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Systematic Review

A Systematic Review of Randomized Trials on the Effectiveness of Opioids for Cancer Pain

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Background: In all recommended guidelines put forth for the treatment of cancer pain, opioids continue to be an important part of a physician's armamentarium. Though opioids are used regularly for cancer pain, there is a paucity of literature proving efficacy for long-term use. Cancer is no longer considered a "terminal disease"; 50% to 65% of patients survive for at least 2 years, and there are about 12 million cancer survivors in the United States. There is a concern about side effects, tolerance, abuse and addiction with long-term opioid use and a need to evaluate the effectiveness of opioids for cancer pain.

Objective: The objective of this systematic review was to look at the effectiveness of opioids for cancer pain.

Study Design: A systematic review of randomized trials of opioids for cancer pain.

Methods: A comprehensive review of the current literature for randomized controlled trials (RCTs) of opioids for cancer pain was done. The literature search was done using PubMed, EMBASE, Cochrane library, clinical trials, national clearing house, Web of Science, previous narrative systematic reviews, and cross references. The studies were assessed using the modified Cochrane and Jadad criteria. Analysis of evidence was done utilizing the modified quality of evidence developed by United States Preventive Services Task Force (USPSTF).

Outcome Measures: Pain relief was the primary outcome measure. Secondary outcome measures are quality of life (QoL) and side effects including tolerance and addiction.

Results: The level of evidence for pain relief based on the USPSTF criteria was fair for transdermal fentanyl and poor for morphine, tramadol, oxycodone, methadone, and codeine.

Limitations: Randomized trials in a cancer setting are difficult to perform and justify. There is a paucity of long-term trials and this review included a follow-up period of only 4 weeks.

Conclusion: This systematic review of RCTs of opioids for cancer pain showed fair evidence for the efficacy of transdermal fentanyl and poor evidence for morphine, tramadol, oxycodone, methadone, and codeine.

Key words: Opioids, pain relief, cancer pain, morphine, hydromorphone, methadone, fentanyl, oxymorphone, hydrocodone, oxycodone, buprenorphine.

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Pain is a highly prevalent and distressing symptom, and a major health problem in cancer patients. The incidence of pain in those receiving active treatment is 24% to 60%, approaches 58% to 69% in patients with advanced cancer, and is 33% in patients after curative therapy (1). The basic approach to treat cancer pain, the 3 step analgesic ladder, was designed by the World Health Organization (WHO) in 1986. This 3-step treatment, according to need from nonopioid analgesics to weak opioids and then strong opioids, has guided the management of pain among cancer patients (2,3). Since then, the Agency for Healthcare Policy and Research (AHCPR) in 1994 (4), the American Pain Society (APS) in 2005 (5), and the National Comprehensive Care Network (NCCN) in 2000 and 2009 (6,7) have established/revised guidelines to help with cancer pain management. Overall there has been an increase in the availability of opioids with adoption of the national policies developed for cancer pain. Opioids continue to be a mainstay in the treatment of cancer pain in all of these treatment guidelines and morphine remains the "gold standard."

Cancer pain is a biopsychosocial experience with a significant cognitive and emotional component. In advanced cancer, the incidence of anxiety is 13% to 79% and depression is seen in 3% to 77% of the patients (8,9). Cancer patients with anxiety and depression express higher levels of pain (8). This would imply an inappropriate use of opioids for the "pain experience" and suffering (10) and there is a strong correlation of high level psychological distress with reporting of high levels of pain (11). There is also a growing concern about opioid abuse and addiction in cancer pain patients and other adverse consequences similar to what is seen in noncancer pain patients (12-28). The relevant literature indicates that the prevalence of addiction to opioids varies from 0% to 7.7% in cancer patients based upon the population studied and the criteria used (13). There remains a concern about long-term use of opioids in patients at risk for substance abuse and/or diversion.

The use of opioids for chronic noncancer pain continues to be debated due to concern for side effects, the lack of long term efficacy, and a growing concern for abuse and addiction to opioids. A systematic review of the literature looking for the efficacy of long-term opioid use for chronic pain found weak evidence for morphine and transdermal fentanyl (14). Many patients discontinue long-term opioid therapy (especially oral opioids) due to adverse events or insufficient pain relief; however, weak evidence suggests that patients who are able to continue opioids long-term experience clinically significant pain relief. Whether quality of life or functioning improves is inconclusive. Many minor adverse events (like nausea and headache) occurred, but serious adverse events, including iatrogenic opioid addiction, were rare (15). The available reviews of opioids for cancer pain do not emphasize trial durations, which vary from a few doses of the drugs over a day to months (29-32). Colson et al (16) concluded Level II-3 evidence for the effectiveness of opioids in cancer pain therapy.

With major advances in oncological therapies, cancer is no longer a "terminal disease." Almost 50-65% of patients live more than 2 years after diagnosis and there are currently around 12 million cancer survivors in the United States. With improved survival there remains the challenge of chronic cancer pain and pain among survivors. Despite opioids' widespread use for cancer pain, there is a paucity of evidence supporting their efficacy in long-term (31). A systematic review of clinical trials in cancer pain revealed a number of methodological flaws and a lack of well designed placebo-controlled trials (33). Long-term controlled trials in the cancer setting are difficult to justify and perform. There is the potential difficulty of recruiting patients with active cancer to controlled clinical trials and an overwhelming symptom burden. A qualitative systematic review evaluating the methodological quality of randomized trials of opioids in cancer pain was done by Bell et al (33). They concluded that there was a need for a uniform and standardized design of trials to produce reliable reports. Adding another complexity to these trials is the challenge of assessing pain in this patient population because of the influence of anxiety and depression on the subjective perception of pain (32).

Despite the lack of significant evidence of effectiveness and potential adverse consequences, opioids are recommended as the mainstay of treatment for cancer pain. Thus, this systematic review is undertaken to summarize the evidence pertaining to the efficacy of short- and long-term opioid therapy for chronic cancer pain.

Methods

The methodology utilized here follows the systematic review process derived from evidence-based systematic reviews and meta-analyses of randomized trials (14,15,34-40); Consolidated Standards of Reporting Trials (CONSORT) guidelines for the conduct of ran-

domized trials (39); Cochrane review guidelines (37); APS guidelines (17,41); Quality of Reporting of Meta-analyses (QUOROM) (35); and the Preferred Reporting Items for Systematic Reviews, and Meta-analyses (PRISMA) (36) statement for conduct of systematic reviews and meta-analyses.

Criteria for Considering Studies for Review

Types of Studies

- Randomized controlled trials (RCTs).

Types of Participants

- Participants included were adults over the age of 18 with cancer-related pain.
- Any pain with cancer etiology.
- Patients treated as outpatient, inpatient, or hospice condition.
- Pain of any intensity and time period.

Types of Interventions

- Any opioid administered, either orally or topically.
- Opioids compared with placebo.
- Opioids compared with other opioids.
- Opioids compared with other adjuvants (including neuropathic agents).
- Any dose for at least 4 weeks.

Types of Outcome Measures

- Minimum of 4 weeks of follow-up.
- Pain relief.
  - Average change in pain scores.
  - Proportion of patients with pain relief of at least of 2 points on a 0-10 scale.
- Health-related QoL and function.

Adverse Events or Side Effects

- Discontinuation from study due to adverse events.
- Discontinuation from study due to insufficient pain relief.

Search Methods for Identification of Studies

Searches were performed from the following sources:

1. PubMed
   www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed
2. EMBASE
   www.embase.com
3. Cochrane Library
   www.thecochranelibrary.com/view/0/index.html
4. U.S. National Guideline Clearinghouse (NGC)
   www.guideline.gov
5. Previous systematic reviews and cross references.

The search period included was from 1966 through July 2011.

Search Strategy

The search terminology included RCTs, all types of cancer pain (nociceptive, neuropathic, and visceral); acute and chronic cancer pain; and all types of opioids (morphine, codeine, oxymorphone, methadone, oxycodone, hydrocodone, hydromorphone, oxymorphone, dihydrocodeine, tramadol, fentanyl, levorphanol, buprenorphine, propoxyphene, meperidine, and pentazocine). The Medical Subject Headings (MeSH) and key words used are listed in Appendix 1.

The literature search was independently performed by a staff member from the library at the MD Anderson Cancer Center at the University of Texas and one of the authors.

Data Collection and Analysis

Selection of Studies

The abstracts were screened in an unblinded standardized manner that compared the identified studies against the inclusion criteria. The abstract and title were analyzed to identify studies that met inclusion criteria. If it was not clear from the abstracts, full texts were requested. The composite list of references obtained was screened to identify studies that met inclusion criteria.

All possibly relevant articles were retrieved in full text and comprehensively assessed for internal validity, quality, and satisfaction of the inclusion criteria:

- Random allocation
- Minimum 4-week follow-up
- Opioid compared with control group
- Pain from malignant etiology
- Pain scores measured.

Data Extraction and Management

Two review authors independently, in an unblinded, standardized manner, extracted the data from the included studies. Disagreements were resolved by discussion between the 2 review authors; if no agreement could be reached, a third author decided.

Measurement of Treatment Effect and Data Synthesis (Meta-Analysis)

Data were summarized using meta-analysis when at least 5 studies per type of opioid administered addressed cancer pain of a particular type (e.g., pancreatic, head, and neck). Qualitative (the direction of a treatment effect) and quantitative (the magnitude of a treatment effect) conclusions were evaluated. Random-effects meta-analyses to pool data were also used (40). The minimum amount of change in pain score to be clinically meaningful has been described as a 2- point change on a scale of 0 to 10 based on findings in trials studying general chronic pain (42-45).

Table 1. *Modified and weighted Cochrane methodological quality assessment criteria.*

CRITERION		Weighted Score (points)
A	Homogeneity	2
B	Comparability of relevant baseline characteristics	5
C	Randomization procedure adequate	4
D	Drop-outs described for each study group separately	3
E	< 20% loss for follow-up	2
	< 10% loss for follow-up	2
F	> 50 patients in the smallest group	8
	> 100 patients in the smallest group	9
G	Interventions included in protocol and described	10
H	Pragmatic study	5
I	Co-interventions avoided or similar	5
J	Placebo-controlled	5
K	Patients blinded	5
L	Outcome measures relevant	10
M	Blinded outcome assessments	10
N	Follow-up period adequate	5
O	Intention-to-treat analysis	5
P	Frequencies of most important outcomes presented for each treatment group	5
TOTAL SCORE		100

Adapted from Koes BW et al. Efficacy of epidural steroid injections for low-back pain and sciatica: A systematic review of randomized clinical trials. *Pain* 1995; 63:279-288 (46).

Methodologic Quality Assessment

Study quality was assessed utilizing Cochrane review criteria (Table 1) utilized in multiple systematic reviews (46-49).

Each study was evaluated by at least 2 authors for stated criteria and any disagreements were discussed with a third reviewer. If there was a conflict of interest with the reviewed manuscript concerning authorship or any other type of conflict, the involved authors did not review the manuscript. Each study was evaluated for quality assessment, clinical relevance, evidence synthesis, or grading of evidence.

Software Used for Assessment

The data were analyzed using SPSS (9.0) statistical software (SPSS Inc., Chicago, IL), Microsoft Access 2003, and Microsoft Excel 2003 (Microsoft Corporation, Redmond, WA). Meta-analyses were done with Comprehensive Meta-Analysis software version 2.0 for Windows (Biostat Inc., Englewood, NJ) (50).

Summary Measures

Summary measures included a 2 point or more reduction in pain scores and relative risk of adverse events and abuse patterns.

Analysis of Evidence

Analysis of evidence was performed based on United States Preventive Services Task Force (USPSTF) criteria (Table 2) (51).

Results

Study Selection

Figure 1 shows a flow diagram of the study selection as recommended by PRISMA (36). Two thousand one hundred fifty-seven abstracts were reviewed from the initial database search and multiple review articles were screened for cross references. Seventy-three full text articles were reviewed and screened. After excluding studies for not meeting the inclusion criteria, 15 studies were identified for methodological quality assessment.

Methodologic Quality Assessment

A methodologic quality assessment of the studies that met inclusion criteria was carried out for 15 studies (52-66) utilizing Cochrane review criteria as shown in Table 3. Studies achieving Cochrane scores of 80 or higher were considered high quality, scores of 60 to

79 were considered moderate quality, and scores of 50 to 59 were considered low quality. Studies scoring less than 50 on Cochrane review were excluded.

Of the 15 studies included, 9 were considered low quality with scores in the 50-59 range (52-58,60,61). Six studies did not meet inclusion criteria since they scored 20-40 on the Cochrane criteria (59,62-66).

Morphine was studied in 6 of the trials, with one study evaluating pancreatic cancer pain (57), one evaluated efficacy for radiation-induced mucositis in head and neck cancer (53), and 4 studies for multiple cancer pain etiologies (52,56,58,61). Oxycodone was evaluated in one study, comparing it to morphine for pancreatic cancer pain (57).

There were 4 studies evaluating transdermal fentanyl, with one evaluating efficacy in metastatic bone pain (55), and 3 studies looking at efficacy in pain from multiple cancers (54,56,61). There were 2 studies evaluating methadone (56,58) for cancer pain associated with multiple malignancies. There were 3 trials evaluating tramadol (52,54,60) for pain associated with multiple malignancies and one study specifically for neuropathic cancer pain (60). One study evaluated com-

Table 2. *Method for grading the overall strength of the evidence for an intervention.*

Grade	Definition
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 RCTs or studies of diagnostic test accuracy).
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 one higher-quality trial or study of diagnostic test accuracy of sufficient sample size; 2 or more higher-quality trials or studies of diagnostic test accuracy with some inconsistency; at least 2 consistent, lower-quality trials or studies of diagnostic test accuracy, 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 U.S. Preventive Services Task Force (51).

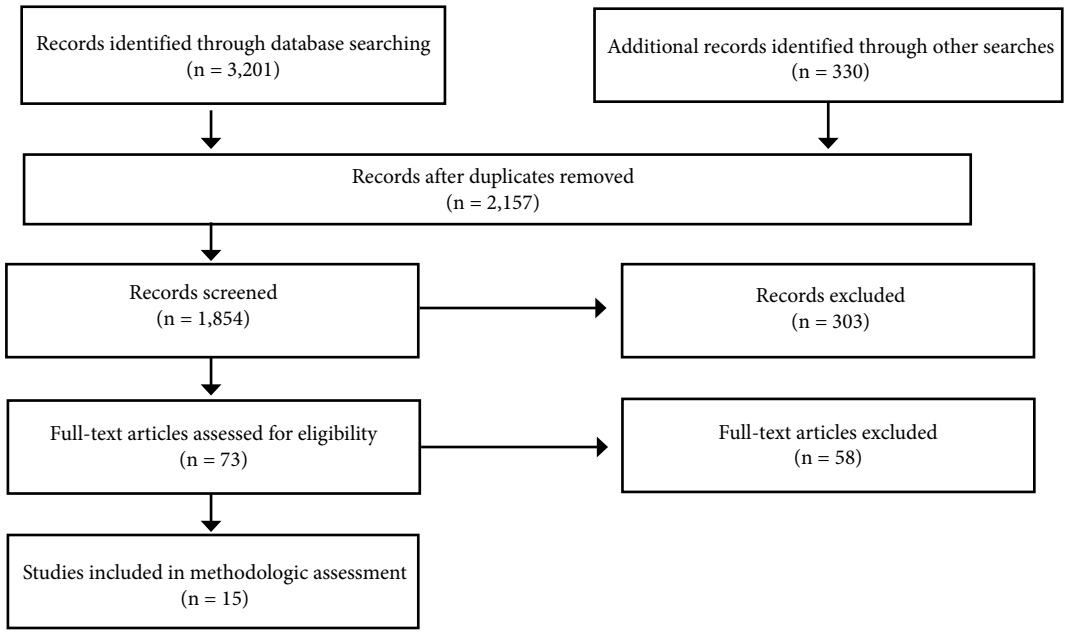

Fig. 1. *Trial flow diagram of literature search.*

Table 3. *Modified and weighted Cochrane methodologic quality assessment criteria.*

		Weighted Score	Van Seventer et al 2003 (61)	Leppert 2001 (52)	Ehrnrooth et al 2001 (53)	Bruera et al 2004 (58)	Mercadante et al 2008 (56)	Mystakidou et al 2005 (55)	Mercadante et al 2010 (57)	Kress et al 2008 (59)	Arbaiza & Vidal 2007 (60)	Marinangeli et al 2007 (54)
1. Study Population:		35										
A	Homogeneity	2	2	2	2	2	2	2	2	2	2	2
B	Comparability of relevant baseline characteristics	5	4	3	4	2	5	4	4	4	4	3
C	Randomization procedure adequate	4	2	2	2	4	4	2	4	4	2	2
D	Dropouts described for each study group separately	3	3	3	3	2	3	3	3	3	3	3
E	< 20% loss for follow-up	2	0	2	0	0	0	2	0	0	0	2
	<10% loss for follow-up	2	0	0	0	0	0	2	0	0	0	2
F	> 50 patients in the smallest group	8	8	0	0	0	0	8	0	0	0	0
	> 100 patients in the smallest group	9	0	0	0	0	0	9	0	0	0	0
2. Interventions:		25										
G	Interventions included in protocol and described	10	10	10	10	10	10	10	10	5	10	10
H	Pragmatic study	5	5	5	5	5	5	5	5	5	0	5
I	Co-interventions avoided or similar	5	5	5	5	5	5	0	0	0	5	5
J	Placebo-controlled	5	0	0	0	0	0	0	0	0	5	0
3. Effect:		30										
K	Patients blinded	5	0	0	3	3	0	0	3	0	5	0
L	Outcome measures relevant	10	6	6	4	10	10	4	10	2	6	8
M	Blinded outcome assessments	10	0	0	5	0	0	0	0	0	0	0
N	Follow-up period adequate	5	3	3	3	3	3	3	3	3	3	3
4. Data Presentation and Analysis:		10										
O	Intention-to-treat analysis	5	5	5	5	5	5	0	5	5	0	5
P	Frequencies of most important outcomes presented for each treatment group	5	5	5	5	0	5	5	5	5	5	5
TOTAL SCORE		100	58	51	56	51	58	59	54	42	50	55

Criteria adapted and modified from Koes BW, Scholten RJ, Mens JM, Bouter LM. Efficacy of epidural steroid injections for low-back pain and sciatica: A systematic review of randomized clinical trials. Pain 1995; 63:279-288 (46).

Table 3 (cont.). *Modified and weighted Cochrane methodologic quality assessment criteria.*

CRITERION:		Weighted Score	Pace et al 2007 (62)	Mercadante et al 2004 (63)	Ferrell et al 1989 (64)	Brema et al 1996 (65)	Mercadante et al 1998 (66)
1. Study Population:		35					
A	Homogeneity	2	2	1	1	2	2
B	Comparability of relevant baseline characteristics	5	3	0	1	4	4
C	Randomization procedure adequate	4	4	2	2	2	2
D	Dropouts described for each study group separately	3	0	0	0	3	3
E	< 20% loss for follow-up	2	2	0	0	0	0
	<10% loss for follow-up	2	2	0	0	0	0
F	> 50 patients in the smallest group	8	0	0	0	0	0
	> 100 patients in the smallest group	9	0	0	0	0	0
2. Interventions:		25					
G	Interventions included in protocol and described	10	5	5	5	5	5
H	Pragmatic study	5	5	5	5	5	5
I	Co-interventions avoided or similar	5	0	0	0	5	0
J	Placebo-controlled	5	0	0	0	0	0
3. Effect:		30					
K	Patients blinded	5	0	0	0	0	0
L	Outcome measures relevant	10	8	4	8	6	8
M	Blinded outcome assessments	10	0	0	0	0	0
N	Follow-up period adequate	5	3	3	3	3	3
4. Data Presentation and Analysis:		10					
O	Intention-to-treat analysis	5	0	0	0	0	0
P	Frequencies of most important outcomes presented for each treatment group	5	5	0	5	5	0
TOTAL SCORE		100	39	20	30	40	32

Criteria adapted and modified from Koes BW, Scholten RJ, Mens JM, Bouter LM. Efficacy of epidural steroid injections for low-back pain and sciatica: A systematic review of randomized clinical trials. Pain 1995; 63:279-288 (46).

bination codeine/acetaminophen with transdermal fentanyl in combination with radiotherapy for metastatic bone pain (55). A meta-analysis was not performed since none of the drugs met criteria; all 5 were homogenous studies for individual pathological condition(s).

Table 4 illustrates studies failing to meet inclusion criteria. These were studies that had a Cochrane score lower than 50.

Study Characteristics

Table 5 illustrates the characteristics of the included studies evaluating the efficacy of opioids.

Marinangeli et al (54) evaluated the possibility of using tramadol with dose titration of fentanyl transdermal patch in patients with advanced cancer. There was a slower dose escalation of fentanyl in patients randomized to tramadol use versus the patients that were ran-

Table 4. *Studies that did not meet inclusion criteria after assessment.*

Manuscript Author	Drugs Studied	Number of Patients	Follow-up Period	Cochrane Score
Kress et al 2008 (59)	New transdermal fentanyl and "standard opioids"	220	30 days	42
Pace et al 2007 (62)	Transdermal buprenorphine, oral morphine, oral tramadol	52	8 weeks	39
Mercadante et al 2004 (63)	Addition of a second opioid may improve opioid response in cancer pain	14	5 weeks	20
Ferrell et al 1989 (64)	Oral morphine	83	6 weeks	30
Brema et al 1996 (65)	Oral tramadol, sublingual buprenorphine	131	51-58 days	40
Mercadante et al 1998 (66)	Dextropropoxyphene, oral morphine	32	38 days	32

domized to fentanyl patch only. Both groups showed equivalent pain relief with a drop in pain score from 4.36 to 1.8 in the tramadol group and 4.51 to 1.6 in the fentanyl only group. The authors (54) concluded that the higher fentanyl consumption seen in the fentanyl only group probably was due to the development of tolerance. However, severe nausea and vomiting were present 50% more in the tramadol and fentanyl patch group versus fentanyl patch only. The results of this study illustrate that while pain relief is the same with or without adding tramadol, the addition of tramadol may provide a slight advantage in the development of tolerance at the cost of increased nausea and vomiting.

Arbaiza and Vidal (60) compared tramadol with placebo for the treatment of neuropathic pain in a randomized, double-blind trial of 36 patients. Tramadol was initiated at a dose of 1 mg/kg every 4 hours and increased to 1.5 mg/kg every 6 hours as needed. Acetaminophen 500 mg tablets, a maximum of 6/24 h was used for breakthrough pain in both arms of the study. Tramadol was more effective than placebo in treating neuropathic cancer pain, resulting in decreased pain intensity, improved Karnofsky score and quality of life (QoL) measures. There was significant nausea and vomiting associated with the use of tramadol. The study included a very small number of patients with significant withdrawals. The proportion of patients completing the study was only 13 in the tramadol group and 12 in the placebo group.

A comparison of morphine versus transdermal fentanyl or oral methadone was compared in 108 patients (36 in each group) by Mercadante et al (56). The authors concluded that all 3 opioids studied were effective and well tolerated and required equal amounts of breakthrough pain medications and other supportive drugs. High withdrawal rates, coupled with small sample sizes, and morphine used as breakthrough pain medication for all 3 groups of patients are multiple factors that reduce the value of any conclusions derived from this evaluation.

Bruera et al (58) compared the efficacy of methadone to morphine as a first line opioid for cancer pain. More than 75% of patients had significant pain relief, defined as 20% improvement in pain expression in both groups in the first week; but the overall pain response at 4 weeks was significantly low. Overall, methadone showed good pain control in this study, but not superior to morphine. This study is flawed with multiple drawbacks including low-dose methadone 15 mg to 35 mg including the breakthrough doses with significant adverse effects followed by a large number of withdrawals.

In a study by Ehrnrooth et al (53), oral morphine was compared to oral nortriptyline for pain from radiation-induced mucositis. A reduction of 10% on the visual analog scale (VAS) score was considered to be the smallest clinically significant difference. At week one, there was a 7.5% reduction in pain in the morphine group and a 6.6% increase in pain in the nortriptyline group. Two weeks post radiation, there was a drop in pain scores in both groups but it was not a statistically significant difference. The authors concluded that although opioids produce greater pain relief, nortriptyline by itself provided sufficient pain control in some of the patients. This was a small study comparing morphine immediate release with nortriptyline with no significant change even at the lowest level of pain reduction of 10%.

Van Seventer et al (61) evaluated the tolerability and treatment satisfaction of transdermal fentanyl compared to sustained-release morphine for mild-to moderate pain. Both treatment groups showed a com-

Table 5. *Characteristics of randomized trials included in analysis*

Manuscript Author(s) Study Design Condition Studied	Cochrane Scores	Number of Patients and Duration of Follow-up	Drugs Administered	Outcomes	Proportion of Patients Completing Study (Placebo or Active Control vs. Treatment Group)	Adverse Events	Authors' Conclusions(s)	Reviewers' Conclusion(s)	Final Results P = Positive N = Negative I = Indeterminate
Improved Cancer Pain Treatment Using Combined Fentanyl TTS and Tramadol Marinangeli et al 2007 (54) Randomized open label trial.	55/100	N = 70, 1. Fentanyl TTS:35. 2. Fentanyl TTS and tramadol:35. Follow-up to 6 months (n = 1), death or exclusion.	1. Fentanyl TTS alone. 2. Fentanyl TTS and tramadol.	1. More than 2 point drop (similar), in VAS score in both arms. 2. Both treatment arms showed statistically significant pain relief. 3.Improved perception of pain treatment by patient, relative, physician on a 4 point scale in both groups, not statistically significant.	Fentanyl TTS 97.1% (34/35). Fentanyl TTS+ tramadol: 94.2% (33/35).	1.Severe nausea and vomiting was observed in 6 patients of the fentanyl TTS +tramadol group and 3 patients of the fentanyl TTS group. 2. Other side effects probably related to study medications: constipation, diarrhea, sedation, mental confusion, pruritus.	Use of tramadol in combination with fentanyl TTS results in a more gradual increase in fentanyl dosage and minimized periods of under dosing and over dosing.	Addition of tramadol reduced overall fentanyl dose and increased time between changes in fentanyl dosages. There was no significant difference in pain intensity between groups. There was a higher rate of adverse events when tramadol was combined with fentanyl versus fentanyl alone but this was not significant. Transdermal fentanyl showed efficacy for pain relief in both study arms, but a lower dose was required with the addition of tramadol.	I Positive for fentanyl in both groups. Negative for addition of tramadol.
Tramadol in the Treatment of Neuropathic Cancer Pain Arabaiza and Vidal 2007 (60) Randomized, double blind, placebo controlled study.	50/100	N = 36. Tramadol:18. Placebo:18. 45 days follow-up.	1.Tramadol 1mg/kg every 6hrs, increased to 1.5mg/kg. 2.Placebo. 3. Acetaminophen 500mg, up to 6 tablets/24 h as rescue analgesia in both study arms.	1.The reduction in mean pain intensity in tramadol group was 57% (6.8 to 2.9) vs. 39% in placebo (7 to 4.3). P < 0.001. 2. Reduction in use on antiepileptic drugs in the tramadol group. P < 0.05 3. Karnofsky Scale: improved by 10.16 points in tramadol group vs. 6.95 points in placebo group. P < 0.001. 4. activities of daily living (ADL) and sleep: statistically significant improvement in the tramadol group. 5. Appetite worsened in both groups.	Tramadol 72.2% (13/18). Placebo 66.6% (12/18).	1. Nausea and vomiting seen in 67% of tramadol group and 22% of placebo group. Three patients in tramadol group withdrew due to severe vomiting. 2. Other adverse events in the tramadol group: somnolence, constipation, dry mouth, general malaise, dizziness, tiredness, and sweaty hands.	Tramadol is a therapeutic option for neuropathic cancer pain. Tramadol was significantly more effective than placebo with respect to pain relief, performance status, improved ADLs, and sleep.	Tramadol was more effective than placebo in treatment of neuropathic cancer pain resulting in decreased pain intensity, improved Karnofsky score, and Quality of Life measures. There was significant nausea and vomiting associated with the use of tramadol.	I

Table 5. (cont.) *Characteristics of randomized trials included in analysis*

Manuscript Author(s) Study Design Condition Studied	Cochrane Scores	Number of Patients and Duration of Follow-up	Drugs Administered	Outcomes	Proportion of Patients Completing Study (Placebo or Active Control vs. Treatment Group)	Adverse Events	Authors' Conclusions(s)	Reviewers' Conclusion(s)	Final Results P = Positive N = Negative I = Indeterminate
Sustained Release Oral Morphine Versus Transdermal Fentanyl and Oral Methadone in Cancer Pain Management Mercadante et al 2008 (56) Prospective randomized controlled study.	58/100	N = 108. Morphine:36. Transdermal fentanyl:- 36. Methadone: 36. 4 wks follow-up.	Starting doses: sustained release oral morphine: 60mg/d. Transdermal fentanyl : 25µg/h. Methadone:15mg/d. One-sixth of the 24 h morphine dose was given as breakthrough medication.	Pain score change: Morphine: 7.0 (6.4-7.5) to 2.5 (1.7-3.3). Fentanyl: 7.0 (6.5-7.6) to 2.4 (2.0-2.8). Methadone: 7.2 (6.5-8) to 3.4 (2.6-4.1). Pain and symptoms (nausea, vomiting, drowsiness, constipation, confusion, dizziness) intensity, QoL.	Morphine: 61.1% (22/36). Fentanyl: 69.4% (25/36). Methadone: 63.8% (23/36).	No significant change in adverse events noted between groups. Adverse events: nausea/ vomiting, drowsiness, constipation, confusion.	All three opioids (sustained-release morphine, fentanyl patch and oral methadone) used as first-line therapy were effective, well tolerated, and required similar amounts of supportive drugs and analgesics.	Sustained-release morphine, fentanyl patch and oral methadone are similarly effective and tolerated. Methadone is less costly. Methadone also required more changes in dosage, thus requiring greater clinical expertise by the provider. Pain intensity and Opioid escalation index (OEI) improved, cost analysis of adjuvant medications revealed no change in all groups, cost analysis of opiates did show methadone was significantly cheaper. Flaw to the study was that morphine was used for breakthrough pain in all 3 study arms.	I Morphine used as breakthrough medication in all 3 study arms.
Methadone Versus Morphine as a First Line Strong Opioid for Cancer Pain: A Randomized, Double Blind Study Bruera et al 2004 (58) Double blind, randomized parallel trial.	51/100	N = 103. Methadone: 49. Morphine: 54. 4 wk follow-up.	Oral methadone 7.5 mg every 12 h and 5 mg every 4 h for breakthrough pain. Oral morphine: 15 mg every 12h and 5 mg every 4h for breakthrough pain.	Both groups with similar numbers of patients reporting 20% or more improvement in pain intensity, rates of patient reported global benefit, OEI, and composite of toxicity. The responder rates were methadone: 49%; morphine: 56%.	68.5% (37/54) Morphine. 59.1% (29/49) Methadone.	Increase rate of adverse events noted in methadone group but not statistically significant. Adverse events: sedation, nausea, confusion, constipation.	More than 75% of patients had significant improvement in pain during the first week. The response rate at 4 weeks was much lower. Methadone did not provide superior analgesia or tolerability when compared to morphine in treatment of cancer pain.	Methadone and morphine had similar efficacy with similar improvement in pain intensity, OEI, and global benefit, but methadone resulted in greater adverse events and dropout rate. There was significant pain relief during the first week but it dropped after that and there was a high dropout rate.	I

Table 5. (cont.) *Characteristics of randomized trials included in analysis*

Manuscript Author(s) Study Design Condition Studied	Cochrane Scores	Number of Patients and Duration of Follow-up	Drugs Administered	Outcomes	Proportion of Patients Completing Study (Placebo or Active Control vs. Treatment Group)	Adverse Events	Authors' Conclusions(s)	Reviewers' Conclusion(s)	Final Results P = Positive N = Negative I = Indeterminate
Randomized Trial of Opioids Versus Tricydic Antidepressants for Radiation-induced Mucositis Pain in Head and Neck Cancer Ehrnrooth et al 2001 (53) Randomized, open parallel study.	56/100	43 patients Morphine:22. Nortriptyline: 21. 2weeks + 2weeks after radiation.	Morphine 5mg x6 and additional doses as needed and nortryptilline:2 mg x2 and increased by 25 mg every 2 d to a max of 150 mg/d. Acetaminophen was used for breakthrough pain in both study arms.	Pain, depression and adverse events. Opioids showed a change in VAS from 39.9 (± 25.5) to 33.5 (± 17.7) and nortriptyline 45.9 (± 28) to 52.6 (± 20.1) at first week and at fourth week VAS fell to 23.1 (± 17.1)in the opioid group and in the nortriptyline group to 32.1 (± 22.5).	Tricyclic antidepressants (TCA) group:38%. Opioid Group: 90%.	Nausea/ vomiting: higher in TCA group. Constipation was higher in opioid group. Arrhythmia seen in TCA group. Neurocortical: slightly more in TCA group.	Patients treated with opioids had lower pain scores compared with patients treated with nortriptyline. 8/21 patients in the TCA group did well without the need for an opioid.	Patients treated with opioids had significantly lower pain scores one and 2 weeks after randomization compared with patients treated with nortriptyline. Patients treated with TCA had increased pain the first week after randomization. There was improvement in depression in both groups, TCA more than opioid, but not significant. Small percentage of patients had satisfactory pain relief in the TCA group in this small short-term trial. There was a high dropout rate in the TCA group.	N
Comparison of TTS Fentanyl With Sustained Release Morphine in the Treatment of Patients Not Using Opioids for Mild to Moderate Pain Van Seventer et al 2003 (61) Randomized comparative trial	58/100	131 patients TTS Fentanyl:67. Morphine:64 and 4 weeks.	TTS fentanyl 25 µg/h. Oral morphine: 30 mg every 12h. Dose was increased by 30-50%.	Efficacy, treatment convenience/ satisfaction, tolerability and safetyby global assessment on 4 point scale. Morphine: 2.0 (± 0.9) to 1.1 (± 1.3). Fentanyl: 1.9 (± 0.9) to 1.5 (± 1.1). Statistically significant pain relief within groups by 11 point numeric rating scale (NRS), but no details on what is considered significant.	Morphine: 41% (59% dropped). Fentanyl: 78% (27% dropped).	More constipation in morphine group. Favorable tolerability of fentanyl by patient and investigator global assessment.	TTS fentanyl as first choice opioid in the treatment of severe cancer-related pain is as effective as sustained release morphine and has a better tolerability profile. Both groups used morphine for breakthrough pain.	Pain control and sleep improved for both. Both fentanyl and morphine reduced pain.	N

Table 5. (cont.) *Characteristics of randomized trials included in analysis*

Manuscript Author(s) Study Design Condition Studied	Cochrane Scores	Number of Patients and Duration of Follow-up	Drugs Administered	Outcomes	Proportion of Patients Completing Study (Placebo or Active Control vs. Treatment Group)	Adverse Events	Authors' Conclusions(s)	Reviewers' Conclusion(s)	Final Results P = Positive N = Negative I = Indeterminate
Analgesic Efficacy and Side Effects of Oral Tramadol and Morphine Administered Orally in the Treatment of Cancer Pain Leppert et al 2001 (52)	51/100	40 patients Tramadol:20. Morphine:20 and 35 days.	Initial dose finding was done using immediate release preparations for 7 days. Oral tramadol:150 to 600 mg. Oral morphine:20 to 200 mg.	Efficacy and side effects, preference of treatment, quality of life. VAS Change Tramadol group: 82 (± 16) to 36.83 (± 20.98). Morphine: 78.5 (± 14.08) to 39.47 (± 22.49).	Tramadol group: 85% (dropouts 15%). Morphine group: 90% (10% dropout).	Intense sweating, anxiety, palpitations, dyspnea, confusion, malaise, constipation, drowsiness, dizziness, difficulty urinating.	Comparable analgesic effects were achieved with morphine and tramadol. Side effects were more with morphine and tramadol showed significantly better QoL. 80% of patients preferred the extended release forms of morphine and tramadol. Authors conclude that tramadol should be used for moderate intensity pain and morphine for "strong" pain.	The use of oral tramadol and morphine at equianalgesic doses were effective in controlling pain for the study period. Surprisingly, tramadol was less effective for neuropathic pain but was associated with better quality of life. Morphine was associated with more severe side effects.	I
Morphine vs. Oxycodone in Pancreatic Cancer Pain Mercadante et al 2010 (57) Randomized controlled study	54/100	60 patients Morphine: 30. Oxycodone: 30 and 4 weeks; with a extension at 8 weeks.	Oral morphine: 30 mg/d. Oral oxycodone: 20mg/d. Oral morphine for breakthrough pain, oral morphine used for breakthrough pain in both study arms	Pain intensity on an 11 point NRS and difference between groups. pain score in the oxycodone group dropped from 7.19 at week 0 to 3.15 at week 4. Pain score in Morphine group dropped from 7.24 at week 0 to 2.35 at week 4	63 % in oxycodone group and 66% in morphine group completed the 4 week study.	Opioid-related side effects including nausea/ vomiting, sedation/ confusion were recorded on a 0 to 3 scale. Nausea, drowsiness, confusion, dry mouth, constipation.	No statistical difference was observed in pain and other symptom scores across the 2 groups.	There was no difference in pain and symptom intensity in both groups. Oxycodone and morphine provided similar analgesia and adverse effects. The sample power dropped at 65% at end of study limiting the statistical validity to compare the 2 groups. Also, morphine was used for breakthrough pain in both study arms, which is a flaw to the study.	I

Table 5. (cont.) *Characteristics of randomized trials included in analysis*

Manuscript Author(s) Study Design Condition Studied	Cochrane Scores	Number of Patients and Duration of Follow-up	Drugs Administered	Outcomes	Proportion of Patients Completing Study (Placebo or Active Control vs. Treatment Group)	Adverse Events	Authors' Conclusions(s)	Reviewers' Conclusion(s)	Final Results P = Positive N = Negative I = Indeterminate
Comparison of Transdermal Fentanyl With Codeine/ Paracetamol in Combination With Radiotherapy for The Management of Metastatic Bone Pain Mystakidou et al 2005 (55)	59/100	460 patients and 2 months.	Transdermal fentanyl and codeine/ paracetamol (acetaminophen).	Pain relief, QoL, overall treatment satisfaction and European Collaborative Oncology Group status. VAS, QoL, and European collaborative oncology group scores showed similar improvement in both groups. Greek-BPI pain scores: Decreased in both groups; statistically greater pain relief in the TTS fentanyl group. Satisfaction score: significantly better in the TTS fentanyl group.	87.3% of patients in fentanyl and 96% in the codeine/ paracetamol (acetaminophen) group were eligible after randomization; 4% of the total withdrew.	Constipation, sleep disturbance, nausea, vomiting, were higher in the codeine / paracetamol (acetaminophen) group.	In combination with radiation, TTS-F was superior to codeine/ paracetamol (acetaminophen) in improving overall satisfaction and pain relief. Similar improvement in QoL and ECOG scores.	Fentanyl patch showed a statistically significant greater pain relief and satisfaction compared to codeine/paracetamol (acetaminophen). Overall both therapies were well tolerated and showed progressive improvement in pain scores and quality of life.	P

parable statistically significant improvement in pain at one and 4 weeks after treatment. A statistically significant difference for constipation and overall impression was seen in favor of the transdermal fentanyl group. Nausea and vomiting, drowsiness, and daytime sleepiness were similar in both groups. Even though the study included a larger number of patients than in other groups, multiple factors confounded the study, including a 59% dropout rate in the morphine group along with more adverse events in the morphine group and a pain scale reduction from 1.9 to 1.5 on a 4 point scale, although the statistical significance may not be clinically relevant.

Leppert (52) studied the analgesic efficacy, side effects, QoL, and satisfaction with treatment of oral tramadol and morphine for cancer pain. The use of oral tramadol and morphine at equianalgesic doses were effective in controlling pain for the study period. Long-term, patients in the tramadol group had increasing pain and had to be switched to morphine. Surprisingly, tramadol was less effective for neuropathic pain but was associated with better QoL. Morphine was associated with more severe side effects and statistically significant drowsiness, difficulty with urination, and dizziness. The authors concluded that tramadol should be used for moderate to intense pain and morphine for "strong" pain. The sample size of the study was small and morphine was associated with significant side effects; oral tramadol doses were very high with questionable outcomes of clinical relevance.

The efficacy of morphine versus. oxycodone in pancreatic cancer pain was evaluated in a randomized trial of 60 patients by Mercadante et al (57). Opioid-related side effects including nausea/vomiting and sedation/confusion were recorded on a 0 to 3 scale. There was no difference in pain and symptom intensity in both groups. It was a relatively small sample size and the sample power dropped at 65% by the fourth week.

In a study by Mystakidou et al (55), the authors compared transdermal fentanyl with codeine/acetaminophen with radiotherapy for metastatic bone pain. Patients in the fentanyl group showed a statistically significant greater pain relief and satisfaction compared to the codeine/acetaminophen group. Overall both therapies were well tolerated and showed progressive improvement in pain scores and QoL. It may be argued that there was a bias since the fentanyl-only group was also allowed to use codeine/acetaminophen for breakthrough pain for the first 12 hours after patch application.

Analysis of Evidence

Morphine

Morphine was studied in 6 trials. There was one study comparing morphine to methadone (58), and another comparing it to methadone and transdermal fentanyl (56). Morphine was studied compared to transdermal fentanyl in another trial for mild to moderate cancer pain (61). There was one trial of morphine versus nortriptyline for radiation-induced mucositis (53), one trial of pancreatic cancer pain comparing it to oxycodone (57), and one with tramadol for moderate to severe cancer pain (52). In comparison with methadone (58), it had similar efficacy and fewer adverse events and fewer dropouts. There was a 56% responder rate in the morphine group for a pain response of 20% and 49% for the methadone group. In the study comparing morphine with transdermal fentanyl and methadone (56), there was more than a 30% difference in pain intensity that was similar to the other 2 drugs and well tolerated in all groups. Compared with fentanyl, morphine was associated with more constipation and a dropout rate of 59% vs. 27% (61). On a 4 point global assessment scale, the pain score dropped from 2.0 (± 0.9) to 1.1 (± 1.3). For pain from radiation-induced mucositis, morphine provided superior analgesia than nortriptyline when evaluated for up to 2 weeks after completion of radiotherapy but only by 10% (53). Morphine showed efficacy in pain relief at 4 weeks with a drop in the pain score from 7.24 to 2.35; there was no difference in pain relief and adverse effects in comparison to oxycodone for pancreatic cancer pain (57).

Thus, none of the studies showed significant evidence for morphine, even though all of them showed morphine to be effective. Morphine was also associated with complaints in clinically relevant populations.

Strength of Evidence

Based on the grading scheme illustrated in Table 2, the evidence was poor for morphine's pain relief efficacy with 2 low quality trials and inconsistent results (53,58).

Oxycodone

Oxycodone was evaluated in one study compared to morphine for pancreatic cancer pain (57). Oxycodone showed efficacy in pain relief at 4 weeks with a drop in pain score from 7.19 to 3.15; there was no difference in

pain relief and adverse effects compared to morphine. In the trial, morphine was used for breakthrough pain in both arms which makes it difficult to interpret the results.

Strength of Evidence

Based on the grading scheme illustrated in Table 2, the efficacy of oxycodone for cancer pain was poor; the major flaw to the above study was the use of morphine for breakthrough pain in both arms (57).

Transdermal Fentanyl

There were 4 studies meeting inclusion criteria evaluating transdermal fentanyl. One study compared it to a combination of codeine/acetaminophen along with radiotherapy for metastatic bone pain (35). Fentanyl patches were much superior to oral codeine/acetaminophen. One study evaluating transdermal fentanyl and morphine (61) showed equal efficacy in pain relief but better tolerability with transdermal fentanyl. Another study compared fentanyl, morphine, and methadone (56), and showed similar efficacy and tolerance with a more than 2-point drop in pain score (also reviewed above in the morphine section). One other study evaluated the influence of tramadol in dose escalation of transdermal fentanyl (54). The addition of tramadol reduced the overall fentanyl requirement and increased the time to dose escalation. The tramadol group had a higher incidence of nausea and vomiting. Overall, fentanyl was shown to be effective in one study in a large number of patients comparing transdermal fentanyl with codeine and acetaminophen (55).

Strength of Evidence

Based on the grading scheme illustrated in Table 2, the evidence was fair based on one RCT (55).

Methadone

There were 2 studies evaluating methadone, one with morphine for cancer pain (58); another study evaluated morphine, methadone, and transdermal fentanyl for cancer pain (56) (both are reviewed above in the morphine section). In the study by Bruera et al (58), there was a 56% responder rate in the morphine group for a pain response of 20% and 49% for the methadone group. Methadone showed comparable efficacy to morphine more adverse effects and higher number of dropouts, 40.8% vs.31.5%.

Strength of Evidence

Based on the grading scheme illustrated in Table 2, the evidence for methadone was poor based on 2 low quality studies with inconsistent results (56,58).

Tramadol

There were 3 trials evaluating tramadol. One trial evaluated the influence of tramadol on the dose escalation of transdermal fentanyl (54). One study evaluated tramadol to placebo for neuropathic cancer pain (60). The third study evaluated tramadol compared to morphine in 20 patients in each group.

Strength of Evidence

Based on the grading scheme illustrated in Table 2, the evidence was poor based on 3 low quality studies (52,54,60).

Codeine/Acetaminophen

One study evaluated combination codeine/acetaminophen with transdermal fentanyl in combination with radiotherapy for metastatic bone pain (55).

Strength of Evidence

Based on the grading scheme illustrated in Table 2, the evidence was poor based on one study comparing with fentanyl which was superior for metastatic bone pain (55).

Adverse Effects

Constipation, nausea and vomiting, drowsiness, and confusion were seen in most of the studies. Fentanyl had a lower incidence of constipation and overall better tolerability (55,61). In a study comparing morphine, methadone, and fentanyl (56), there was no difference in the side effect profile. Morphine showed a higher incidence of drowsiness, difficulty passing urine, and dizziness than tramadol (52). The addition of tramadol to transdermal fentanyl was associated with a higher rate of adverse events (54). Tramadol showed a higher incidence of nausea, vomiting, constipation, and somnolence when compared to placebo (60). In comparison to fentanyl and methadone (56) and with oxycodone (57), morphine showed a similar side effect profile.

Discussion

This manuscript synthesized the evidence collected from a systematic review of randomized trials of opioids (morphine, codeine, methadone, oxycodone, tramadol, and fentanyl) for cancer pain. The evidence obtained from this review showed fair evidence for

transdermal fentanyl and poor evidence for morphine, codeine, methadone, oxycodone, and tramadol based on strict methodologic quality assessment criteria and grading of the evidence.

This is different from previous reviews of the literature evaluating opioids for cancer pain where there was no defined follow-up period for inclusion (11,17,18,67-71). All inclusive trials were low quality based on Cochrane criteria. There were only 9 trials (52-58,60,61) that met inclusion criteria and were used for assessment and analysis of evidence. There was only one placebo-controlled trial (60), whereas all other inclusive studies (52,54-58,61) compared various opioids with one other and one study compared morphine with nortriptyline (53). Most studies used different pain intensity measures and the variability in the clinically significant pain relief as defined in the studies. This systematic review of RCTs of opioids for cancer pain showed fair evidence for the efficacy of transdermal fentanyl. Evidence for morphine, oxycodone, methadone, tramadol, and codeine was poor. There were no studies that met inclusion criteria and methodologic quality assessment criteria for other opioids.

Morphine was evaluated in 6 trials (52,53,56-58,61) comparing it to nortriptyline in one study (53), and to other opioids in 5 studies. Based on the USPTF grading scheme (51), there is fair evidence for the efficacy of pain relief with morphine based on 2 high quality trials (53,58). Evidence is poor for improvement in QoL. Morphine was associated with a higher incidence of constipation compared with fentanyl (61). Adverse effects were more frequent with morphine when compared to tramadol with a statistically significant difference in the incidence of drowsiness, difficulty in voiding urine, and dizziness (52). Oxycodone was evaluated in one trial with morphine and showed weak evidence (57). Overall it showed no difference in pain relief and adverse effects in comparison to morphine but it was flawed as both arms used morphine for breakthrough pain. Fentanyl was graded fair for efficacy of pain relief and QoL based on one high quality trial (55). Overall, there were 5 studies comparing fentanyl with other opioids. There were fewer incidences of constipation with fentanyl (61) compared to morphine. The evidence for tramadol was fair for pain relief and improvement of QoL based on 2 low quality trials (52,60). The evidence for methadone, oxycodone, and codeine was poor due to the lack of trials meeting criteria. Misuse and or abuse of opioids was not assessed in these trials.

The challenges of the symptom burden in the cancer patient make it difficult to perform high quality trials. Significant methodological flaws have been identified, including small trial size, the lack of uniform measures of pain, as well as variability in the definition of statistically significant "pain relief." Also, there are no comparisons of opioids with other interventions, (i.e., placebo, neuropathic and adjuvant medications, injections, and blocks). A recent review of observational trials (16) has shown the level of evidence as II-3 and recommendations were IC/strong based on USPSTF criteria (51). There is a need for well designed randomized, placebo-controlled trials to look at the long-term efficacy of opioids for cancer pain, and that measure adverse events, QoL, tolerance, and addiction. Such trials will help prevent overestimation of treatment effects, but are rarely seen in cancer patients for ethical reasons.

In summary, several published guidelines and consensus statements recommended the use of opioids in chronic cancer patients. However, it appears that there is no concrete evidence of the effectiveness and safety of opioids in cancer pain. Thus, it appears that the foundation of the argument for the use of opioids is the unique analgesic efficacy of opioids, based on surveys, case series, and occasional open-label follow-up studies, as well as very few randomized controlled trials and epidemiological studies (72-90). Thus, opioids, though recommended to be utilized in cancer pain, must be applied with caution and also with appropriate monitoring so they do not lead to similar practices of abuse as are seen in chronic noncancer pain (18-25,91-99).

Conclusion

This systematic review of randomized trials of opioids for cancer pain showed fair evidence for the efficacy of transdermal fentanyl and poor evidence for morphine, tramadol, oxycodone, methadone, and codeine. There were numerous other opioids that were included in various trials but did not meet the inclusion criteria.

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Appendix 1

MeSH Headings

Morphine	Fentanyl
Hydromorphone	Oxycodone
Pentazocine	Methadone
Codeine	Dextromoramide
Heroin	Dextropropoxyphene
Meptazinol	Sufentanil
Alfentanil	Nalbuphine
Meperidine	Tramadol
Buprenorphine	Analgesics, Opioid
Pain	Neoplasms

Keywords

"oral transmucosal fentanyl citrate"	dihydrocodeine
remifentanil	dipipanone
opioid*	opiate*
neoplas*	oncol*
canc*	cancer* p
pain	randomized controlled trial
controlled clinical trial	randomized
placebo	randomly
trials	humans
meta analysis	systematic review
placebo	

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