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, dependence, 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
E ven 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
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
   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, dihydromorphone, 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.*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Operationalization of Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Was the method of randomization adequate?</td>
<td>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.</td>
<td>Yes/No/Don’t Know</td>
</tr>
<tr>
<td>B. Was the treatment allocation concealed?</td>
<td>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.</td>
<td>Yes/No/Don’t Know</td>
</tr>
<tr>
<td>C. Were the groups similar at baseline regarding the most important prognostic factors?</td>
<td>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).</td>
<td>Yes/No/Don’t Know</td>
</tr>
<tr>
<td>D. Was the patient blinded to the intervention?</td>
<td>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 &quot;yes&quot; for patient, care provider and outcome assessor (unless it is clear that one of these is not blinded)</td>
<td>Yes/No/Don’t Know</td>
</tr>
<tr>
<td>E. Was the care provider blinded to the intervention?</td>
<td>Cointerventions should either be avoided in the trial design or similar between the index and control groups. Code &quot;yes&quot; 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.</td>
<td>Yes/No/Don’t Know</td>
</tr>
<tr>
<td>F. Was the outcome assessor blinded to the intervention?</td>
<td>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.</td>
<td>Yes/No/Don’t Know</td>
</tr>
<tr>
<td>G. Were cointerventions avoided or similar?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. Was the compliance acceptable in all groups?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. Was the drop-out rate described and acceptable? ≤15% drop out rate is acceptable.</td>
<td>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.</td>
<td>Yes/No/Don’t Know</td>
</tr>
<tr>
<td>J. Was the timing of the outcome assessment in all groups similar?</td>
<td>Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.</td>
<td>Yes/No/Don’t Know</td>
</tr>
<tr>
<td>K. Did the analysis include an intention-to-treat analysis? “Yes” if less than 5% of no-treatment excluded.</td>
<td>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.</td>
<td>Yes/No/Don’t Know</td>
</tr>
</tbody>
</table>

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 2. Jadad quality rating for primary studies*.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Scoring</th>
<th>Operationalization of Criteria</th>
<th>Criteria Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization: Was the study described as randomized (use of words such as randomly, random, and randomization)?</td>
<td>Yes = 1 No = 0</td>
<td>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.)</td>
<td>0 - 2</td>
</tr>
<tr>
<td>Blinding: Was the study described as double-blind?</td>
<td>Yes = 1 No = 0</td>
<td>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)</td>
<td>0 - 2</td>
</tr>
<tr>
<td>Withdrawals and drop-outs: Was there a description of withdrawals and dropouts?</td>
<td>Yes = 1 No = 0</td>
<td>Only 0 or 1 possible.</td>
<td>0 or 1</td>
</tr>
</tbody>
</table>

OVERALL SCORE = 1 – 5 (max score is 5)


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).
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 3 were considered as high 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).
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.

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

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<th>Follow-up Period</th>
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<td>Max et al 1988 (102)</td>
<td>Codeine</td>
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Table 5. Assessment of trials for inclusion criteria.

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<th>Pain Condition(s)</th>
<th>Duration of Chronic Pain</th>
<th>Previous Pharmacotherapy</th>
<th>Follow-up Period</th>
<th>Pain Relief</th>
<th>Outcome Measures</th>
<th>Adverse Events</th>
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Table 6. Methodologic quality assessment of randomized trials utilizing Cochrane review criteria.

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<th>Care Provider Blinded</th>
<th>Outcome Assessor Blinded</th>
<th>Co-interventions Avoided or Similar</th>
<th>Compliance Acceptable in All Groups</th>
<th>Drop-out Rate Described and Acceptable</th>
<th>Timing of Outcome Assessment in All Groups Similar</th>
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<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>11/11</td>
</tr>
<tr>
<td>Nicholson et al 2006 (159)</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
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<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>5/11</td>
</tr>
<tr>
<td>Rauck et al 2007 (160)</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>3/11</td>
</tr>
<tr>
<td>Vondrackova et al 2008 (162)</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>3/11</td>
</tr>
<tr>
<td>Vorsanger et al 2008 (163)</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>8/11</td>
</tr>
<tr>
<td>Webster et al 2006 (164)</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>9/11</td>
</tr>
<tr>
<td>Wild et al 2010 (165)</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>5/11</td>
</tr>
</tbody>
</table>

DK = Don't know
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>
<thead>
<tr>
<th>Author, Year, Title</th>
<th>Randomization</th>
<th>Blinding</th>
<th>Reporting of Withdrawals</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afilalo et al 2010 (143)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5/5</td>
</tr>
<tr>
<td>Allan et al 2005 (144)</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3/5</td>
</tr>
<tr>
<td>Babul et al 2004 (145)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5/5</td>
</tr>
<tr>
<td>Binsfeld et al 2010 (146)</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3/5</td>
</tr>
<tr>
<td>Burch et al 2007 (147)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5/5</td>
</tr>
<tr>
<td>Buynak et al 2010 (148)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5/5</td>
</tr>
<tr>
<td>Galer et al 2005 (149)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5/5</td>
</tr>
<tr>
<td>Gana et al 2006 (150)</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4/5</td>
</tr>
<tr>
<td>Hale et al 2007 (151)</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>4/5</td>
</tr>
<tr>
<td>Hanna et al 2008 (153)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5/5</td>
</tr>
<tr>
<td>Jamison et al 1998 (154)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2/5</td>
</tr>
<tr>
<td>Karlsson and Berggren 2009 (155)</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3/5</td>
</tr>
<tr>
<td>Katz et al 2007 (156)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5/5</td>
</tr>
<tr>
<td>Markenson et al 2005 (157)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5/5</td>
</tr>
<tr>
<td>Mongin et al 2004 (158)</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4/5</td>
</tr>
<tr>
<td>Nicholson et al 2006 (159)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2/5</td>
</tr>
<tr>
<td>Rauck et al 2007 (160)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2/5</td>
</tr>
<tr>
<td>Vondrakova et al 2008 (162)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5/5</td>
</tr>
<tr>
<td>Vorsanger et al 2008 (163)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5/5</td>
</tr>
<tr>
<td>Webster et al 2006 (164)</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4/5</td>
</tr>
<tr>
<td>Wild et al 2010 (165)</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3/5</td>
</tr>
</tbody>
</table>
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. 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.

Mean percent change from baseline to week 12 of the 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 prolonged tension phase showed reduction of pain scores from 6.8 and 6.9 to 3.9 and 4.1.

Transdermal fentanyl: 50 mcg or night.

Fentanyl vs. Morphine: 0-100 VAS: 56 vs. 56.

Pain score (mean, 0-100 VAS): 56 vs. 56.

Fentanyl vs. Morphine: 57% vs. 3.3%.

Pain score (mean, 0-100 VAS): 56 vs. 56.

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Fentanyl vs. Morphine: 57% vs. 3.3%.

Pain score (mean, 0-100 VAS): 56 vs. 56.

Fentanyl vs. Morphine: 0-100 VAS: 56 vs. 56.

Pain score (mean, 0-100 VAS): 56 vs. 56.
Table 8 (cont). Characteristics of randomized trials included in analysis.

<table>
<thead>
<tr>
<th>Manuscript Author(s) Study Design Condition Studied</th>
<th>Cochrane and Jadad Scores</th>
<th>Number of Patients and Duration of Follow-up</th>
<th>Drugs Administered</th>
<th>Outcomes</th>
<th>Proportion of Patients Completing Study (Placebo vs. Treatment Group)</th>
<th>Adverse Events</th>
<th>Authors’ Conclusion(s)</th>
<th>Study Conclusion(s)</th>
<th>Final Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burch et al 2007 (147) Randomized, double-blind, placebo-controlled trial Osteoarthritis</td>
<td>9/11 and 5/5</td>
<td>N=646</td>
<td>Placebo=214</td>
<td>Tramadol=422</td>
<td>Follow-up: 12 weeks</td>
<td>Tramadol Con-</td>
<td>Approximately 59% of the patients in tramadol group had a 4-point improvement in pain vs placebo 47%.</td>
<td>Tramadol=292 of 432 completed the study (68%)</td>
<td>Placebo=143 of 214 completed the study (67%)</td>
</tr>
<tr>
<td>Buynak et al 2010 (148) Randomized, double-blind, placebo and active-controlled trial Chronic low back pain</td>
<td>9/11 and 5/5</td>
<td>N=981</td>
<td>Tapentadol=321</td>
<td>Oxycodone CR=334</td>
<td>Placebo=326</td>
<td>Follow-up: 12 weeks</td>
<td>Tapentadol ER: 100-250 mg twice a day Oxycodeone HCL controlled release: 20-50 mg twice a day</td>
<td>Tapentadol ER and oxycodone CR significantly reduced average pain intensity vs. placebo at week 12 and throughout the maintenance period.</td>
<td>Proportion of patients completing the study: Placebo 152/326 (47%)</td>
</tr>
<tr>
<td>Galer et al 2005 (149) Randomized, double-blind, controlled clinical trial Non-neuropathic pain</td>
<td>10/11 and 5/5</td>
<td>N=828</td>
<td>STUDY A N=327</td>
<td>STUDY B N=308</td>
<td>STUDY C N=193</td>
<td>Follow-up: 12 weeks</td>
<td>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)</td>
<td>The 3 studies (A, B, and C) consistently demonstrated that the addition of methorphan (DM) to morphine (MS) failed to enhance opioid analgesia.</td>
<td>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.</td>
</tr>
<tr>
<td>Gana et al 2006 (150) Randomized, double-blind, placebo-controlled trial Osteoarthritis</td>
<td>8/11 and 4/5</td>
<td>N=1,020</td>
<td>100 mg=203</td>
<td>200 mg=203</td>
<td>300 mg=204</td>
<td>400 mg=205</td>
<td>Placebo=205</td>
<td>Follow-up: 12 weeks</td>
<td>Extended-release tramadol: 100, 200, 300 or 400 mg once daily</td>
</tr>
</tbody>
</table>
### Table 8 (cont). Characteristics of randomized trials included in analysis.

<table>
<thead>
<tr>
<th>Manuscript Author(s)</th>
<th>Study Design Condition Studied</th>
<th>Cochrane and Jadad Scores</th>
<th>Number of Patients and Duration of Follow-up</th>
<th>Drugs Administered</th>
<th>Outcomes</th>
<th>Proportion of Patients Completing Study (Placebo vs. Treatment Group)</th>
<th>Adverse Events</th>
<th>Author’s Conclusion(s)</th>
<th>Study Conclusion(s)</th>
<th>Final Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hale et al 2007 (151)</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>9/11 and 4/5</td>
<td>N=143</td>
<td>OPANA ER: Median, 60 mg; range, 20 to 260 mg</td>
<td>Placebo=73</td>
<td>Follow-up: 12 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low back pain</td>
<td></td>
<td>N=135</td>
<td>OPANA ER: 1200-1800 mg/day</td>
<td>Placebo=70</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N=138</td>
<td>Gabapentin: 10-80 mg/day</td>
<td>Placebo=160</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N=36</td>
<td>Sustained-release morphine + short acting oxycodone</td>
<td>Immediate-release oxycodone + naproxen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N=36</td>
<td>Transdermal buprenorphine patches: 5, 10, 15, 20 mcg/h, up to 2 patches same time</td>
<td>Tramadol doses: 150, 200, 300 and 400 mg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N=338</td>
<td>Placebo=169</td>
<td>Placebo=169</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N=119</td>
<td>All patients completed the first 2 phases of the study. Only one participant dropped out after 7 months.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In the controlled-release oxycodone group, only 56% of patients took twice daily doses, whereas 44% took the medication 3 or 4 times daily. 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. 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.

46% in morphine group and 50% of the patients in the oxycodone group completed the study. At least one adverse event was reported in 80% of the patients.

Drugs

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Condition Studied</th>
<th>Number of Patients and Duration of Follow-up</th>
<th>Proportion of Patients Completing Study (Placebo or Active Control vs. Treatment Group)</th>
<th>Adverse Events</th>
<th>Authors' Conclusion(s)</th>
<th>Study Conclusion(s)</th>
<th>Final Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>Low back pain</td>
<td>10/11 and 5/5 (N=205)</td>
<td>Oxymorphone ER: 39.2 ± 26.4 mg; Placebo: 44 ± 5 mg; Follow-up: 12 weeks</td>
<td>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 group (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).</td>
<td>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. 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.</td>
<td></td>
<td>Positive</td>
</tr>
</tbody>
</table>

Randomized, double-blind, placebo-controlled trial

Osteoarthritis

Patients randomized= 109
Controlled-release oxycodone= 56
Placebo= 51
Follow-up: 13 weeks

Only 20% of the patients in the CR oxycodone treatment group achieved at least 50% pain relief at the end of 90 days vs. 59% of the patients in the placebo group. CR oxycodone= 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.

A substantial proportion of patients failed to complete the study, even in CR oxycodone group.

At least one adverse event: 58% (61/105) vs. 44% (44/100).

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.

At least 70% 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.

At least one adverse event: 58% (61/105) vs. 44% (44/100)

Negative

Randomized, double-blind, placebo-controlled trial

Osteoarthritis

Mongin et al 2004

N=431
Tramadol once daily= 215
Tramadol twice daily= 216
Follow-up: 12 weeks

Tramadol once daily= 182 of 216 completed the study (85%)
Tramadol twice daily= 179 of 216 completed the study (83%)

Adverse events were reported more in tramadol twice daily 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.

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.

At least one adverse event was reported in 80% of the patients.

73% of patients in the study experienced no pain or mild pain immediately prior to taking the morning dose of medication.

Negative

Randomized, double-blind, placebo-controlled trial

Low back pain

Nicholson et al 2006

N=112
Controlled-release oxycodone= 59
Follow-up: 24 weeks

Sustained-release oxycodone twice daily (mean improvement from baseline): 84.7 ± 66.14 (127 mg morphine equivalent)

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
Overall, the pain scores decreased 4.5 at endpoint with at least 40% decrease in both groups, with less constipation in the tapentadol group. Even though all Tapentadol ER 100 to 250 mg twice a day = 87/129 of tramadol ER patients had reductions of over 40%, the difference was not significant among the active treatment groups. The majority of adverse events were mild or moderate in intensity.

Among patients tolerating and obtaining pain relief from tramadol ER treatment for 12 weeks main- tained pain relief more effectively than placebo. 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. 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
Systematic Review of Opioids in Chronic Pain

(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 patients (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 osteoarthritis 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, the 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 osteoarthritis 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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