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Systematic Review

A Systematic Review of Randomized Trials of Long-Term Opioid Management for Chronic Non-Cancer Pain

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Background: Even though opioids have been used for pain for thousands of years, opioid therapy for chronic non-cancer pain is controversial due to concerns regarding the long-term effectiveness and safety, particularly the risk of tolerance, dependance, or abuse. While the debate continues, the use of chronic opioid therapy for chronic non-cancer pain has increased exponentially. Even though evidence is limited, multiple expert panels have concluded that chronic opioid therapy can be effective therapy for carefully selected and monitored patients with chronic non-cancer pain.

Study Design: A systematic review of randomized trials of opioid management for chronic non-cancer pain.

Objective: The objective of this systematic review is to evaluate the clinical efficacy of opioids in the treatment of chronic non-cancer pain.

Methods: A comprehensive evaluation of the literature relating to opioids in chronic non-cancer pain was performed. The literature was evaluated according to Cochrane review criteria for randomized controlled trials (RCTs) and Jadad criteria.

A literature search was conducted by using PubMed, EMBASE, Cochrane library, ECRI Institute Library, U.S. Food and Drug Administration (FDA) website, U.S. National Guideline Clearinghouse (NGC), Database of Abstracts of Reviews of Effectiveness (DARE), clinical trials, systematic reviews and cross references from systematic reviews.

The level of evidence was classified as good, fair, or poor based on the quality of evidence developed by the United States Preventive Services Task Force (USPSTF) and used by other systematic reviews and guidelines.

Outcome Measures: Pain relief was the primary outcome measure. Other outcome measures were functional improvement, withdrawals, and adverse effects.

Results: Based on the USPSTF criteria, the indicated level of evidence was fair for Tramadol in managing osteoarthritis. For all the drugs assessed, including Tramadol, for all other conditions, the evidence was poor based on either weak positive evidence, indeterminate evidence, or negative evidence.

Limitations: A paucity of literature, specifically with follow-up beyond 12 weeks for all types of opioids with controlled trials for various chronic non-cancer pain conditions.

Conclusions: This systematic review illustrated fair evidence for Tramadol in managing osteoarthritis with poor evidence for all other drugs and conditions. Thus, recommendations must be based on non-randomized studies.

Key words: Chronic non-cancer pain, opioids, opioid efficacy, opioid effectiveness, significant pain relief, functional improvement, adverse effects, morphine, hydrocodone, hydromorphone, fentanyl, tramadol, buprenorphine, methadone, tapentadol, oxycodone, oxymorphone, systematic reviews, randomized trials

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Even though opioids have been used for thousands of years to treat pain, they continue to be one of the most commonly prescribed medications for pain (1-6), and have been well accepted for acute pain, post surgical pain, and palliative care; however, there is debate about whether opioids are appropriate for the treatment of chronic non-cancer pain (1-8). The efficacy of opioids for chronic non-cancer pain has been demonstrated in only short-term trials, including those for neuropathic pain, but the evidence is limited about the efficacy and effectiveness of these agents over the long duration of treatment typical for chronic non-cancer pain (1-4,7,8).

Chronic pain has been defined by the American Society of Interventional Pain Physicians (ASIPP) as, "pain that persists 6 months after an injury and beyond the usual course of an acute disease or a reasonable time for a comparable injury to heal, that is associated with chronic pathologic processes that cause continuous or intermittent pain for months or years, that may continue in the presence or absence of demonstrable pathologies; may not be amenable to routine pain control methods; and healing may never occur" (9,10). Persistent pain interfering with daily activities is common; however, chronic persistent pain is separate from chronic pain syndrome which has been defined as a complex condition with physical, psychological, emotional, and social components. The prevalence of chronic pain in the adult population ranges from 2% to 40% with a median point prevalence of 15% (9-12). Further, age related prevalence of persistent pain appears to be much more common in the elderly associated with functional limitations and difficulty in performing daily life activities (11-14).

Several published guidelines and consensus statements recommend the judicious use of opioids in appropriately selected patients with chronic non-cancer pain who have not responded to other treatments and analgesic medications (1-4,7,8,15-17). Also, multiple systematic reviews have been conducted evaluating the efficacy, effectiveness, side effects, abuse and diversion, and other factors (7,8,18-31). However, concrete evidence of the effectiveness and safety of opioids in chronic pain has not been demonstrated. The foundation of the argument for the use of opioids is the unique analgesic efficacy of opioids, based on surveys, case series, occasional open-label follow-up studies, as well as some randomized controlled trials (RCTs) and epidemiological studies. Recent guidelines by Chou and Huffman (8) and Noble et al (7) yielded useful guidance. Noble et al (7) concluded that many patients discontinue long-term opioid therapy due to adverse events or insufficient pain relief; however, weak evidence suggests that patients who were able to continue opioids long-term experience clinically significant pain relief. The findings regarding quality of life or functional improvement were inconclusive. They also cautioned that the evidence supporting these conclusions is weak, and longer-term studies are needed to identify the patients who are more likely to benefit from treatment. Chou and Huffman (8) concluded that chronic opioid therapy can be an effective therapy for carefully selected and monitored patients with chronic non-cancer pain. They also pointed out that opioids are also associated with potentially serious harms, including opioid-related adverse effects and outcomes related to the abuse potential of opioids. Nevertheless, both guidelines recommended opioids in the face of weak evidence.

The purpose of this systematic review is to summarize the evidence pertaining to the efficacy of long-term opioid therapy for chronic non-cancer pain.

1.0 Methods

The methodology utilized here follows the systematic review process derived from evidence-based systematic review and meta-analysis of randomized trials (32-39), Consolidated Standards of Reporting Trials (CONSORT) guidelines for the conduct of randomized trials (40,41), Cochrane guidelines (7), Chou and Huffman (8) guidelines, and Quality of Reporting of Meta-analyses (QUOROM) (35) and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (36) for conduct of systematic reviews and meta-analyses.

1.1 Criteria for Consideration of the Studies

1.1.1 Types of Studies

- Randomized controlled trials (RCTs).

1.1.2 Types of Participants

- Adults aged at least 18 years with pain due to any cause other than cancer lasting for at least 3 months prior to trial enrollment.
- Previous non-opioid pharmacotherapy must have failed before beginning opioids.

1.1.3 Types of Interventions

- Any opioid administered either orally or topically.
- Any dose for at least 12 weeks.

1.2 Types of Outcome Measures

- Minimum of 12 weeks of follow-up.
- Pain relief.
  - Average change in pain scores.
  - Proportion of patients with at least 50% pain relief.
- Health-related quality of life and function.

1.3 Adverse Events or Side Effects

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

1.4 Search Methods for Identification of Studies

Searches were performed from the following sources:

1. PubMed from 1966

www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed

2. EMBASE from 1980

www.embase.com/

3. Cochrane Library

www.thecochranelibrary.com/view/0/index.html

4. ECRI Institute Library

www.ecri.org/Pages/default.aspx

5. U.S. Food and Drug Administration (FDA) website from 1977

www.usda.gov/wps/portal/usda/usdahome

6. U.S. National Guideline Clearinghouse (NGC) from 1998

www.guideline.gov/

7. Previous systematic reviews and cross references
8. Database of Abstracts of Reviews of Effectiveness (DARE)

www.crd.york.ac.uk/crdweb/Home.aspx?DB=DARE

9. Clinical Trials

clinicaltrials.gov/

Search period included from 1966 to September 2010.

1.5 Search Strategy

The search terminology included RCTs, chronic non-cancer pain, all types of chronic pain (nociceptive, neuropathic, and visceral; and low back, thoracic, neck, musculoskeletal, rheumatic, localized, generalized, chest, headache, joint pain, arthritis, psychogenic pain), all types of opioids (morphine, codeine, oxymorphone, methadone, oxycodone, hydrocodone, hydromorphone, oxymorphone, dihydrocodeine, tramadol, fentanyl, levorphanol, buprenorphine, propoxyphene, meperidine, tapentadol, and pentazocine).

At least 2 of the review authors independently, in an unblinded standardized manner, performed each search. Accuracy was confirmed by a statistician. All searches were combined to obtain a unified search strategy. Any disagreements between reviewers were resolved by a third author and consensus.

1.6 Data Collection and Analysis

1.6.1 Selection of Studies

- Two review authors screened the abstracts, in an unblinded standardized manner, of all identified studies against the inclusion criteria.
- They then retrieved all possibly relevant articles in full text for comprehensive assessment of internal validity, quality, and satisfaction of inclusion criteria.

1.6.2 Assessment of Methodologic Quality

Two review authors independently assessed, in an unblinded standardized manner, the internal validity of all the studies.

The methodologic quality assessment was performed in a manner to avoid any discrepancies which were evaluated by a third reviewer and consensus was reached.

Methodologic quality assessment criteria are described in Tables 1 and 2 (37,38).

1.6.3 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, it was planned a third author would decide.

1.6.4 Assessment of Heterogeneity

Whenever meta-analysis was conducted, the I-squared (I2) statistic was used to identify heterogeneity (42). Combined results with I2 > 50% were considered substantially heterogenous.

We divided the evidence base by mode of drug administration, either topical or oral, to reduce clinical heterogeneity.

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

Data were summarized using meta-analysis when at least 5 studies per type of opioid administration addressed chronic non-cancer pain (e.g., tra-

Table 1. *Criteria list for methodological quality assessment**.

Criteria	Operationalization of Criteria	Score
***A. Was the method of randomization adequate*?**	A random (unpredictable) assignment sequence. An example of adequate methods is a computer generated random number table and use of sealed opaque envelopes. Methods of allocation using DOB, date of admission, hospital numbers, or alternation should not be regarded as appropriate.	Yes/No/ Don't Know
B. Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	Yes/No/ Don't Know
C. Were the groups similar at baseline regarding the most important prognostic factors? *"Yes", if similar:* • *Age & gender* • *Description of type of pain* • *Intensity, duration or severity of pain*	In order to receive a "yes," groups have to be similar in baseline regarding demographic factors, duration or severity of complaints, percentage of patients with neurologic symptoms, and value of main outcome measure(s).	Yes/No/ Don't Know
D. Was the patient blinded to the intervention?	The reviewer determines if enough information about the blinding is given in order to score a "yes": Use the author's statement on blinding, unless there is a differing statement/reason not to (no need for explicit information on blinding). If a study notes it is double-blind, code "yes" for patient, care provider and outcome assessor (unless it is clear that one of these is not blinded)	Yes/No/ Don't Know
***E. Was the care provider blinded to the intervention*?**		
F. Was the outcome assessor blinded to the intervention?		
G. Were cointerventions avoided or similar?	Cointerventions should either be avoided in the trial design or similar between the index and control groups. Code "yes" if there is a statement about co-intervention medications being used or not used, e.g.: rescue analgesics not allowed or note about which rescue analgesics were permitted or if rescue analgesics are outcomes.	Yes/No/ Don't Know
H. Was the compliance acceptable in all groups?	The reviewer determines if the compliance to the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). Code "yes" if protocol violations are reported or if actual compliance data is reported.	Yes/No/ Don't Know
I. Was the drop-out rate described and acceptable? *≤15% drop out rate is acceptable.*	The number of participants who are included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 15% and does not lead to substantial bias, a "yes" is scored.	Yes/No/ Don't Know
J. Was the timing of the outcome assessment in all groups similar?	Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.	Yes/No/ Don't Know
K. Did the analysis include an intention-to-treat analysis? *"Yes" if less than 5% of no-treatment excluded.*	All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of noncompliance and cointerventions.	Yes/No/ Don't Know
This list includes only the internal validity criteria (N=11) that refer to characteristics of the study that might be related to selection bias (criteria A and B), performance bias (criteria D, E, G, and H), attrition bias (criteria I and K) and detection bias (criteria F and J). The internal validity criteria should be used to define methodologic quality in meta-analysis.		

* Table adapted from methods developed by the Cochrane Back Review Group (van Tulder, Furlan, Bombardier, Bouter, and Editorial Board of the Cochrane Collaboration Back Review Group) *Spine (Phila Pa 1976)* 2003; 28:1290-1299 (37).

Table 2. *Jadad quality rating for primary studies**.

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

* Jadad AR et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Controlled Clin Trials* 1996; 17:1-12 (38).

madol – 5 studies meeting inclusion criteria evaluating individual conditions of chronic pain), low back pain or osteoarthritis. 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 (39).

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 (or 20 percentage points), based on findings in trials studying general chronic pain (43), chronic musculoskeletal pain (44), and chronic low back pain (32-34,45,46), which have been commonly utilized. However, recent descriptions of clinically meaningful improvement have been described as significant improvement, either with pain relief or functional status as 50% (47-50). Consequently, for this analysis, we have utilized clinically meaningful pain relief of at least a 4-point change on an 11-point scale of 0 to 10, or 50% pain relief from the baseline as clinically significant.

1.6.6 Integration of Heterogeneity

The evidence was assessed separately by mode of administration, either oral or transdermal, by the drug administered (i.e., morphine, oxymorphone, etc.), and by the predominant pain condition treated (i.e., low back pain, osteoarthritis, etc.). The meta-analysis was performed only if there were at least 5 studies meeting inclusion criteria available for each variable.

Statistical heterogeneity was explored using univariate meta-regression (51).

1.6.7 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) (52).

Meta-analyses were done with Comprehensive Meta-Analysis software version 2.0 for Windows (Biostat Inc., Englewood, NJ) (53).

1.7 Summary Measures

Summary measures included 50% or more reduction of pain in at least 40% of the patients, or at least 4 points decrease in pain scores and relative risk of adverse events including side effects and abuse patterns.

1.8 Analysis of Evidence

Analysis of evidence was performed based on United States Preventative Services Task Force (USPSTF) criteria (Table 3) (54), which have been utilized by others (8).

Table 3. *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.

Source: Chou R, Huffman L. *Use of Chronic Opioid Therapy in Chronic Noncancer Pain: Evidence Review*. American Pain Society; Glenview, IL: 2009 (8). Adapted from methods developed by U.S. Preventive Services Task Force (54).

2.0 Results

2.1 Study Selection

Figure 1 shows a flow diagram of the study selection as recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (36).

2.2 Inclusion Criteria

Of the 111 randomized trials identified (55-165), Table 4 illustrates the list of excluded studies, the majority of them being for short-term follow-up, whereas some other studies were excluded due to secondary analysis, evaluation of breakthrough pain, postsurgical pain, or drug levels.

Table 5 illustrates assessment of the 23 trials for inclusion criteria. Twenty-one studies met inclusion criteria (143-151,153-160,162-165). Thus, 2 of the 23 studies were excluded from the methodologic quality assessment (152,161).

2.3 Methodologic Quality Assessment

A methodologic quality assessment of the studies meeting inclusion criteria was carried out utilizing Cochrane review criteria and Jadad criteria as shown in Tables 6 and 7. Studies achieving Cochrane scores of 9 or higher and Jadad criteria of at least 4 were considered as high quality, 6 to 8 of Cochrane and Jadad criteria of at least 3 were considered as moderate quality, whereas 5 to 6 of Cochrane and at least 2 of Jadad were considered as low quality. Studies scoring less than 5 on Cochrane review and/or less than 2 on Jadad score were excluded.

Nine studies were considered as high quality with Cochrane scores of 9 or higher of 11 and Jadad scores of at least 4 of 5 (147-149,151,153,156,158,162,164). Six studies were considered as of moderate quality with 6 to 8 of 11 Cochrane criteria and at least 3 of 5 Jadad criteria (143,145,150,155,157,163), whereas 5 studies were considered low quality based on Cochrane review criteria scores of 5 to 6 (144,146,154,159,165), and at least 2 of Jadad criteria. One study (160) scored 3 of 11 of Cochrane criteria; thus, was excluded from further analysis.

On the included condition-specific studies, 8 studies evaluated low back pain (144,148,151,154,156,163-165), 4 studies evaluated chronic pain (146,149,159,162), 8 studies evaluated osteoarthritis (143,145,147,150,155,157,158,165), and one study evaluated diabetic neuropathy (153).

Of the 8 studies evaluating low back pain, 3 were considered as low quality (144,154,165), one was considered as moderate quality (163), and 4 were considered as high quality (148,151,156,164).

Of the 4 studies evaluating chronic pain, 2 were considered as low quality (146,159) and 2 were considered as high quality (149,162).

Of the 8 studies evaluating osteoarthritis, one study was of low quality (165), one study was of moderate quality (155), and 6 studies were of high quality (143,145,147,150,157,158).

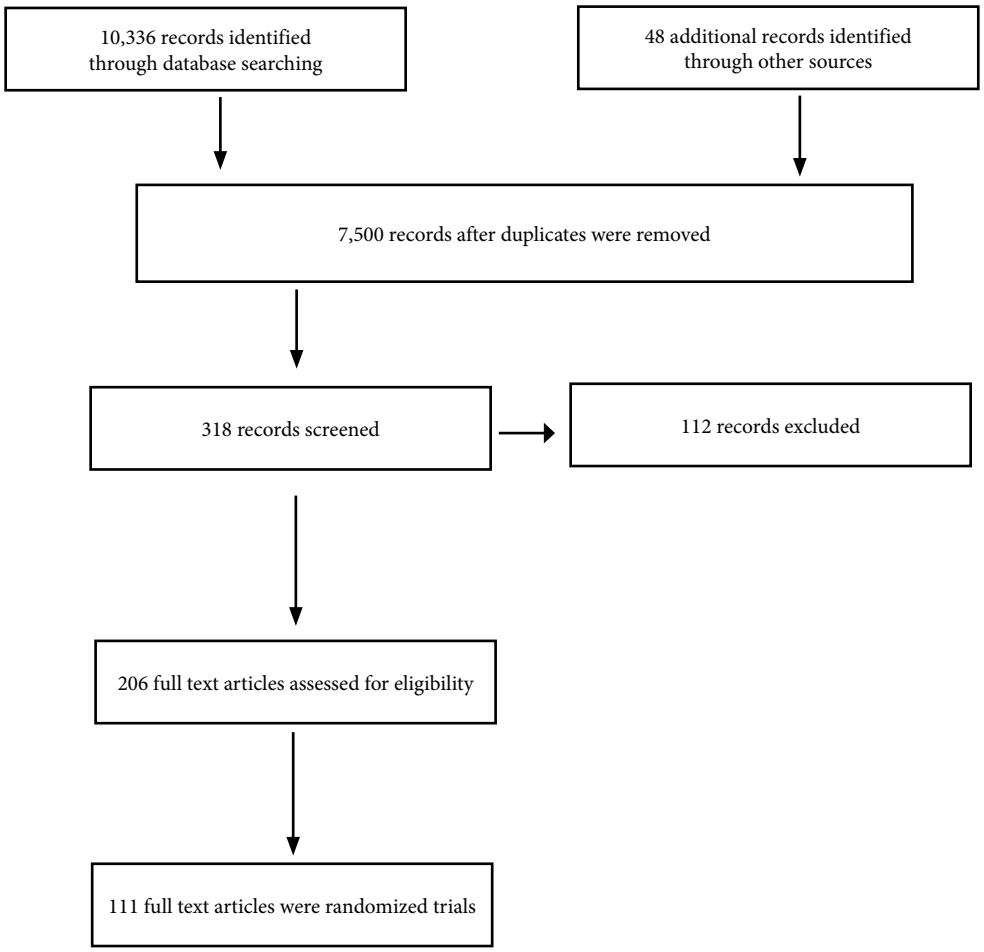

Fig. 1. *Flow diagram of literature search.*

The only study evaluating diabetic neuropathy (153) was rated as high quality.

2.4 Meta-Analysis

All the studies were evaluated for inclusion of meta-analysis.

Oxycodone was evaluated in 4 trials for its effectiveness in low back pain (148,154,164,165), 3 trials in chronic pain (146,159,162), 3 trials in osteoarthritis (143,157,165), and one trial in diabetic neuropathy (153).

Tramadol was evaluated for its use in osteoarthritis in 5 trials (145,147,150,155,158), of which 2 studied osteoarthritis of the knee (145,158) and one studied osteoarthritis of the knee and hip (155) and one for management of low back pain (163).

Morphine was evaluated for managing chronic pain in 2 trials (149,159) and low back pain in 2 trials (144,154).

Oxymorphone was studied in 2 trials for low back pain (151,156). Fentanyl was evaluated for low back pain in one trial (144).

Hydromorphone was evaluated for chronic pain in one study (146).

Tapentadol was evaluated for osteoarthritis in 2 trials (143,165) and in 2 trials for low back pain

Table 4. *List of excluded studies.*

Manuscript Author(S)	Drugs Studied	Reason for Exclusion	
		Follow-up Period	Other Reasons
Adler et al 2002 (55)	Tramadol	3 weeks	
Aqua et al 2007 (56)	Oxymorphone	_____	Postoperative pain
Aurilio et al 2009 (57)	Buprenorphine	4 weeks	
Beaulieu et al 2007 (58)	Tramadol	4 weeks	
Beaulieu et al 2008 (59)	Tramadol	8 weeks	
Bodalia et al 2003 (60)	Tramadol	2 weeks	
Caldwell et al 1999 (61)	Oxycodone	5 weeks	
Caldwell et al 2002 (62)	Morphine	4 weeks	
Chang et al 2009 (63)	Hydromorphone	_____	Intravenous postoperative
Chindalore et al 2005 (64)	Oxycodone	3 weeks	
Cowan et al 2005 (65)	Morphine	_____	Abstinence
Daniels et al 2009 (66)	Tapentadol/oxycodone	_____	Postoperative
Daniels et al 2009 (67)	Tapentadol/oxycodone	_____	Postoperative
Etropolski et al 2010 (68)	Tapentadol	4 weeks	Dose conversion
Frank et al 2008 (69)	Dihydrocodeine	2 weeks	
Gatti et al 2009 (70)	Morphine	5 weeks	Breakthrough pain
Gilron et al 2005 (71)	Morphine	5 weeks	
Gimbel et al 2003 (72)	Oxycodone	6 weeks	
Gordon et al 2010 (73)	Buprenorphine	6 weeks	
Gordon et al 2010 (74)	Buprenorphine	8 weeks	
Gould et al 2009 (75)	Oxymorphone	_____	Secondary analysis
Grosset et al 2005 (76)	Hydromorphone	1 week	
Hale et al 1997 (77)	Codeine	1 week	
Hale et al 2005 (78)	Oxymorphone	3 weeks	
Hale et al 1999 (79)	Oxycodone	2 weeks	
Hale et al 2007 (80)	Oxycodone	6 weeks	
Hamann & Sloan 2007 (81)	Morphine	1 week	Role of oral naltrexone in intrathecal morphine
Harati et al 2000 (82)	Tramadol	6 weeks	
Harke et al 2001 (83)	Morphine	8 days	
Hartrick et al 2009 (84)	Tapentadol/oxycodone	2 weeks	
Huse et al 2001 (85)	Morphine	4 weeks	
James et al 2010 (86)	Buprenorphine	7 weeks	
Jensen & Ginsberg 1994 (87)	Tramadol	2 weeks	
Kalso et al 2007 (88)	Transdermal Fentanyl and Morphine	_____	Secondary analysis
Katz et al 2010 (89)	Morphine	_____	Pharmacokinetics
Khoromi et al 2007 (90)	Morphine	9 weeks	
Kivitz et al 2006 (91)	Oxymorphone	2 weeks	
Kleinert et al 2008 (92)	Tapentadol	< 1 day	Post-surgical pain
Landau et al 2007 (93)	Buprenorphine	5 weeks	
Lange et al 2010 (94)	Tapentadol & oxycodone	Pooled analysis	
Langford et al 2006 (95)	Fentanyl	6 weeks	
Likar et al 2007 (96)	Buprenorphine	2 weeks	
Litkowski et al 2005 (97)	Oxycodone	_____	Post op dental pain
Ma et al 2008 (98)	Oxycodone	4 weeks	

Table 4 (cont.). *List of excluded studies.*

Manuscript Author(S)	Drugs Studied	Reason for Exclusion	
		Follow-up Period	Other Reasons
Malonne et al 2004 (99)	Tramadol	2 weeks	
Malonne et al 2005 (100)	Tramadol	4 weeks	
Matsumoto et al 2005 (101)	Oxymorphone	4 weeks	
Max et al 1988 (102)	Codeine	6 hours	
McIlwain and Ahdieh 2005 (103)	Oxymorphone	3 weeks	
Morley et al 2003 (104)	Methadone	2 day	
Moulin et al 1996 (105)	Morphine	9 weeks	
Mullican et al 2001 (106)	Tramadol	4 weeks	
Munera et al 2010 (107)	Buprenorphine	5 weeks	
Nicholson et al 2006 (108)	Morphine	2 weeks	
Niemann et al 2000 (109)	Morphine vs Fentanyl	4 weeks	
Norrbrink & Lundeberg 2009 (110)	Tramadol	4 weeks	
Palangio et al 2002 (111)	Hydrocodone vs. oxycodone	1 week	
Parris et al 1998 (112)	Oxycodone	1 week	
Paulson et al 2005 (113)	Alvimopan	3 weeks	
Perrot et al 2006 (114)	Tramadol	< 2 weeks	
Petrone et al 1999 (115)	Tramadol	4 weeks	
Portenoy et al 2007 (116)	Fentanyl	_____	Breakthrough pain
Raber et al 1999 (117)	Tramadol	2 weeks	
Raja et al 2002 (118)	Morphine and methadone	8 weeks	
Ralphs et al 1994 (119)	Opiate reductions	4 weeks	
Rauck et al 2006 (120)	Morphine/oxycodone	4 weeks	
Roth et al 2000 (121)	Oxycodone	5 weeks	
Rowbotham et al 2003 (122)	Levorphanol	8 weeks	
Ruoff 1999 (123)	Tramadol	2 weeks	
Ruoff et al 2003 (124)	Tramadol	2 weeks	
Salzman et al 1999 (125)	Oxycodone	3 weeks	
Sandner-Kiesling et al 2010 (126)	Oxycodone & naloxone	Pooled analysis	
Simpson et al 2007 (127)	Fentanyl	_____	Breakthrough pain
Sindrup et al 1999 (128)	Tramadol	_____	Drug levels
Sindrup et al 1999 (129)	Tramadol	4 weeks	
Sorge & Stadler 1997 (130)	Tramadol	3 weeks	
Sorge and Sittl 2004 (131)	Buprenorphine	< 1 week	
Stegmann et al 2008 (132)	Tramadol	_____	Post operative pain
Tessaro et al 2010 (133)	Oxycodone	4 weeks	
Thorne et al 2008 (134)	Tramadol	8 weeks	
Vorsanger et al 2007 (135)	Tramadol	Post hoc analysis	
Vorsanger et al 2010 (136)	Tapentadol, oxycodone	Post hoc analysis	
Wallace et al 2007 (137)	Hydromorphone	6 weeks	
Watson & Babul 1998 (138)	Oxycodone	4 weeks	
Watson et al 2003 (139)	Oxycodone	4 weeks	
Webster et al 2008 (140)	Alvimopan	6 weeks	
Wilder-Smith 2001 (141)	Tramadol/dihydrocodeine	4 weeks	
Zautra & Smith 2005 (142)	Oxycodone	2 weeks	

Table 5. Assessment of trials for inclusion criteria.

Manuscript Author(s)	Drug(s) Studied	# of Patients	Age (Yrs.)	Pain Condition(s)	Duration of Chronic Pain	Previous Pharmaco-therapy	Follow-up Period	Pain Relief	Outcome Measures	Adverse Events
Afilalo et al 2010 (143)	Tapentadol and Oxycodone	1,030	Yes	Osteoarthritis of knee	Yes	Yes	12 weeks	Yes	No	Yes
Allan et al 2005 (144)	Morphine & fentanyl	680	Yes	Low back pain	Yes	Yes	13 months	Yes	Yes	Yes
Babul et al 2004 (145)	Tramadol	246	Yes	Knee osteoarthritis	Yes	Yes	12 weeks	Yes	Yes	Yes
Binsfeld et al 2010 (146)	Hydromorphone & Oxycodone	512	Yes	Chronic pain	Yes	Yes	24 weeks	Yes	Yes	Yes
Burch et al 2007 (147)	Tramadol	646	Yes	Osteoarthritis	Yes	Yes	12 weeks	Yes	No	Yes
Buynak et al 2010 (148)	Tapentadol and Oxycodone	981	Yes	Low back pain	Yes	Yes	12 weeks	Yes	No	Yes
Galer et al 2005 (149)	Morphine	828	Yes	Chronic pain	Yes	Yes	13 weeks	Yes	No	Yes
Gana et al 2006 (150)	Tramadol	1,020	Yes	Osteoarthritis	Yes	Yes	12 weeks	Yes	Yes	Yes
Hale et al 2007 (151)	Oxymorphone	143	Yes	Low back pain	Yes	Yes	12 weeks	Yes	No	Yes
Hale et al 2009 (152)	Tapentadol and Oxycodone	878	Yes	Osteoarthritis of hip & knee	Yes	Yes	13 weeks	No	No	Yes
Hanna et al 2008 (153)	Oxycodone	338	Yes	Diabetic neuropathy	Yes	Yes	12 weeks	Yes	Yes	Yes
Jamison et al 1998 (154)	Oxycodone/Morphine	36	Yes	Low back pain	Yes	Yes	16 weeks	Yes	Yes	Yes
Karlsson and Berggren 2009 (155)	Buprenorphine patches and Tramadol	135	Yes	Osteoarthritis hip & knee	Yes	Yes	12 weeks	Yes	No	Yes
Katz et al 2007 (156)	Oxymorphone	205	Yes	Low back pain	Yes	Yes	12 weeks	Yes	No	Yes
Markenson et al 2005 (157)	Oxycodone	109	Yes	Osteoarthritis	Yes	Yes	13 weeks	Yes	Yes	Yes
Mongin et al 2004 (158)	Tramadol	431	Yes	Knee osteoarthritis	Yes	Yes	12 weeks	Yes	Yes	Yes
Nicholson et al 2006 (159)	Morphine & Oxycodone	112	Yes	Chronic pain	Yes	Yes	24 weeks	Yes	Yes	Yes
Rauck et al 2007 (160)	Morphine & Oxycodone	392	Yes	Low back pain	Yes	Yes	4 months optional	Yes	Yes	Yes
Simpson et al 2008 (161)	Oxycodone	322	Yes	Chronic pain	Yes	No	12 weeks	No	No	Yes
Vondrackova et al 2008 (162)	Oxycodone	464	Yes	Chronic pain	Yes	Yes	12 weeks	No	No	Yes
Vorsanger et al 2008 (163)	Tramadol	386	Yes	Low back pain	Yes	Yes	12 weeks	Yes	Yes	Yes
Webster et al 2006 (164)	Oxytrex (oxycodone + ultralow-dose naltrexone)	719	Yes	Low back pain	Yes	Yes	12 weeks	Yes	Yes	Yes
Wild et al 2010 (165)	Tapentadol and Oxycodone	1,121	Yes	Low back pain, osteoarthritis	Yes	Yes	One-year	Yes	No	Yes

Table 6. *Methodologic quality assessment of randomized trials utilizing Cochrane review criteria.*

Author, Year, Title	Random-ization	Concealed Treatment Allocation	Baseline Group Similarity	Patient Blinded	Care Provider Blinded	Outcome Assessor Blinded	Co-interventions Avoided or Similar	Compliance Acceptable in All Groups	Drop-out Rate Described and Acceptable	Timing of Outcome Assessment in All Groups Similar	Intention to Treat Analysis	Score
Afilalo et al 2010 (143)	YES	YES	YES	YES	YES	YES	YES	NO	NO	YES	NO	8/11
Allan et al 2005 (144)	YES	NO	YES	NO	NO	NO	YES	NO	NO	YES	YES	5/11
Babul et al 2004 (145)	YES	YES	YES	YES	YES	YES	YES	NO	NO	YES	NO	8/11
Binsfeld et al 2010 (146)	YES	NO	YES	NO	NO	NO	YES	NO	NO	YES	YES	5/11
Burch et al 2007 (147)	YES	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES	9/11
Buynak et al 2010 (148)	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	NO	9/11
Galer et al 2005 (149)	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	10/11
Gana et al 2006 (150)	YES	YES	NO	YES	YES	YES	YES	NO	NO	YES	YES	8/11
Hale et al 2007 (151)	YES	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES	9/11
Hanna et al 2008 (153)	YES	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES	9/11
Jamison et al 1998 (154)	YES	NO	NO	NO	NO	NO	YES	YES	YES	YES	NO	5/11
Karlsson and Berg-gren 2009 (155)	YES	NO	YES	NO	NO	NO	YES	YES	YES	YES	YES	7/11
Katz et al 2007 (156)	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	10/11
Markenson et al 2005 (157)	YES	YES	YES	YES	YES	YES	YES	NO	NO	YES	NO	8/11
Mongin et al 2004 (158)	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	11/11
Nicholson et al 2006 (159)	YES	YES	NO	NO	NO	NO	YES	YES	NO	YES	NO	5/11
Rauck et al 2007 (160)	YES	NO	NO	NO	NO	NO	YES	NO	NO	YES	NO	3/11
Vondrackova et al 2008 (162)	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	10/11
Vorsanger et al 2008 (163)	YES	YES	NO	YES	YES	YES	YES	NO	NO	YES	YES	8/11
Webster et al 2006 (164)	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	NO	9/11
Wild et al 2010 (165)	YES	NO	YES	NO	NO	NO	YES	NO	NO	YES	YES	5/11

DK = Don't know

(148,165).

There was one trial which evaluated Buprenorphine for osteoarthritis (155).

None of the drugs met inclusion criteria for meta-analysis; thus, no meta-analysis was performed.

2.5 Study Characteristics

Table 8 illustrates the study characteristics of the included studies evaluating the efficacy of opioids.

2.6 Methodologic Quality Assessment for Bias

Methodologic quality assessment data utilizing Cochrane review criteria is illustrated in Table 6. This table shows adequate data with regards to adequacy of randomization, concealment allocation, and blinding of patients. Twenty-one of 23 studies were assessed for quality assessment. Of these, one trial (160) evaluating morphine and oxycodone in low back pain was excluded due to low quality scores.

Blinding of patients, health care providers, data collectors, and outcome assessors were also evaluated utilizing Cochrane review criteria as shown in Table 6, which were present in 15 of the 20 trials evaluated. However, 16 of 20 studies were deficient with regards to dropouts, loss to follow-up, and other reasons. They are considered the major disadvantage of all the trials evaluated for this systematic review.

2.7 Analysis of Evidence

2.7.1 Tramadol

Tramadol was assessed in 6 randomized trials (145, 147,150,155,158,163). The effectiveness of tramadol in managing chronic low back pain was evaluated in one study (163), 2 studies evaluated osteoarthritis of the knee (145,158), one studied osteoarthritis of the knee and hip (155), and the other 2 studied osteoarthritis of various joints (147,150). None of the studies provided data in terms of 50% pain relief. Thus, the criteria of reduction of at least 4 points or 40% in the pain scores was considered as significant.

Table 7. *Methodologic quality assessment of randomized trials utilizing Jadad scoring criteria.*

Author, Year, Title	Randomization	Blinding	Reporting of Withdrawals	Score
Afilalo et al 2010 (143)	2	2	1	5/5
Allan et al 2005 (144)	2	0	1	3/5
Babul et al 2004 (145)	2	2	1	5/5
Binsfeld et al 2010 (146)	2	0	1	3/5
Burch et al 2007 (147)	2	2	1	5/5
Buynak et al 2010 (148)	2	2	1	5/5
Galer et al 2005 (149)	2	2	1	5/5
Gana et al 2006 (150)	1	2	1	4/5
Hale et al 2007 (151)	2	2	0	4/5
Hanna et al 2008 (153)	2	2	1	5/5
Jamison et al 1998 (154)	1	0	1	2/5
Karlsson and Berggren 2009 (155)	2	0	1	3/5
Katz et al 2007 (156)	2	2	1	5/5
Markenson et al 2005 (157)	2	2	1	5/5
Mongin et al 2004 (158)	1	2	1	4/5
Nicholson et al 2006 (159)	1	0	1	2/5
Rauck et al 2007 (160)	1	0	1	2/5
Vondrackova et al 2008 (162)	2	2	1	5/5
Vorsanger et al 2008 (163)	2	2	1	5/5
Webster et al 2006 (164)	1	2	1	4/5
Wild et al 2010 (165)	2	0	1	3/5

Table 8. *Characteristics of randomized trials included in analysis.*

Manuscript Author(s) Study Design Condition Studied	Cochrane and Jadad 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' Conclusion(s)	Study Conclusion(s)	Final Results
Afilalo et al 2010 (143) Randomized, double-blind, active and placebo-controlled trial Osteoarthritis of knee	8/11 and 5/5	N=1,030 Tapentadol ER=346 Oxycodone CR=345 Placebo=339 Follow-up: 12 weeks	Tapentadol ER: 100-250 mg twice daily Oxycodone CR: 20-50 mg twice daily Placebo	♦ Improvement in pain intensity in the tapentadol ER was 32% compared with the placebo 24.3% compared to 17.3% in the oxycodone CR group.	♦ 60.2% of the patients in the placebo group, 52.6% of the patients in the tapentadol ER group, and 34.5% in the oxycodone CR group completed the study.	♦ At least one adverse event was noted with 61.1% in placebo group, 75.9% in tapentadol ER group, and 87.4% in the oxycodone CR group. ♦ Incidences of gastrointestinal related adverse effects were 26.1% in placebo group, 43% in tapentadol group, and 67.3% in oxycodone CR group.	♦ Treatment with Tapentadol ER 100-250 mg twice daily or oxycodone HCl CR 20-50 mg twice daily was effective for the management of moderate to severe chronic osteoarthritis-related knee pain	♦ Tapentadol ER reduced average pain intensity > 50 in only 32% of the patients vs. 24.3% in the placebo group and 17.3% in the oxycodone CR group.	Indetermined
Allan et al 2005 (144) Randomized, controlled, parallel group trial Low back pain	5/11 and 3/5	N=680 Transdermal fentanyl=338 Sustained release morphine=342 Follow-up: 13 months	Transdermal fentanyl: 50 mcg Sustained release morphine: 140 mg	♦ Pain score (mean, 0-100 VAS): 56 vs. 56. ♦ Severe pain at rest or night. ♦ Rescue strong opioids use: 52% (154/296) vs. 53% (154/291) ♦ Quality of life (SF-36): no differences	Transdermal fentanyl=48% Sustained release morphine=53% Total=51% Adverse events leading to discontinuation of trial medication Fentanyl vs. Morphine 37% vs. 31%	Overall Fentanyl vs Morphine: 87% vs. 91% • Constipation 52% vs.65% • Nausea 54% vs. 50% • Vomiting 29% vs. 26% • Somnolence 27% vs. 30% • Increased sweating 26% vs. 16% • Dizziness 25% vs. 24% • Pruritus 15% vs. 20% • Diarrhea 18% vs. 14%	♦ The prolonged opioid therapy was associated with clinically meaningful improvements in chronic low back pain patients. ♦ Both sustained release preparations can safely be used in patients who have not received strong opioids before.	♦ There was significant improvement at 25 mm level compared to baseline, providing a 44% decrease. ♦ Quality of life functioning improved some with physical health and none with mental health. ♦ High withdrawal and adverse events.	Indetermined
Babul et al 2004 (145) Randomized, double-blind, placebo-controlled trial Osteoarthritis of knee	8/11 and 5/5	N=246 Tramadol extended-release=124 Placebo=122 Follow-up: 12 weeks	Tramadol ER: starting dose 100 mg; final dose 400 mg	♦ Outcomes related to pain and physical function were better with tramadol ER than placebo. ♦ Mean percent change from baseline to week 12 of pain index was 45% for tramadol and 25% for placebo.	♦ Tramadol ER: 61 of 124 patients (49%) ♦ Placebo: 63 of 122 patients (52%) ♦ Discontinuation rate was significantly higher for tramadol ER compared to placebo (27% vs. 7%).	♦ The adverse events were higher for patients treated with tramadol ER (79% vs. 64%). ♦ Common adverse events occurring at least in 5% of patients were: diarrhea, constipation, nausea, vomiting, dizziness, headache, somnolence, and pruritus for patients treated with tramadol ER and constipation, nausea, dizziness, and headache for patients treated with placebo.	The treatment with tramadol ER results in statistically significant and clinically important and sustained improvements in pain, stiffness, physical function, global status, and sleep in patients with chronic pain.	♦ Mean percent change from baseline to week 12 of pain index was 45% for tramadol and 25% for placebo. ♦ Only approximately 50% of the patients completed the study (less than sample size).	Indetermined
Binsfeld et al 2010 (146) Randomized, comparative, parallel group trial Chronic pain with 57% of the patients with low back pain	5/11 and 3/5	Randomized= 512 OROS hydromorphone=254 SR oxycodone=250	Median doses: OROS hydromorphone: 16 mg SR oxycodone: 40 mg	♦ Both treatments reduced pain by at least 2.8 points considered as a relevant change by the authors. ♦ Patients in the extension phase showed reduction of pain scores from 6.8 and 6.9 to 3.9 and 4.1.	♦ 115/254 in OROS hydromorphone group completed the study (45%) ♦ 108/250 in SR oxycodone group completed the study (43%) ♦ Most withdrawals were related to adverse events.	♦ Over 80% of the patients in both groups experienced at least one adverse event. ♦ The majority of the 90% total number of adverse events were classified as mild or moderate. The most common side effects were nausea, constipation, vomiting, diarrhea, headache, dizziness, somnolence, hyperhydrosis, pruritus, and fatigue.	The results of this open-label study showed that once daily OROS hydromorphone is safe and well-tolerated for chronic pain and as efficacious as twice-daily SR oxycodone.	The sample size was calculated at 151 patients per treatment arm and in both groups the number of patients completing the study was lower than the sample size.	Indetermined

Table 8 (cont). *Characteristics of randomized trials included in analysis.*

Manuscript Author(s) Study Design Condition Studied	Cochrane and Jadad 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' Conclusion(s)	Study Conclusion(s)	Final Results
Burch et al 2007 (147) Randomized, double-blind, placebo-controlled trial Osteoarthritis	9/11 and 5/5	N=646 Placebo=214 Tramadol=432 Follow-up: 12 weeks	Tramadol Contramid: 200 mg or 300 mg Placebo	♦ Approximately 59% of the patients in tramadol group had 4-point improvement in pain vs placebo 47%. ♦ The generic improvement of patients was 80% in the tramadol group and 69% in the placebo group.	♦ Tramadol=292 of 432 completed the study (68%) ♦ Placebo=143 of 214 completed the study (67%) ♦ Significant withdrawals due to adverse events:	Total: Placebo vs. Tramadol 5% (11/214) vs. 10% (44/432) • Nausea 6% vs. 15% • Constipation 4% vs. 14% • Dizziness/ vertigo 4% vs. 10% • Somnolence: 4% vs. 7%	♦ Both the 200 mg and 300 mg of tramadol doses contributed to the overall superiority of tramadol. ♦ The results confirm that tramadol given once daily is an efficacious and safe treatment for pain due to osteoarthritis.	♦ Even though results are somewhat weak, a significant proportion of patients showed a 4-point change in numeric pain rating scale. ♦ Withdrawals were 32% in the treatment group.	Positive
Buynak et al 2010 (148) Randomized, double-blind, placebo and active-controlled trial Chronic low back pain	9/11 and 5/5	N=981 Tapentadol=321 Oxycodone CR=334 Placebo=326 Follow-up: 12 weeks	Tapentadol ER: 100-250 mg twice a day Oxycodone HCL controlled release: 20-50 mg twice a day Placebo	Tapentadol ER and oxycodone CR significantly reduced average pain intensity vs. placebo at week 12 and throughout the maintenance period.	Proportion of patients completing the study: Placebo 152/326 (47%) Tapentadol ER 166/321 (52%) Oxycodone CR 133/334 (40%)	Tapentadol ER was associated with a lower incidence treatment-emergent adverse events than oxycodone CR. Gastrointestinal side effects including constipation, nausea, and vomiting were among the most commonly reported side effects with reports of 26.3% in placebo, 43.7% in tapentadol ER group, and 61.9% in oxycodone CR group.	Tapentadol ER (100 – 250 mg b.i.d.) effectively relieved moderate to severe chronic low back pain over 15 weeks and had better gastrointestinal tolerability than oxycodone HCl CR (20 – 50 mg twice a day)	Even though tapentadol showed a better adverse event profile, the pain relief appears to be only slightly better than placebo.	Indetermined
Galer et al 2005 (149) Randomized, double-blind, controlled clinical trial Non-neuropathic pain	10/11 and 5/5	N=828 STUDY A N=327 STUDY B N=308 STUDY C N=193 Follow-up: 12 weeks	Average daily morphine dose: STUDY A MS/DM (1:1) STUDY B MS/DM (1:1) MS/DM (2:1) MS STUDY C MS/DM (1:1)	The 3 studies (A, B, and C) consistently demonstrated that the addition of dextromethorphan (DM) to morphine (MS) failed to enhance opioid analgesia.	Discontinuations ranged from a low of 36% to 40% in Study C, with 43 to 46% in Study B, to over 50% in Study A.	Approximately 90% of the patients experienced at least one adverse event. The most frequent adverse events in each treatment group were constipation, somnolence, nausea, headache, dizziness, and pruritus. Discontinuations were slightly higher in MS/DM groups.	The results suggest that adding the NDMA antagonist, DM, to opioids does not add any clinical benefit.	This is a large study incorporating multiple designs complicating the interpretation of the data with no differences among groups.	Indetermined
Gana et al 2006 (150) Randomized, double-blind, placebo-controlled trial Osteoarthritis	8/11 and 4/5	N=1,020 100 mg=203 200 mg=203 300 mg=204 400 mg=205 Placebo=205 Follow-up: 12 weeks	Extended-release tramadol: 100, 200, 300 or 400 mg once daily Placebo	♦ Significant differences were noted for the daily pain scores. • Baseline scores from 65.8 to 71.5 showed changes of 15 in the placebo group compared to 23.5 to 27.1 in the treatment group.	558 of 1,020 participants completed 12 weeks of treatment=55%	♦ Any adverse events: 84% vs. 76% vs. 73% vs. 71% vs 56% ♦ At least one minor or moderate adverse event: 12.5% ♦ At least one serious adverse event: 3.0% vs. 1.5% vs. 2.0% vs. 1.5% vs. 1.0% ♦ Most adverse events were mild or moderate. ♦ Common adverse events: constipation, nausea, dizziness, somnolence.	Tramadol ER 100 to 300 mg once daily was associated with significant improvement in pain intensity and physical function.	Even though results are reported as positive, the change was minimal with less than 2 points.	Indeterminate

Table 8 (cont). *Characteristics of randomized trials included in analysis.*

Manuscript Author(s) Study Design Condition Studied	Cochrane and Jadad 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' Conclusion(s)	Study Conclusion(s)	Final Results
Hale et al 2007 (151) Randomized, double-blind, placebo-controlled trial Low back pain	9/11 and 4/5	N=143 OPANA ER=70 Placebo=73 Follow-up: 12 weeks	OPANA ER: Median, 60 mg; range, 20 to 260 mg Placebo Rescue medication was also provided	♦ Change in pain intensity from baseline to the final visit was 8.7 ± 3.0 versus 31.6 ± 2.9. ♦ Net difference of pain improvement -23.0 mm.	Placebo=18/73 (25%) OPANA ER=49/70 (70%) Withdrawal due to adverse event: 10% (7/70) vs. 11% (8/72) During the 12-week treatment period, 30% of OPANA ER patients discontinued treatment with 11% discontinuing for lack of efficacy.	♦ 70% of the patients reported at least one adverse event. ♦ The most frequent adverse events were nausea, constipation, headache, and somnolence. ♦ 53% of the placebo patients discontinued due to lack of efficacy.	In opioid-experienced patients with chronic, moderate to severe low back pain, OPANA ER provided efficacious, long-term analgesia and was generally well-tolerated.	Rating decreased from 67.6 in OPANA ER group to 31.6 with approximately over 40% improvement in pain scores.	Positive
Hanna et al 2008 (153) Randomized, double-blind, placebo-controlled study Diabetic neuropathy	9/11 and 5/5	N=338 Placebo=169 OxyContin =1 69 Follow-up: 12 weeks	Gabapentin: 1200-1800 mg/day OxyContin: 10-80 mg /day	♦ More patients in the oxycodone group rated study drug as good or very good at relieving pain and better than their pre-study medication than did patients in the placebo group (56% versus 41%). ♦ Oxycodone patients reported at least 30% reduction in pain.	128/169 completed the study in placebo group (78%) 121/169 completed the study in OxyContin (74%) Premature termination due to adverse events: oxycodone group 64%.	Adverse events were more commonly reported in oxycodone group (88%) versus placebo group (71%). The most common adverse events were constipation, nausea, fatigue, dizziness, and somnolence.	♦ The study provided the first evidence that co-administration of prolonged-release oxycodone and existing gabapentin therapy has a clinically meaningful effect in painful diabetic neuropathy	♦ Considering the low dose oxycodone therapy with significant proportion of patients completing the study and less than usual adverse events ,-the study appears to be positive.	Positive
Jamison et al 1998 (154) Randomized, open, repeated-dose trial of one NSAID and 2 opioid regimens Chronic low back pain	5/11 and 2/5	N=36 No opioid=12 Set Dose=13 Titrated Dose=11 Follow-up: 52 weeks	Sustained-release morphine + short acting oxycodone Immediate-release oxycodone + naproxen	♦ Few differences were found in activity or hours of sleep, or between average pre-treatment and post-treatment phone-interview and questionnaire variables. ♦ The patients preference was for short-acting opioids as more helpful than the longer-acting medication.	All patients completed the first 2 phases of the study. Only one participant dropped out after 7 months.	Three participants discontinued opioid therapy after one-month because of the adverse effects and intolerance to the medication. The most frequently reported adverse events included dry mouth, drowsiness, headache, constipation, and nausea.	♦ Opioid therapy has a positive effect on pain and mood, but little effect on activity and sleep. ♦ Tapered-off opioid treatment is palliative and without long-term benefit.	The improvements were clinically insignificant in a small study.	Negative
Karlsson and Berggren 2009 (155) Randomized, open-label, controlled, parallel-group noninferiority trial Ostearthritis of hip and/or knee	7/11 and 3/5	N=135 7-day buprenorphine patch=69 Tramadol=66 Follow-up: 12 weeks	Transdermal buprenorphine patches: 5, 10, 15, 20 mcg/h, up to 2 patches same time Tramadol doses: 150, 200, 300 and 400 mg/day	♦ The mean change in the pain scores was 2.26 in buprenorphine gp vs. 2.09 in tramadol gp. ♦ 7 days patch prefered.	♦ 80% of the patients in the buprenorphine group and 70% of the patients in the tramadol group completed the study. ♦ 10 patients (14.5%) in the 7-day buprenorphine patch group and 19 patients (29.2%) in the tramadol tablet group withdrew from the study due to adverse events.	The most common adverse events in the 7-day buprenorphine group vs. tramadol group Buprenorphine vs. tramadol Nausea: 30.4 % / 24.6% Constipation: 18.8% /7.7% Dizziness: 15.9% / 4.6% Fatigue: 13 % / 18.5% Pain: 14.5% /12.3%	In patients with chronic, moderate to severe OA pain of the hip and/or knee, 7-day low-dose buprenorphine patches were an effective and well-tolerated analgesic.	The decrease in the pain scores, though similar, was only slightly higher than 2 points.	Indeterminate

Table 8 (cont). *Characteristics of randomized trials included in analysis.*

Manuscript Author(s) Study Design Condition Studied	Cochrane and Jadad 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' Conclusion(s)	Study Conclusion(s)	Final Results
Katz et al 2007 (156) Randomized, double-blind, placebo-controlled trial Low back pain	10/11 and 5/5	N=205 Oxymorphone ER=105 Placebo=100 Follow-up: 12 weeks	Oxymorphone ER: mean dosage 39.2 ± 26.4 mg Rescue medication of oxymorphone: 5 mg was utilized 4-6 hours.	♦ 86% experienced a greater than 50% decrease in pain intensity in oxymorphone group vs. 55% in placebo group. ♦ Pain intensity increased significantly more in placebo group than in oxymorphone group.	47 of 100 patients completed the study in the placebo gropu (47%) 71 of 105 patients in oxymorphone ER group completed the study (68%) Withdrawal due to adverse event: 9% (9/105) vs. 8% (8/100)	At least 70% of the patients reported one adverse event. Most common adverse events were constipation (26%), somnolence (19%), nausea (18%), dizziness, headache, and pruritus. At least one adverse event: 58% (61/105) vs. 44% (44/100)	The proportion of patients experiencing a 50% or greater reduction in average pain intensity was 86% in the oxymorphone group compared to 55% in placebo group.	♦ An enrichment enrollment, randomized withdrawal study design. ♦ All patients were allowed oxymorphone immediate release as a rescue medication.	Positive
Markenson et al 2005 (157) Randomized, double-blind, placebo-controlled trial Osteoarthritis	8/11 and 5/5	Patients randomized=109 Controlled-release oxycodone=56 Placebo=51 Follow-up: 13 weeks	Controlled-release oxycodone: 44 ± 5 mg Placebo	Only 20% of the patients in the CR oxycodone treatment group achieved at least 50% pain relief at the end of 90 days vs. 5.9% of the patients in the placebo group.	CR oxycodone=23 of 56 completed the study (41%) Placebo=13 of 51 completed the study (25%)	♦ A total of 93% of patients in the CR oxycodone group and 55% of the patients in the placebo group reported adverse events. ♦ Common adverse events were constipation, nausea, somnolence, dizziness, pruritus, headache, diarrhea, vomiting, and sweating.	♦ Treatment with controlled-release oxycodone of patients with osteoarthritis with persistent moderate to severe pain resulted in significant pain control and improvements in physical functioning.	♦ Only 20% of the patients experienced more than 50% pain relief in CR oxycodone group. ♦ A substantial proportion of patients failed to complete the study, even in CR oxycodone group.	Negative
Mongin et al 2004 (158) Randomized, double-blind, parallel controlled comparative study Osteoarthritis	11/11 and 4/5	N=431 Tramadol once daily=215 Tramadol twice daily=216 Follow-up: 12 weeks	Tramadol ER 100-400 mg once daily Tramadol ER 100-400 mg twice daily Median optimal dose=200 mg in both groups	♦ In the daily ratings, 73% of all patients indicated that their pain was mild / barely noticeable or absent at the end of the dosing interval. ♦ Patient global rating "effective" or "very effective": 83%	Tramadol once daily=182 of 215 completed the study (85%) Tramadol twice daily=179 of 216 completed the study (83%)	Adverse events were reported moreso in tramadol twice a day patients with dizziness or vertigo 37% vs. 26%, vomiting 14% vs. 8%, and headache 18% vs. 13%, while tramadol once daily patients reported more somnolence 30% vs. 21%. At least one adverse event was reported in 80% of the patients.	Tramadol once daily formulation provides sustained analgesic efficacy over the entire 24-hour dosing interval and a clinically favorable safety profile, both of which will provide a clear clinical benefit.	73% of patients in the study experienced no pain or mild pain immediately prior to taking the morning dose of medication.	Positive
Nicholson et al 2006 (159) Randomized comparative trial Chronic pain over 50% with low back pain	5/11 and 2/5	N=112 Controlled release morphine=53 Controlled release oxycodone =59 Follow-up: 24 weeks	Extended-release morphine (Kadian) once daily: 78.7 ± 55.62 Sustained-release oxycodone twice daily (mean improvement from baseline): 84.7 ± 66.14 (127 mg morphine equivalent)	♦ Clinically meaningful reduction of pain as defined by at least 2 point reduction in visual numeric scale score was found in both groups of patients. ♦ At week 24, both groups indicated significantly increased global assessment of therapy.	46% in morphine group and 50% in CR oxycodone group completed the study. Only 46% of the patients in the morphine group and 50% of the patients in the oxycodone group completed the study.	A total of 61% experienced an adverse event. The most common adverse events were constipation, nausea, somnolence, fatigue, headache, peripheral edema, dizziness, sedation, cognitive disorder.	Patients taking long acting morphine once or twice daily, whereas 44% of those taking oxycodone took doses more frequently 3 or 4 times daily, with both treatments effective.	In the controlled-release oxycodone group, only 56% of patients took twice daily doses, whereas 44% took the medication 3 or 4 times daily.	Indeterminate

Table 8 (cont). *Characteristics of randomized trials included in analysis.*

Manuscript Author(s) Study Design Condition Studied	Cochrane and Jadad 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' Conclusion(s)	Study Conclusion(s)	Final Results
Vondrackova et al 2008 (162) Randomized, double-blind, placebo-controlled trial Chronic pain	10/11 and 5/5	N=464 Oxycodone PR=151 Oxycodone PR/naloxone PR=154 Placebo=158 Follow-up: 12 weeks to 12 months	Oxycodone PR/naloxone PR: 40/mg day Oxycodone PR: 40 mg/day Placebo	Pain values were lower in patients receiving oxycodone PR/naloxone PR compared with those receiving oxycodone PR or placebo, with improved sleep in oxycodone groups and bowel function in nalaxone group.	Placebo 133/158 (84%) Oxycodone PR 133/151 (88%) Oxycodone PR/naloxone PR 136/154 (88%)	Common adverse events were constipation, nausea, headache, vomiting, and diarrhea. The majority of adverse events were mild or moderate in intensity.	Oxycodone PR/naloxone PR is superior to placebo, and comparable to oxycodone PR, with regards to analgesic efficacy.	Even though significant improvements have been described, there was no data available to assess the proper improvement.	Indeterminate
Vorsanger et al 2008 (163) Randomized, double-blind, placebo-controlled trial Low back pain	8/11 and 5/5	N=386 Tramadol ER 300 mg=128 Tramadol ER 200 mg=129 Placebo=129 Follow-up: 12 weeks	Tramadol ER 300 mg once daily Tramadol ER 200 mg once daily Placebo	Pain scores decreased from 72.4 to 31.2 mm in the tramadol ER 300 mg group, from 71.6 to 31.4 mm in the tramadol ER 200 mg group, and 69.6 to 33.8 mm in the placebo group.	68/129 of placebo group completed the study (53%) 86/128 of tramadol ER 300 mg group completed the study (67%) 87/129 of tramadol ER 200 mg group completed the study (67%)	Any adverse event: 76% vs. 61% vs. 57% (P=0.003) Nausea: 29% vs. 27% vs. 28% Dizziness: 15% vs. 14% vs. 17% Vomiting: 7% vs. 8% vs. 7% Constipation: 23% vs. 26% vs. 19% Somnolence: 10% vs. 13% vs. 12% Fatigue: 7% vs. 6% vs. 5%	Among patients tolerating and obtaining pain relief from tramadol ER, continuation of tramadol ER treatment for 12 weeks maintained pain relief more effectively than placebo.	Even though patients in tramadol group obtained significant pain relief, placebo group also showed pain relief of 50%.	Indeterminate
Webster et al 2006 (164) Randomized, double blind, placebo and active-controlled trial Low back pain	9/11 and 4/5	N=719 Oxycodone 4 times a day=206 Oxytrex 4 times a day=206 Oxytrex twice a day=206 Placebo=101 Follow-up: 18 weeks	Oxycodone: 10 mg to a total of 80 mg per day Oxytrex 4 times a day: OXY 2.5 mg + NTX 0.001 mg to a total of OXY 20 mg + NTX .001 mg Oxytrex twice a day: OXY 5 mg + NTX 0.001 mg to a total of OXY 40 mg + NTX .001 mg	♦ All 3 active treatment arms showed significant improvements in the physical and functional status without significant differences among the active treatment groups. ♦ Patients taking Oxytrex twice a day reported 55% less physical dependence than patients on oxycodone.	Placebo=42 of 101 (42%) Oxycodone 4 times a day=101 of 206 (49%) Oxytrex 4 times a day=87 of 206 (42%) Oxytrex twice a day=98 of 206 (48%)	The most common adverse events were constipation, dizziness, somnolence, pruritus, nausea, vomiting with a higher proportion of the patients experiencing side effects in oxycodone group compared to placebo group.	The analgesic effect of Oxytrex was achieved at a significantly lower total average daily oxycodone dose with improved safety of Oxytrex versus oxycodone with significant reductions in the opioid-related side effects.	Even though all oxycodone group patients had reduction of pain scores of over 40%, the placebo group also had a reduction of 32% in their scores.	Indeterminate
Wild et al 2010 (165) Randomized, controlled, comparative study Low back pain or osteoarthritis	5/11 and 3/5	Randomized=1,121 Tapentadol ER=894 Oxycodone CR=223 Follow-up: one-year	Tapentadol ER: 100 to 250 mg twice a day Oxycodone CR: 20-50 mg twice a day	Mean pain score decreases were from baseline of 7.6 to 4.4 in tapentadol ER group and from 7.6 to 4.5 in oxycodone group at endpoint.	78/223 of patients in Oxycodone CR group completed the study (35%) 413/894 of patients in tapentadol ER group completed the study (46.2%)	Overall 86% of the patients in the tapentadol ER group and 91% of the patients in the oxycodone CR group experienced at least one adverse event. The most common adverse events included constipation, nausea, dizziness, somnolence, vomiting, headaches, fatigue, and pruritus.	Tapentadol ER 100 to 250 mg twice a day was associated with better gastrointestinal tolerability than oxycodone CR 20-50 mg twice a day and provided sustainable relief of pain.	Overall, the pain scores decreased from 7.6 to 4.4 or 4.5 at endpoint with at least 40% decrease in both groups, with less constipation in the tapentadol group.	Positive

Of the 3 studies evaluating arthritis of multiple joints (147,150,155), only one was positive (147) and 2 studies were indeterminate (150,155). Between the 2 studies evaluating osteoarthritis of the knee (145,158), one study was positive (158) and the second study was indeterminate (145). The single study evaluating effectiveness in low back pain (163) was indeterminate.

2.7.1.1 Strength of Evidence

Based on grading for overall strength of evidence for intervention as illustrated in Table 3, the evidence for tramadol in managing various chronic painful conditions is variable from fair to poor. For osteoarthritis of multiple joints, of the 2 placebo controlled trials (147,150) with high methodologic quality, one study was shown to be positive (147) and the second one was shown to be indeterminate (150). The third study was a parallel group comparison study (155) with moderate methodologic quality; it was indeterminate, with the summary of evidence leading to an assessment of fair for osteoarthritis of multiple joints.

In managing osteoarthritis of the knee, one placebo-controlled trial with high methodologic quality was indeterminate (145), a second comparative trial with high methodologic quality (158) showed positive results, and a third trial showed indeterminate results in a parallel group study (155) with the summary of evidence as fair.

In managing low back pain, there was only one placebo-controlled study (163) with high methodologic quality criteria, which was shown to be indeterminate, with the summary of evidence as poor.

2.7.2 Oxycodone

Oxycodone was evaluated for its role in managing chronic pain of various types in 10 studies (143, 146,148,153,154,157,159,162,164,165). Of these, researchers evaluated effectiveness for low back pain in 4 studies (148,154,164,165), for chronic non-cancer pain in 3 studies (146,159,162), for osteoarthritis in 3 studies (143,157,165), and in one trial the role of oxycodone in patients receiving gabapentin in diabetic neuropathy (153). Of the 10 studies, 2 of them included 50% pain relief as the criterion standards, whereas the remaining used various types of criteria.

Of the 10 reports provided, 2 studies, a high quality, placebo-controlled trial (153), and a low quality comparative trial (165), provided positive evidence; 6 trials, 4 of which were placebo-controlled trials with high methodologic quality (143,148,162,164), and 2 comparative trials with low methodologic quality (146,159), provided indeterminate evidence; and 2 studies, a placebo controlled study with high methodologic quality (157) and an open study with low methodologic quality (154) provided negative evidence.

2.7.2.1 Strength of Evidence

Based on grading for overall strength of evidence for an intervention as illustrated in Table 3, for low back pain, the evidence was poor with a low quality open label study showing negative results (154) and 2 placebo-controlled high quality studies (148,164) showing indeterminate results.

For chronic pain, one placebo-controlled, high quality study (162) and 2 comparative trials with low methodologic quality assessment (146,159), all showed indeterminate results. Consequently, the evidence was poor in managing chronic pain.

For management of osteoarthritis, of the 2 high quality placebo-controlled trials (143,157), one was indeterminate (143) and the second one was negative (157), whereas one low quality comparative trial (165) showed positive results with an overall conclusion of poor evidence.

For diabetic neuropathy, only one placebo controlled trial of high quality (153) showed weak positive evidence, with overall poor evidence.

2.7.3 Morphine

Four randomized trials were identified evaluating the role of morphine in managing chronic pain of various types (144,149,154,159). Of these, 2 low quality trials evaluated low back pain (144,154) and 2 studies, one high quality (149) and one low quality (159), evaluated chronic pain. None of the trials were placebo-controlled.

2.7.3.1 Strength of Evidence

Based on grading for overall strength of evidence for an intervention as illustrated in Table 3, the evidence for morphine in managing chronic low back pain or chronic non-cancer pain was poor.

Two non-placebo controlled trials evaluating low back pain, one parallel group (144) and one comparative trial (154), with low quality of methodology, showed either indeterminate (144) or negative evidence (154). For chronic pain, 2 comparative trials, one high quality

(149) and the second one low quality (159), showed indeterminate evidence.

2.7.4 Oxymorphone

Two trials evaluated efficacy and safety of oxymorphone in patients with chronic low back pain; one study recruited opioid naïve patents (156) and the other study enlisted opioid experienced patients (151). Both were randomized placebo-controlled, enriched enrollment trials and were graded as high quality studies. However a significant number of participants in both studies dropped out; as a result at the final assessment the total number of subjects in each study was less than the number calculated for powering the study. In the study by Hale (151), 60 patients per treatment group were needed to provide 90% power at a 5% significance level, while the participants that completed the study were 49/70 in the treatment arm and 18/73 in the placebo arm. In the Katz study (156), a smaller effect size (0.45) was anticipated and it was estimated that 80 patients per treatment group were needed to provide 80% power at 5% significance. The number of participants completing the study was 71/105 in the treatment group and 47/100 in the placebo group. Even though both studies demonstrated that compared to patients in the placebo group, a higher percentage of patients in the treatment group reported clinically significant pain relief, the significance of these findings is questionable because of the high drop out rate and failure to meet the number needed to power the study.

2.7.4.1 Strength of Evidence

Based on available evidence (151, 156), i.e., only 2 studies of insufficient power, there is not enough evidence to assess the efficacy of oxymorphone on outcomes in patients with chronic low back pain. Hence, we conclude the overall strength of evidence as illustrated in Table 3, is poor.

2.7.5 Tapentadol

Three studies evaluated the role of tapentadol in managing osteoarthritis and low back pain (143,148,165). Of the 3 studies, one low quality study evaluated both osteoarthritis and low back pain (165) with positive results, one high quality study evaluated ostearthritis of the knee (143), and one high quality study that evaluated low back pain only (148) showed indeterminate results.

2.7.5.1 Strength of Evidence

Based on the grading of overall strength of evidence as illustrated in Table 3, evidence is poor for tapentadol in managing osteoarthritis and chronic low back pain, with one low quality study being positive with weak evidence (165) and 2 high quality studies being indeterminate (143,148).

2.7.6 Fentanyl

Fentanyl was assessed in only one low quality, randomized, parallel group trial evaluating low back pain (144). Results of this study were indeterminate.

2.7.6.1 Strength of Evidence

Based on grading for overall strength of evidence as illustrated in Table 3, the evidence is poor for fentanyl in managing low back pain with one low quality, parallel group, randomized trial, with indeterminate evidence (144).

2.7.7 Hydromorphone

One low quality, randomized, comparative trial evaluated hydromorphone comparing it with oxycodone in managing chronic pain (146).

2.7.7.1 Strength of Evidence

Based on grading for overall strength of evidence as illustrated in Table 3, the evidence was poor for hydromorphone for managing chronic pain with one low quality comparative trial showing indeterminate evidence (146).

2.7.8 Buprenorphine

One moderate quality, open-label, parallel group randomized trial evaluated transdermal buprenorphine with tramadol in managing osteoarthritis of the hip and knee (155) with indeterminate results.

2.7.8.1 Strength of Evidence

Based on grading for overall strength of evidence as illustrated in Table 3, the evidence was poor for transdermal buprenorphine for managing ostearthritis based upon a single moderate quality, randomized, comparative trial (155).

3.0 Discussion

In this systematic review, the efficacy of opioids (transdermal fentanyl and buprenorphine, oral morphine, tramadol, oxycodone, oxymorphone, tapentadol, and hydromorphone) was evaluated in patients

with multiple pain conditions including chronic pain, low back pain, osteoarthritis, and diabetic neuropathy. The results showed fair evidence for administration of tramadol in osteoarthritis of multiple joints, and knee osteoarthritis. However, for all other agents, including tramadol, in all conditions, the evidence was very weak or negative leading to the conclusion of poor evidence.

This systematic review evaluated only randomized trials with a minimum 12-week follow-up, meeting the inclusion criteria, as well as methodologic quality assessment criteria. Thus, the results of the efficacy evaluation might be somewhat different than previous systematic reviews and guideline syntheses, leading to differences in conclusions.

Tramadol was assessed in 6 randomized trials (145, 147,150,155,158,163) and of these, 4 were placebo controlled (145,147,150,163), one was comparative (158) and one a parallel group trial (155). Among the studies evaluating the role of tramadol in osteoarthritis of multiple joints, of the 2 placebo controlled trials (147,150), one was positive and the second one was indeterminate. The third parallel-group trial (155) was also indeterminate. All the authors concluded that tramadol provided statistically and clinically significant improvement in pain relief. These studies also concluded that tramadol provided in divided doses or as once daily extended release was well tolerated and effective; however, the results showed borderline results and significant withdrawals. Burch et al (147) showed weak results, but a significant proportion of patients showed a 4-point change in Numeric Rating Scale (NRS) with withdrawals of 32% in the treatment group. This was the only study with a weak but positive conclusion by the authors of the systematic review. The other 2 studies (150,155), one placebo controlled and the second one a parallel group, showed results which were indeterminate. Gana et al (150) showed a positive change with less than 2 points, whereas Karlsson and Berggren (155) also showed a change of approximately 2 points.

In evaluation of the role of tramadol in osteoarthritis of the knee, 2 studies (145,158) were included with one placebo controlled trial (145) and the second one a comparative trial (158). Even though the authors concluded in both studies that tramadol was an effective modality for osteoarthritis of the knee, the mean percentage change from baseline was 45% for tramadol and 25% for placebo (145), whereas in the second study by Mongin et al (158), 73% of the patients in the study experienced no pain or mild pain immediately prior to taking the morning dose of medication and had transient and non-serious side effects. Thus, the comparative evaluation (158) was considered as a positive trial and the placebo controlled trial (145) was indeterminate.

The sole study of low back pain (163) was a placebo controlled trial with indeterminate results. The authors concluded that among patients tolerating and obtaining pain relief from tramadol, it provided good pain relief compared to the placebo; however, patients in the tramadol group as well as the placebo group obtained significant relief. The differences between the reduction of pain with placebo versus tramadol were not substantially higher.

Consequently, even though tramadol is presented to show fair evidence, it is weak.

Oxycodone, one of the most commonly used drugs, was evaluated for its role in managing chronic pain of various types in 10 studies (143,146,148,153,154,157, 159,162,164,165). However, only one high quality placebo-controlled trial (153) and a low quality comparative trial (165) provided positive evidence. In evaluation of oxycodone, there were 4 studies evaluating low back pain (148,154,164,165). One comparative study with low methodologic quality was positive (165). Two placebo controlled trials (148,164), both with high quality, were indeterminate, one open-label study with low quality (154) was negative.

In evaluation of chronic pain, all 3 trials met inclusion criteria (146,159,162). One placebo-controlled with high methodologic quality criteria (162), and 2 comparative trials with low methodologic quality assessment criteria (146,159), were indeterminate.

For osteoarthritis, of the 3 studies (143,157,165), 2 were placebo-controlled and high quality (143,157) and one was a comparative trial with low methodologic quality (165) judged to be positive, whereas of the 2 high quality placebo-controlled trials, one was indeterminate (143) and the second one was negative (157). The one single trial evaluating diabetic neuropathy, which was placebo-controlled with high methodologic quality (153), was positive.

Consequently, based on the above synthesis of evidence, on balance most authors concluded that either oxycodone was effective or safer than other drugs compared, even though the effectiveness illustrated was not substantially higher than other groups, with tapentadol and tramadol. The side effects were lower in those drugs than oxycodone. The effect on physical functioning, mood, and activity was also low. There was

a significant proportion of withdrawals in patients receiving oxycodone. Adding naltrexone has been touted as advantageous, even though the evidence is indeterminate. Consequently, despite its extensive use and the large number of studies, the evidence was poor for low back and chronic pain, osteoarthritis, and diabetic neuropathy, based on either negative, indeterminate, or very weak positive evidence.

It was surprising that morphine was evaluated in only 4 trials that met the inclusion criteria (144,149,154,159) and only one of them was of high quality (149). Of the 2 low quality studies evaluating low back pain, one was negative (154) and the second one was indeterminate (144), whereas for chronic pain, both studies were indeterminate, with one low quality comparative trial (159) and the second one a high quality comparative trial (149).

Consequently, the administration of morphine for multiple conditions showed a lack of significant evidence.

Oxymorphone, an agent which is not commonly used, was evaluated in 2 studies (151,156) for low back pain yielding poor evidence. One placebo controlled trial, methodologically of high quality, showed positive results (151); however, these results were weak. An improvement was seen of approximately 40% in pain scores; however, rescue medication was provided to the majority of the patients. The second study (156) reported 50% or greater reduction in average pain intensity in 86% of the patients receiving oxymorphone. However, 55% of the patients in the placebo group also obtained 50% pain relief. Both studies used an enrichment enrollment protocol with a high rate of responders; also, break through oxymorphone immediate release was available for all patients. These studies were inadequately powered due to high drop out rates and failure to meet the number of participants needed to power the study.

Tapentadol, a relatively new drug, and most commonly used in acute pain, has been studied for managing chronic pain of osteoarthritis and low back in 3 randomized trials (143,148,165). Of the 3 studies evaluating tapentadol, 2 scored high on methodologic quality assessment (143,148), whereas the third study was comparative with low methodologic quality assessment (165). Both placebo controlled trials (143,148), one evaluating osteoarthritis (143) and one evaluating low back pain (148), even though methodologically of high quality, provided indeterminate evidence with only 32% of the patients receiving greater than 50% pain relief for osteoarthritis (143). One comparative evaluation with low methodologic quality showed positive results (165). Thus, even though tapentadol at the present time has poor evidence, it appears that this new drug may have potential, similar to effects as other opioids, and with fewer side effects.

Allan et al (144) compared transdermal fentanyl with sustained release morphine. They concluded that transdermal fentanyl and sustained release morphine both provided excellent pain relief, but morphine was associated with more constipation. Even though results appear to be positive, both groups showed high withdrawal rates and high adverse events with significant improvement at a 25 mm level compared to baseline. The study also showed that there was quality of life function improvement with physical health, but none with mental health. Consequently, though commonly used, transdermal fentanyl appears to lack evidence in randomized trials.

Hydromorphone was evaluated in only one study of low methodologic quality (146). Once daily hydromorphone was compared with sustained release oxycodone in participants with chronic pain with or without low back pain. It was considered to be safe and well tolerated for chronic pain, and as being as efficacious as twice-daily sustained-release oxycodone. However, less than 50% of the patients completed the study, thereby failing to meet the sample size criteria.

Consequently, there is no significant evidence for hydromorphone based on the low quality comparative trial (146) with indeterminate evidence.

Buprenorphine, not commonly used in the United States, has been studied for its role in managing osteoarthritis of the hip and knee, applied transdermally. In a parallel group, comparative trial (155), transdermal buprenorphine was shown to be effective and well-tolerated with analgesic effects similar to tramadol. However, the decrease in the pain scores, though similar in both groups, was only approximately 2 points.

Consequently, the evidence for buprenorphine continues to be poor because of a paucity of randomized trials.

Chou et al (8,166-168) recommended that safe and effective chronic opioid therapy for chronic non-cancer pain requires clinical skills and knowledge in both the principles of opioid prescribing, and in the assessment and management of risks associated with opioid abuse, addiction, and diversion. This recommendation was based on their conclusion of the systematic review that evidence was limited in many areas related to us-

ing opioids for chronic non-cancer pain. These recommendations are considered by some as biased considering the strong negative recommendations they have provided for other guidelines (8,166-176). It appears that guideline preparers have a different mindset with a priori decisions in favor of opioids and rehabilitation techniques compared with interventional techniques in assessment of pain relief, validity criteria, and outcomes assessment (173-183). These recommendations by Chou et al (8,166-168) and other guideline preparers, (177-183) are in contrast to evidence-based medicine (EBM) and comparative effectiveness research principles, guidelines, and applications (32-34,45,166-189). Further, there is evolving evidence for the effectiveness of interventional techniques in multiple areas which has been to some extent ignored by the guideline developers; they have a major focus on lack of evidence, overuse and abuse, even though additional evidence has been rapidly evolving (32-34,169-230).

Noble et al (7) concluded that many patients discontinue long-term oral opioid therapy due to adverse events or insufficient pain relief. They also concluded that there was weak evidence suggesting that patients who continue taking opioids long-term experience clinically significant pain relief. Further, they concluded that whether a patient's quality of life or function improves is inconclusive.

Noble et al (7) expressed significant concern that many participants in the included studies, particularly those treated with orally administered opioids, were so dissatisfied with adverse events or insufficient pain relief that they discontinued participating in the studies. Generally, there is no data provided on these participants after they dropped out of the studies, which makes it impossible to say whether they continued opioid therapy under different protocols or not. We found similar results. Noble et al (7) concluded that for participants able to continue opioids in the studies, evidence (albeit weak) suggests that, for all analyzed models of administration, their pain scores were lower on average than before therapy began, and that this relief could be maintained long-term for over 6 months. However, this data continues to be limited in this systematic review. While all the authors concluded that there was significant improvement in their pain scores, as well as functional status improvement, the application of strict criteria of a 40% decrease in pain scores or 50% improvement and significant improvement of functional status of 30% to 40% were rarely encountered.

Non-inclusion of observational studies with long-term follow-up may have affected our conclusions. However, with the emerging principles of evidence-based medicine, for this particular review, we decided to analyze the evidence based on randomized trials only. Further, it was our intent to evaluate short- and long-term relief with long-term being over 6 months. There were 3 trials which studied over 6 months (144,154,165). The present systematic review has multiple limitations based on the paucity of randomized placebo-controlled evidence for various types of opioids and multiple conditions they are treated with. Consideration of the observational data may be essential in these circumstances (1-4,7,15-18,231).

Future well-designed research is essential to improve the evidence for opioid therapy in chronic non-cancer pain. Clearly, it is important not only that we seek the development of a comprehensive evidence base regarding the effectiveness of opioid pharmacotherapy, but also effective guidance for both prescribing clinicians and governmental policy-makers (232). Clinicians and researchers are called upon to meet the challenge of addressing opioid therapy in a purposeful and coherent manner, rather than continuing to follow the uncoordinated process that has created the present situation. Researchers continue to face a transitional research challenge: problems in clinical practice and at the policy level must guide relevant research at multiple scientific levels including basic science (232).

4.0 Conclusion

This systematic review of randomized trials for multiple opioids utilized for managing various chronic pain conditions, showed fair evidence for tramadol in managing osteoarthritis. For all other conditions and all other drugs including tramadol, the evidence was poor based on either weak positive evidence or indeterminate or negative evidence.

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