trial funded by pharmaceutical industry	Assessed 6 criteria: randomization; allocation; concealment; masking; loss to follow-up; similarity between baseline characteristics of treatment groups; and use of intention-to-treat analysis	Meta-analysis using a fixed-effects model	1,019 received tramadol or tramadol/paracetamol; 920 received placebo or active-control	Tramadol or tramadol + paracetamol	Tramadol versus placebo Pain: -8.5 (0 to 100 scale, 95% confidence interval [CI]), -12.0 - -5.0 Likelihood of at least moderate improvement: RR 1.37 (95% CI, 1.2 - 1.5); no. needed to treat to benefit (NNTB) = 6 (95% CI, 4-9)	Tramadol versus placebo Minor adverse events: RR 2.27 Major adverse events: RR 2.6, no. needed to treat to harm (NNTH) = 8 (95% CI, 7-12)	7
Chou, 2003 ²⁶ Comparative efficacy and safety of long-acting oral opioids for chronic noncancer pain: a systematic review	To assess benefits and harms of long-acting opioids for chronic noncancer pain	Cochrane Library (2002, Issue 1), MEDLINE, and EMBASE (both through October 2002) Language: English	24 total: 16 RCTs 8 observational studies	Randomized trials (for comparative benefits and harms) and observational studies (for adverse events only) of nonparenteral long-acting opioids for chronic noncancer pain Limitations: No randomized trial was rated good quality and observational studies were of generally poorer quality than the trials. Included studies were of relatively short duration: 5 days to 16 weeks	Tool with predefined criteria used to assess internal and external validity	Qualitative, strength of evidence assessed based on criteria developed by the US Preventive Task Force and the National Health Service Center for reviews and Dissemination (UK)	RCTs: 1,427 Observational: 1,190	Long-acting and short-acting opioids for chronic noncancer pain. Opioids evaluated: transdermal fentanyl, long-acting oral oxycodone, morphine, codeine and dihydrocodeine	Insufficient evidence to prove that any long-acting opioid is associated with more benefits compared to any other long-acting opioid, or whether long-acting opioids as a class are associated with more benefits compared to short-acting opioids. Fair evidence that long-acting oxycodone and short-acting oxycodone are equally effective for pain control.	Insufficient evidence to determine that any long-acting opioid is associated with fewer harms compared to any other long-acting opioid, or that long-acting opioids as a class are associated with fewer harms compared to short-acting opioids. Rates of abuse and addiction not reported in the trials.	6

Table 3. Continued

AUTHOR, YEAR, TITLE	PURPOSE OF STUDY	DATABASES SEARCHED, DATE OF LAST SEARCH	NO. 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	NO. OF PATIENTS (TREATMENT AND CONTROL)	INTERVENTIONS	RESULTS	ADVERSE EVENTS	OVERALL QUALITY RATING*
Clark, 2004 ³⁰ and safety of transdermal fentanyl and sustained-release oral morphine in patients with cancer and chronic non-cancer pain	Efficacy To assess benefits and harms of transdermal fentanyl (TDF) versus sustained-release morphine (SRM) for cancer pain (CP) and chronic noncancer pain (CNCP)	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) of TDF with minimum treatment duration of 28 days. Limitations: Short (28-day) treatment period. Inclusion of uncontrolled studies	Studies not quality rated	Simple pooling (does not appear weighted) and means compared using 2-sided <i>t</i> tests. Risk of AEs compared using Fisher exact test	1220 total for pooled efficacy data	Transdermal fentanyl vs sustained-release oral morphine	SRM vs. TDF, CNCP subgroup Pain (change from baseline to day 28): -17.7 ± 26.2 (n = 121) vs -21.0 ±/-24.4 (n = 271), <i>P</i> = NS Pain "right now": -16.5 ± 28.9 vs -24.1 ± 28.7, <i>P</i> = 0.017	SRM (n = 488) vs TDF (n = 1285), CNCP subgroup Any AE: 87.3% vs. 71.2%, <i>P</i> < 0.001 Drug discontinued due to AE: 19.3% vs. 20.4%, <i>P</i> = NS Deaths: 0% vs. 0.2%, <i>P</i> = NS Constipation: 52% vs. 17%, <i>P</i> < 0.001 Nausea: 39% vs. 30%, <i>P</i> < 0.001 Somnolence (CNCP and CP groups combined): 25% vs. 13%, <i>P</i> < 0.001	2
Deshpande, 2007 ⁴⁰ for chronic low back pain (Cochrane Review)	To assess 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 using a fixed or random effects model	944 total	Oral opioid or tramadol	Tramadol (with or without acetaminophen) vs placebo Pain relief (SMD): 0.71 (95% CI 0.39-1.02) Function (SMD): 0.17 (95% CI 0.04-0.30)	Tramadol (with or without acetaminophen) vs placebo (risk differences) Headache: 9% (95% CI, 6% to 12%), 3 trials Nausea: 3% (95% CI, 0% to 6%), 3 trials Somnolence: 9% (95% CI, 5% to 13%), 2 trials Constipation: 8% (95% CI, 4% to 12%), 2 trials Dry mouth: 7% (95% CI 4% to 10%), 2 trials Dizziness: 8%	7

Table 3. Continued

AUTHOR, YEAR, TITLE	PURPOSE OF STUDY	DATABASES SEARCHED, DATE OF LAST SEARCH	NO. 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	NO. OF PATIENTS (TREATMENT AND CONTROL)	INTERVENTIONS	RESULTS	ADVERSE EVENTS	OVERALL QUALITY RATING*
Devulder, 2005 ⁴¹	Assess quality of life (QoL) and patient function on long-term opioids for chronic noncancer 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	Blinded or open-label trials with either a randomized, controlled, or an observational design Limitations: Few trials reported quality of life outcomes. Only 6 of 11 included trials were RCTs	Jadad	Qualitative, no formal method described	2,877	Transdermal fentanyl (TDF) or sustained-release oral morphine	3 of 4 RCTs and 4 of 5 observational studies reported an improvement in QoL on transdermal fentanyl or sustained-release oral morphine compared to baseline	(95% CI, 4% to 12%), 2trials adverse events ranged widely across studies for transdermal fentanyl and placebo	2
Eisenberg, 2005 ⁴⁴	To assess benefits and harms of opioids for neuropathic pain	MEDLINE (through November 2004), Cochrane Central Register of Controlled Trials (through 4th quarter, 2004). Language: not specified	22 total 8 intermediate 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 long-term benefits and harms. Drop-outs not reported. Five of eight Intermediate	Jadad Scale	Meta-analysis using a fixed effects model	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	403 patients Opioid vs placebo, overall mean pain intensity, intermediate-term (8 days to 8 weeks) results: opioid 14 points lower, 95% CI, 18-10, P < .001 (meta-analysis 263 opioid, 258 placebo-treated patients) No consistent reduction in disability with opioids.	Opioid versus placebo (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; No. of dropouts due to AEs in 4 studies: 13.5% (33/244) opioids	7

Table 3. Continued

AUTHOR, YEAR, TITLE	PURPOSE OF STUDY	DATABASES SEARCHED, DATE OF LAST SEARCH	NO. 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	NO. OF PATIENTS (TREATMENT AND CONTROL)	INTERVENTIONS	RESULTS	ADVERSE EVENTS	OVERALL QUALITY RATING*
Furlan, 2006 ⁵³	To assess benefits and harms of opioids for chronic noncancer pain	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	term trials used a crossover design Trials of any opioid administered by oral, transdermal or rectal routes ≥ 7 days with outcome data on pain, function or side effects Limitations: Trials limited in duration. Only 17 of 41 trials were adequately randomized. High drop-out rates in opioid (33%) and control (38%) groups	Jadad scale	Meta-analysis using a random effects model	6019	Any opioid administered by oral, transdermal or rectal routes >7 days	Opioids vs placebo 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) Tramadol vs placebo: Pain: SMD, -0.57, 95% CI, -0.70 to -0.44 (9 trials); function: SMD, -0.30, 95% CI, 0.45-0.16 (6 trials) Opioids vs other drugs: Pain relief: SMD, -9.95, 95% CI, 0.32-0.21 (8 trials); function: SMD, +0.16, 95% CI, +0.03 to +0.20 (3 trials)	vs 7.6% (12/156) placebo Opioids vs placebo (absolute risk differences) Constipation: 16%, 95% CI, 10% to 22%; Nausea: 15%, 95% CI, 11% to 19%; Dizziness/vertigo: 8%, 95% CI, 5% to 12%; Somnolence/drowsiness: 9%, 95% CI 5% to 13%; Vomiting: 5%, 95% CI, 2% to 7%; Dry skin/itching/pruritus: 4%, CI 1% to 6%. Opioids vs. other drugs Nausea: 14%, 95% CI 4% to 25%; Constipation: 9%, 95% CI 1% to 17%; Drowsiness: 6%, 95% CI 0% to 11%; Tramadol vs. placebo Diarrhea: -2%, 95% CI, -3% to 0%	7
Hollingshead, 2006 ⁵⁷	To assess benefits and harms of tramadol for neuropathic pain (Cochrane Review)	Cochrane Neuromuscular Disease Group Trials Register, MEDLINE, EMBASE and LILACS (all to June 2005)	6	Randomized and "quasi-randomized" controlled trials of tramadol versus placebo for neuropathic pain Limitations: Differences in methodology	Cochrane Collaboration system	Meta-analysis using a fixed effects model	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	No life-threatening AEs or AEs requiring hospitalization or prolonged hospital stays Withdrawal due to side effects: RR, 5.4 (95% CI, 1.6 to	5

Table 3. Continued

AUTHOR, YEAR, TITLE	PURPOSE OF STUDY	DATABASES SEARCHED, DATE OF LAST SEARCH	NO. 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	NO. OF PATIENTS (TREATMENT AND CONTROL)	INTERVENTIONS	RESULTS	ADVERSE EVENTS	OVERALL QUALITY RATING*
				among included studies. Pain relief rated on different scales. Short duration: 4-7 weeks					trial with 40% pain relief: combined relative benefit 1.8 (95% CI, 1.4-2.3). NNT for 50% pain relief = 3.8 (95% CI, 2.8-6.3) Tramadol vs clomipramine NS (1 poor quality trial)	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	
Kalso, 2004 ⁷⁶	To assess benefits and harms of World Health Organization step 3 opioids for chronic noncancer pain	MEDLINE, EMBASE, (through August 2003) Cochrane Library (on-line September 2003) and the Oxford Pain Relief Database (1950-1994). Language: no language restriction reported	15 total; 11 trials of oral opioids reported here (IV interventions not included here)	Randomized, double-blind trials of WHO step 3 opioids versus placebo for chronic noncancer pain that reported pain intensity outcomes. Limitations: Limited duration (4 days to 8 weeks). High drop-out rate; only 66% completed. In the 5 studies that tested concealment of blinding, majority of patients and investigators could distinguish opioid from active and inactive placebo	Jadad scale for quality with addition of 5-item validity scale (Smith et al, 2000)	Meta-analysis using a fixed effect model	1,145 total 1025 in oral trials, reported here	Oral opioid vs placebo: Morphine (5 trials), morphine or methadone (1 trial), oxycodone (4 trials).	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 ($P < .05$ to $P < .001$ in 7 trials); Sleep quality: improvement with opioids in all 7 studies reporting; Depression: NS in 6 studies; Function (various measures) No significant differences (5 studies).	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-	7

Table 3. Continued

AUTHOR, YEAR, TITLE	PURPOSE OF STUDY	DATABASES SEARCHED, DATE OF LAST SEARCH	NO. 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	NO. OF PATIENTS (TREATMENT AND CONTROL)	INTERVENTIONS	RESULTS	ADVERSE EVENTS	OVERALL QUALITY RATING*
										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	
Martell, 2007 ⁸³ Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction	To assess benefits and harms of opioids for chronic low back pain	MEDLINE (through February 2005), EMBASE (through February 2005), Cochrane Central Register of Controlled Clinical Trails (through 3rd quarter 2004), PsychInfo (through February 2005). Language: English only	9 in meta-analysis 26 total	Studies of 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 evaluated efficacy for longer than 16 weeks. Only 2 studies diagnosed substance disorder using validated instrument	Jadad (1996) and Downs (1998)	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 using a fixed or random effects model (based on an assessment of homogeneity of studies)	Not explicitly reported	Oral, topical or transdermal opioids	Opioid vs placebo or non-opioid control Pain: SMD -0.20, 95% CI -0.49 to +0.11; P = 0.14 (4 trials) Opioid vs opioid Pain, change from baseline (opioid arms pooled): SMD -0.93, 95% CI -1.89 to -0.03; P = 0.06 (5 trials)	Prevalence of lifetime substance abuse disorders: 36% to 56%; Estimates of prevalence of current substance abuse disorders: as high as 43%; Aberrant medication-taking behaviors: 5% to 24%	6
Moore, 2005 ⁹⁴ Prevalence of opioid adverse events in chronic	To assess harms of opioids for chronic noncancer pain	MEDLINE, EMBASE, Cochrane Library (all through July	34	Double-blind trials of oral opioids with placebo or active control	Jadad scale	Simple pooling (does not appear weighted)	5,546	Oral opioids used to treat chronic non-cancer pain	See Adverse Events column	Opioid vs placebo, average event rate (95% CI) range Dry mouth: 25%	2

Table 3. Continued

AUTHOR, YEAR, TITLE	PURPOSE OF STUDY	DATABASES SEARCHED, DATE OF LAST SEARCH	NO. 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	NO. OF PATIENTS (TREATMENT AND CONTROL)	INTERVENTIONS	RESULTS	ADVERSE EVENTS	OVERALL QUALITY RATING*
nonmalignant pain: systematic review of randomized trials of oral opioids		2004). Language: no language restriction reported		comparators used to treat CNC pain with ≥ 0 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						(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)	
Noble, 2008 ⁹⁹ Long-term opioid therapy for chronic noncancer pain: A systematic review and meta-analysis of efficacy and safety	To assess benefits and harms of long-term opioid therapy for chronic noncancer pain	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 of patients treated with opioids for CNCP for ≥ 6 months Limitations: Low quality trials, high dropout rates. Poor assessment and reporting of adverse events. Lack of control groups. Only	14-item instrument developed by ECRI (available from author)	Meta-analysis using a fixed effects model	total: 3,079 oral: 1,504; transdermal: 1,391 intrathecal not reported here	Oral or transdermal opioids for treating moderate to severe pain due to nociceptive or neuropathic pain or both	(with 2,042 patients) "specifically mentioned" opioid addiction. 1/2,042 was reported as having possibly experienced addiction. Presumed addiction rate = 0.042% Withdrawal due to insufficient pain relief: oral opioids (6-18 months): 13.1% (95%CI,	Withdrawal due to adverse events: Oral opioids: 30.4% (95% CI, 19.9% to 43.4%), follow-up time range, 6-18 months Transdermal: 17.6% (95% CI, 6.6% to 39.2%), at 12-48 months follow-up. Substantial heterogeneity in both oral ($i^2 = 94.9%$) and	7

Table 3. Continued

AUTHOR, YEAR, TITLE	PURPOSE OF STUDY	DATABASES SEARCHED, DATE OF LAST SEARCH	NO. 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	NO. OF PATIENTS (TREATMENT AND CONTROL)	INTERVENTIONS	RESULTS	ADVERSE EVENTS	OVERALL QUALITY RATING*
				7/17 studies specifically reported opioid addiction					11.7-15.5%), I ² = 91.04%; Transdermal (12-48 months): 5.8% (95%CI, 4.2% to 7.9%), I ² = 52.2% Pain: oral opioids (16-18 months): SMD, 1.99 (95% CI, 1.17-2.80), I ² = 86.6% transdermal: insufficient data	transdermal trials (I ² = 98.2%) Most commonly reported adverse events (data not provided): gastrointestinal (constipation, nausea, dyspepsia), headache, fatigue/lethargy/ somnolence, urinary (retention, hesitancy, "disturbance")	
Sandoval, 2005 ¹¹⁹ Oral methadone for chronic noncancer pain: a systematic literature review of reasons for administration, prescription patterns, effectiveness and side effects	To assess benefits and harms of oral methadone for 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	Studies of any design in which oral methadone was given for relief of chronic pain of noncancer origin and a pain outcome was reported. 13 case reports (31 patients), 7 case series (495 patients), 1 RCT (19 patients) Limitations: Only 1 trial (cross-over), possibility of publication bias. Study quality uneven	Quality of uncontrolled studies not measured. Jahad scale used for the one trial included	Qualitative, method unclear	545	Oral methadone	Pain outcomes: methadone (20 mg/d) 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/d. Maximum dose: 20-930 mg/d	20 uncontrolled studies (225 patients) reported adverse events. Nausea and/or vomiting: 23.6% sedation: 18.5% (41), itching and/or rash: 13% constipation: 11.7%	2

Abbreviations: RCT, randomized controlled trial; CI, confidence interval; SMD, standardized mean difference; RR, relative risk; TDF, transdermal fentanyl; SRM, sustained-release morphine; CP, cancer pain; CNCP, chronic noncancer pain.
* See Table 4 for complete quality rating criteria scores.

Table 4. Quality* Ratings of Systematic Reviews on Efficacy of Opioids for Chronic Noncancer Pain

<i>AUTHOR, YEAR, TITLE</i>	<i>SEARCH METHODS?</i>	<i>COMPREHENSIVE?</i>	<i>INCLUSION CRITERIA?</i>	<i>BIAS AVOIDED?</i>	<i>VALIDITY CRITERIA?</i>	<i>VALIDITY ASSESSED?</i>	<i>METHODS FOR COMBINING STUDIES?</i>	<i>APPROPRIATELY COMBINED?</i>	<i>CONCLUSIONS SUPPORTED?</i>	<i>OVERALL QUALITY</i>
Cepeda, 2006 ²⁵	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Chou, 2003 ²⁶	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	6
Clark, 2004 ³⁰	Partial	Partial	Yes	Cannot tell	No	No	Yes	No (pooled across RCTs and non-RCTs)	Cannot tell	2
Deshpande, 2007 ⁴⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Devulder, 2005 ⁴¹	Yes	Yes	Yes	Partial	Yes	Partial (assessed but not analyzed)	No	No	No	2
Eisenberg, 2005 ⁴⁴	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Furlan, 2006 ⁵³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Hollingshead, 2006 ⁶⁷	Yes	Yes	Yes	Cannot tell	Yes	Yes	Yes	Partial	Yes	5
Kalso, 2004 ⁷⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Martell, 2007 ⁸³	Partial	Yes	Yes	Cannot tell	Yes	Yes	Yes	Yes	Yes	6
Moore, 2005 ⁹⁴	Yes	Yes	Yes	Partial	Partial	NA (only 1 trial included)	No	Cannot tell	Cannot tell	2
Noble, 2008 ⁹⁹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Sandoval, 2005 ¹¹⁹	Yes	Yes	Yes	Partial	Partial (none for observational studies)	NA (only 1 trial included)	No (no rationale for combining observational studies)	Cannot tell (pooled observational studies)	Cannot tell	2

* See Appendix 4 for complete quality criteria.