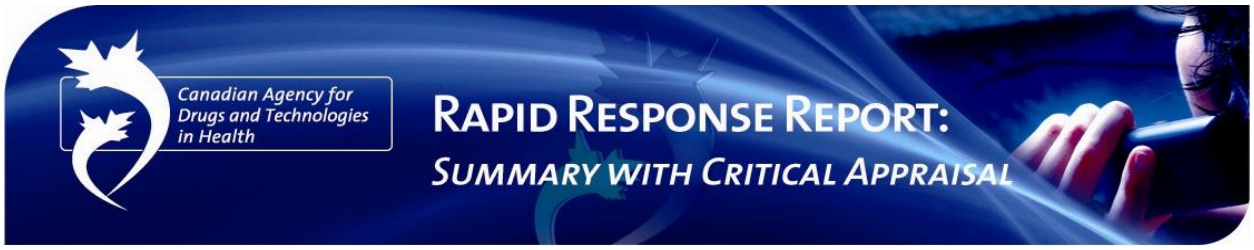

TITLE: Buprenorphine for Chronic Pain: A Review of the Clinical Effectiveness

DATE: 06 January 2017

Buprenorphine is an opioid analgesic available in Canada as transdermal patches and sublingual tablets (tablets also contain naloxone).[1,2] Buprenorphine/naloxone is indicated for substitution treatment in opioid drug dependence in adults whereas transdermal buprenorphine is indicated for the management of pain severe enough to require daily, continuous, long-term opioid treatment. Buprenorphine produces typical opioid agonist effects and in higher doses its agonist effects reach a ceiling and it can act as an antagonist. This property distinguishes it from morphine. It has high affinity for mu opioid receptors but only weakly activates them.[3] For this reason, buprenorphine may be less likely to cause respiratory depression than full opioid agonists such as fentanyl or morphine.[4] When buprenorphine is given concomitantly with other opioids, it antagonizes the effects of the other opioids by displacing them from the mu receptors. This can lead to withdrawal syndrome if buprenorphine is added to another opioid. If buprenorphine is withdrawn while the dose of the other opioid is being increased, it can increase the risk of overdose.[3]

The role of opioids in chronic cancer pain has been well established but their role and the relative effectiveness of opioids such as buprenorphine in the context of chronic non-cancer pain is unclear.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of buprenorphine for the treatment of adults with chronic pain?

2. What is the comparative clinical effectiveness of buprenorphine doses greater than 24 mg per day compared with daily doses of 24 mg or less?

3. What is the clinical effectiveness of buprenorphine when tapering opioid doses for adults with chronic pain?

KEY FINDINGS

Buprenorphine results in modest reductions in pain in adults with chronic non-cancer pain, relative to placebo. There is no evidence that other opioids are superior to buprenorphine for treating chronic non-cancer pain.

No relevant evidence was identified regarding the use of buprenorphine at doses greater than 24 mg per day, or when tapering opioid doses for adults with chronic pain.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including Medline, Embase, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and December 1, 2016.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1. Rapid Response reports are organized so that the evidence for each research question is presented separately.

Table 1: Selection Criteria

Population	Adults with chronic non-cancer pain
Intervention	Q1, Q3: Buprenorphine alone or in combination with naloxone (e.g. Suboxone, BuTrans); Q2: Buprenorphine >24mg daily;
Comparator	Q1: long-acting opioids (morphine, hydromorphone, oxycodone, fentanyl); Q2: Buprenorphine ≤ 24 mg daily; Q3: no buprenorphine
Outcomes	Clinical effectiveness (e.g. pain reduction), safety and harms (e.g. respiratory depression, other adverse events, abuse, misuse, withdrawal symptoms), successful reduction of opioid use
Study Designs	Health Technology Assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies with comparator groups (for safety only)

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, were included in a selected systematic review, or if they included

buprenorphine for different types of pain but the analyses did not permit evaluation of the effects of buprenorphine for non-cancer pain, or were published prior to 2011.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[5] Randomized studies were critically appraised using the Downs and Black instrument.[6] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 370 citations were identified in the literature search. Following screening of titles and abstracts, 322 citations were excluded and 48 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of the potentially relevant articles, 30 publications were excluded for various reasons, while 18 publications summarizing four systematic reviews and nine RCTs, met the inclusion criteria and were included in this report (some studies were reported analyses in more than one publication). One excluded Cochrane systematic review[7] searched for evidence on the use of buprenorphine for neuropathic pain but did not identify any relevant studies for inclusion. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Study Design

Four relevant systematic reviews including transdermal buprenorphine RCTs were identified,[8-12] including two Cochrane reviews.[8-10] One systematic review used network meta-analysis methods[12] and one used meta-analysis to analyze the buprenorphine data.[8] The number of relevant buprenorphine trials in the systematic reviews was low (range 1-4 trials). The dates for the literature searches of the systematic reviews were: 1966-2008,[12] 1966-2010,[11] "up to 2012,"[8] and 1966-2012."[9,10]

Six of the RCTs identified were double-blind,[13-22] and three were open label.[23-25] Two studies used a non-inferiority design.[16,25] Four studies used an enrichment design, which excluded patients who were non-responsive and/or intolerant to buprenorphine.[13,14,17-22]

Country of Origin

The systematic reviews were authored by groups from the USA,[11] Europe/Canada,[8,12] and USA/Canada.[9,10]

Of the nine RCTs identified, four were from groups in the USA,[13,14,17-22] two from Australia,[15,24] one from the UK,[25] one from China,[16] and one from Italy.[23]

Patient Population

Two systematic reviews included trials in patients with osteoarthritis,[8,11] one in patients with chronic back pain,[9,10] and one in patients with non-cancer pain.[12]

Five RCTs included patients with lower back pain,[13,14,17-22,24] one with musculoskeletal pain,[16] one with AIDS and neuropathic pain,[23] one with non-malignant pain,[24] and one with osteoarthritis.[25] One study was performed in patients older than 60 years of age.[25] Three studies enrolled only opioid naïve patients[13,15,17-20,24] or only opioid experienced patients.[14,21-23]

Interventions and Comparators
Trials in all four systematic reviews examined studies comparing transdermal buprenorphine (dose range 5-40 mcg/hour) to either placebo,[8-10] tramadol,[11] or morphine.[12]

Two RCTs used buccal buprenorphine[13,14] and the others used transdermal buprenorphine.[15-25] Comparators used in the trials included placebo,[13-15,17-20] tramadol,[16] transdermal fentanyl,[23,24] codeine,[25] and oxycodone.[21,22]

Outcomes

All systematic reviews and RCTs included measures of pain. Several RCTs also measured impact of study medications on sleep,[13,15-22,24,25] use of rescue medication,[13,15-25] quality of life,[17-22,25] and disability.[13,14,17-22]

Summary of Critical Appraisal

All systematic reviews included a comprehensive literature search and the quality of the systematic reviews was moderate to high. Three of the systematic reviews included duplicate reviewers for data extraction.[8,9,11] Quality assessment of included trials was performed by the authors of all systematic reviews, but it was not always clear how quality of individual trials was accounted for in their conclusions.[12] The Cochrane review in which data were pooled from the buprenorphine trials, used appropriate methods for pooling.[8] The network meta-analysis did not provide enough information about their methods to assess the appropriateness of their approach.[12]

All RCTs except two[23,24] were sponsored by pharmaceutical companies that manufacturer buprenorphine products and/or included authors who were employees of those companies. The two studies in which there was no stated conflict of interest had clear objectives (to compare transdermal buprenorphine with transdermal fentanyl), but were poorly reported and designed. These two studies were low quality because they were open label and were not adequately designed to test non-inferiority or superiority.[23,24] There was one additional open-label RCT in which transdermal buprenorphine was compared to codeine. The risk of bias was higher in this study because of lack of blinding and a high rate of patient withdrawal (45%).[25] The internal validity of several RCTs was compromised due to the patient dropout rates >30%[15,17,21,25] and/or differential dropout rates in the buprenorphine treatment group relative to the comparator group.[14-17,24]The generalizability of the results of some studies is limited because these studies only randomized patients who demonstrated previous response and that they could tolerate treatment with buprenorphine.[13,14,17,21]

Summary of Findings

1. *What is the clinical effectiveness and safety of buprenorphine for the treatment of adults with chronic pain?*

Buprenorphine versus tramadol

One systematic review summarized a single, non-inferiority, 12-week,open label RCT (N=135) which was rated poor to moderate quality and compared transdermal buprenorphine to tramadol in patients with osteoarthritis of the hip and/or knee.[11] The mean changes in pain scores were similar between the buprenorphine and tramadol groups. Adverse event rates were (transdermal buprenorphine versus tramadol): nausea: 30%/25%; constipation: 19%/8%; dizziness: 16%/5%; fatigue: 13%/19%; pain: 15% /12%. Given the quality of the study, the authors of the systematic review considered that the results of the study were "indeterminate."[11]

Buprenorphine versus transdermal fentanyl

Two small, poor quality, open-label RCTs evaluated the relative effects of transdermal buprenorphine with transdermal fentanyl in 40 AIDS patients with neuropathic pain[23] and 46 patients with nonmalignant pain.[24] The mean change in pain scores were similar in buprenorphine and fentanyl groups, but the trials did not appear to be designed to test non-inferiority or superiority between the treatment groups. No meaningful conclusions can be made regarding relative efficacy or harms of these two drugs based on these trials.

Buprenorphine versus codeine

One moderate quality, open label, non-inferiority RCT evaluated the relative effects of transdermal buprenorphine and oral codeine in patients with osteoarthritis.[25] Buprenorphine plus paracetamol was non-inferior to codeine plus paracetamol based on mean pain score after 12 weeks. The investigators measured several sleep-related outcomes including sleep adequacy, number of hours slept, snoring, shortness of breath and headache. While the authors did not perform statistical analyses on the sleep results, there was no clear advantage for either treatment after 12 weeks of treatment. The rates of the most commonly reported adverse events were (transdermal buprenorphine versus codeine): constipation: 26%/32%; nausea: 40%/25%; vomiting: 11%/8%; erythema: 27%/0%; pruritus: 17%/0%; dizziness: 14%/6%.

Buprenorphine versus oxycodone

One double blind RCT with three treatment groups, evaluated the relative effects of transdermal buprenorphine (5 mcg/hour or 20 mcg/hour) with immediate release oxycodone. The study was not designed to make comparisons between buprenorphine 20 mcg/hr and oxycodone.[21] It was designed to compared buprenorphine 5mcg/hr with buprenorphine 20mcg/hr. The comparison between the buprenorphine 5mcg/hr and oxycodone treatment groups was considered a secondary analysis used for assay sensitivity.[21] Statistically significant differences favouring the buprenorphine 20 mcg/hour group compared to buprenorphine 5 mcg/hour were observed for average pain, SF-36 domains of physical health, bodily pain and overall physical (all $P < 0.01$), but there were no statistically significant differences between buprenorphine groups for physical functioning, general health, vitality, social functioning, emotional role or mental health.[22] The final pain scores appeared similar in the buprenorphine 20 mcg/hour and oxycodone groups, but the trial was not powered to detect differences for this comparison.

Buprenorphine versus morphine

One network meta-analysis was identified that included three buprenorphine trials in patients with back pain.[9,10] A statistically significant difference was found in the network meta-analysis for the comparison of morphine to buprenorphine in studies of non-cancer pain, favouring morphine (weighted mean difference: 8.0, 95% confidence interval [CI]: 0.6 to 15.4; N=4963 patients in 19 studies).

Buprenorphine versus placebo

Two systematic reviews[8,9] and four RCTs[13-15,17] compared either transdermal buprenorphine[8,9,15,17] or buccal buprenorphine[13,14] to placebo. In the systematic reviews and the randomized trials, the results for mean pain scores, or mean change in pain scores from baseline favoured buprenorphine over placebo and the results were consistently statistically significant. Improvements in pain scores of 30% or greater have been suggested as clinically meaningful.[17,26] The results for the outcome of proportion of patients with ≥30% decrease in pain score favoured placebo in one systematic review[9] and there was no statistically significant differences observed for this outcome in three RCTs.[9,13,15,17] The two systematic reviews found statistically significant improvements in some measures of pain for buprenorphine compared to placebo, but the results for measures of function did not consistently favour buprenorphine over placebo. One of the systematic reviews found that adverse events and withdrawals due to adverse events occurred more frequently in the placebo group, relative to the buprenorphine group (P<0.01 for both).[8] All four placebo-controlled RCTs reported some data on adverse events.[13-15,17] The most common adverse events in patients taking buprenorphine were nausea, constipation, vomiting, dizziness, headache, somnolence and application site reactions with transdermal buprenorphine.[13-15,17] Rates of adverse effects in one good quality, 12-week,double-blind placebo-controlled RCT[17] were (transdermal buprenorphine versus placebo): nausea (13% vs 11%), vomiting (4% vs 2%), constipation (4% vs 1%), administration site conditions (17% vs 16%), dizziness (4% vs 1%), headache (5% vs 5%), somnolence (2% vs 2%). Improvements in a measure of disability were seen favouring buprenorphine in one trial,[13] but were not observed in a second trial.[14] Likewise, improvements in measures of sleep favoured buprenorphine in one RCT,[17] but was not corroborated by the results of another trial.[13]

2. *What is the comparative clinical effectiveness of buprenorphine doses greater than 24 mg per day compared with daily doses of 24 mg or less?*

No relevant literature was identified that evaluated the comparative clinical effectiveness of oral buprenorphine at doses greater than 24 mg per day compared with daily doses of 24 mg or less.

3. *What is the clinical effectiveness of buprenorphine when tapering opioid doses for adults with chronic pain?*

No relevant literature was identified that evaluated the effectiveness of buprenorphine when tapering opioid doses for adults with chronic pain.

Limitations

Given the varied nature of chronic, non-cancer pain, the generalizability of the individual studies may be limited to the pain etiologies and the specific study populations (e.g. osteoarthritis, low

back pain, opioid naïve, opioid experienced, buprenorphine prior responders). For example, the results of the study in AIDS patients with neuropathic pain may not be generalizable to patients with osteoarthritic pain.

Bias has been observed in published findings of some industry sponsored research and while most of the RCTs identified in this report were of at least moderate quality, seven of the nine studies were sponsored by manufacturers of buprenorphine products.[27-29]

There were no systematic reviews that exclusively investigated the role of buprenorphine in non-cancer chronic pain. The systematic reviews were of limited usefulness because they did not include many buprenorphine trials in patients with chronic non-cancer pain. The buprenorphine trial analyses tended to form minor parts of the systematic reviews. In addition, the most recent systematic review was published in 2014, and therefore, there is a need to update the systematic reviews and perform network meta-analyses including the more recent studies.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The available evidence indicates that transdermal buprenorphine results in modest improvements in pain relative to placebo in patients with several types of non-cancer chronic pain. The improvements in pain relative to placebo did not meet a suggested standard for minimum clinical significance (>30% pain reduction) in some studies, but there was evidence from several studies that buprenorphine improved some domains of quality of life relative to placebo.

While one systematic review suggested that buprenorphine was inferior to morphine, the overall evidence does not suggest that other opioids are superior to buprenorphine with respect to pain reduction in chronic non-cancer pain. This needs to be investigated in further trials and high quality network meta-analyses that incorporate the most recent buprenorphine data.

While claims have been made that buprenorphine is associated with a lower risk of adverse events such as constipation, cognitive dysfunction and respiratory depression,[30] we did not identify any high quality evidence to support these claims in the context of chronic non-cancer pain. The available evidence is insufficient to assess the relative harms of buprenorphine to other opioids in patients with chronic non-cancer pain.

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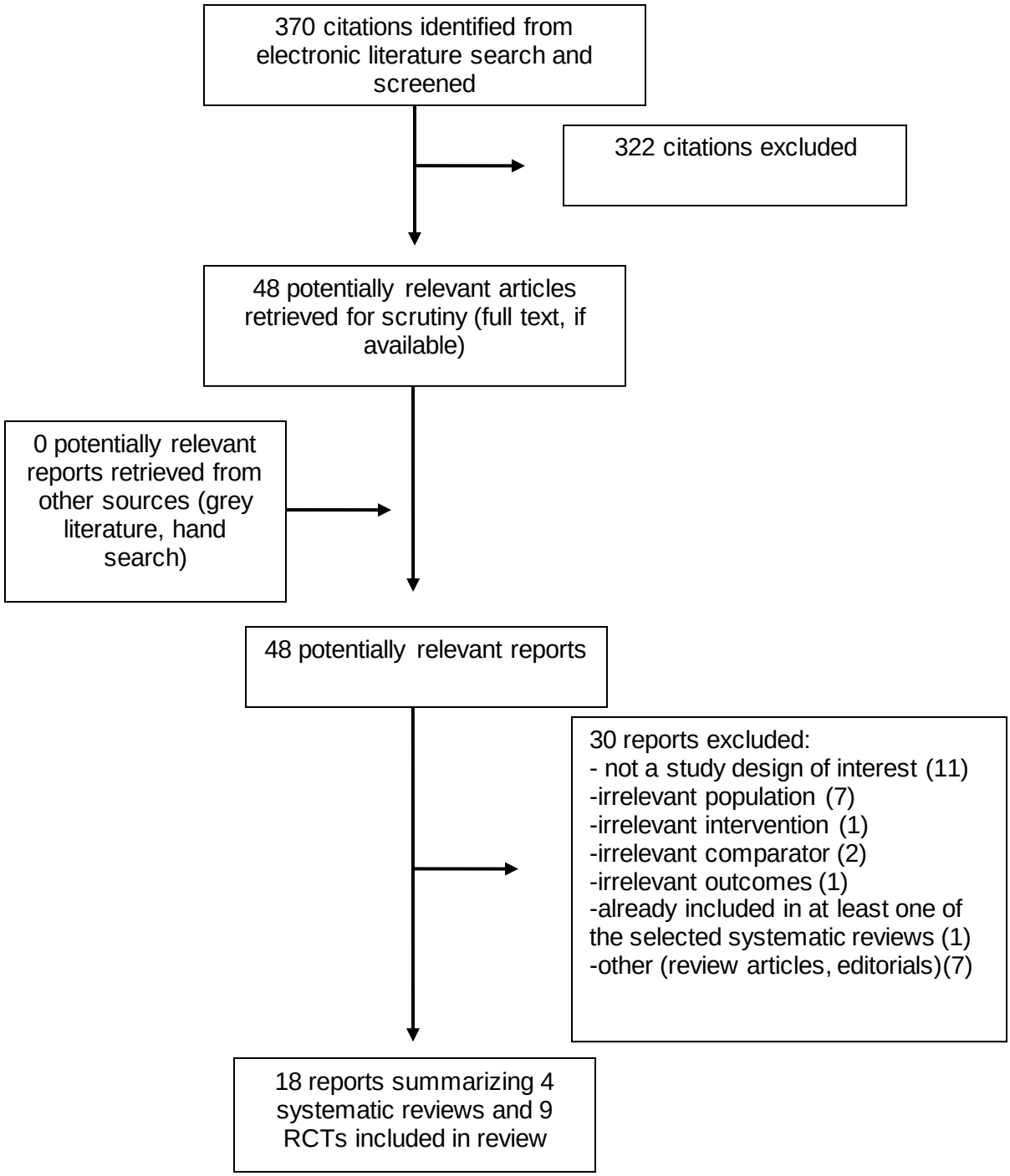
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
da Costa 2014 (Cochrane)[8]	Of 22 RCTs (N=8275), 4 used buprenorphine	4 trials with 1401 patients with OA of knee or hip	Buprenorphine transdermal (5-20 mcg/hr)	Placebo or no treatment	Pain, AE, WDAE, Function
Chaparro 2014 (Cochrane)[9,10]	Of 15 RCTs (N=5540), 2 used buprenorphine	2 trials with 653 patients with chronic low back pain	Buprenorphine transdermal (5-40 mcg/hr)	Placebo	Pain, AE, disability
Manchikanti 2011 (USA)[11]	Of 21 RCTs, 1 used buprenorphine	1 trial with 135 patients with OA of knee or hip	Buprenorphine transdermal (5-20 mcg/hr)	Tramadol (150-400 mg/day)	Pain, AE, patient preference,
Bekkering 2011 (UK)[12]	Of 56 included RCTs, 3 used buprenorphine in non-cancer pain	3 trials with 781 patients with non-cancer pain	Buprenorphine transdermal 5-20 mcg/hr	Morphine (via network meta-analysis)	Pain intensity

AE = adverse event; O/A = osteoarthritis; RCT = randomized controlled trial; WDAE = withdrawals due to adverse events

Table A2: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
Rauck 2016[13] USA	Double blind RCT, excluded non-responders, 12 weeks	462 adults with moderate to severe chronic lower back pain. Opioid naive.	Buprenorphine buccal film 150-450 mcg every 12 hours	Placebo	Pain, rescue medication, PGIC, RMDQ, AE, MOS
Gimbel 2016[14] USA	Double blind RCT, excluded non-responders, 12 weeks	511 adults with moderate to severe chronic lower back pain. Opioid experienced.	Buprenorphine buccal film 150-900 mcg every 12 hours	Placebo	Pain, PGIC, RMDQ, AE
Simpson 2016[15] Australia	Double blind RCT, 12 weeks	186 patients with diabetic peripheral neuropathic pain, excluded prior opioid users	Transdermal buprenorphine 5-40 mcg/hr titrated to effect	Placebo	Pain, use of rescue medication ,DSIS, SF-MPQ, PGIC, CGIC
Leng 2015[16] China	Double blind RCT, 8 weeks, non-inferiority	280 adults with moderate to severe musculo-skeletal pain	Transdermal buprenorphine 5-20 mcg/hr + placebo	Placebo + sustained release tramadol 200-400mg/day	Pain, sleep disturbance, use of rescue medication
Canneti 2013[23] Italy	Open label RCT, 60 days	40 advanced AIDS patients with severe chronic neuropathic pain. Opioid experienced	Transdermal buprenorphine 35 mcg/hr	Transdermal fentanyl 25 mcg/hr	Total pain, rescue analgesia, SF-12, adverse events, CD4+, CD8+
Mitra 2013[24] Australia	Open label RCT, 12 months	46 adults with nonmalignant persistent pain, mostly from lower back. Opioid naïve.	Transdermal buprenorphine titrated to effect	Transdermal fentanyl titrated to effect	Pain, physical activity, rescue medication, doctor visits, sleep, mood, AE
Conaghan 2011[25] UK	Open label RCT, 22 weeks, non-	220 adults (≥60 years) with OA.	Transdermal buprenorphine 5-25 mcg/hr	Oral codeine 60-240 mg/day titrated to	Pain, rescue medication

Table A2: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
	inferiority		titrated to effect, plus paracetamol 4g/day	effect, plus paracetamol 4g/day	, laxative use, MOS, WOMAC OA index, TSQM, EQ-5D,
Steiner [Opioid Naïve] 2011[17-20] USA	Double-blind RCT, enrichment phase excluded non-responders, 12 weeks	541 adults with moderate to severe low back pain mostly due to OA or IVDD. Patients were proven responsive to buprenorphine through screening. Minimal or no previous opioid exposure.	Transdermal buprenorphine 10 or 20mcg/hr	Placebo	Pain over 24 hours at week 12 (primary), MOS, other analgesic usage, PGIC, ODI, BPI, MOS, SF36, adverse events,
Steiner [Opioid Experienced] 2011[21,22] USA	Double-blind RCT, enrichment phase excluded non-responders, 12 weeks	662 adults with moderate to severe low back pain mostly due to OA or IVDD. Patients were proven responsive to buprenorphine through screening. Opioid experienced.	Transdermal buprenorphine 5 or 20 mcg/hr	Oxycodone immediate release 40 mg/day	Pain over 24 hours at week 12 (primary), MOS, other analgesic usage, PGIC, ODI, BPI, MOS, SF36, adverse events,

BPI= Brief Pain Inventory; EQ-5D= Euroqol; DSIS= daily sleep interference scale; IVDD= intravertebral disc disease; MOS=Medical Outcomes of Sleep scale; OA= osteoarthritis; ODI= Oswestry Disability Index; PGIC= patient global impression of change; RCT = randomized controlled trial; RMDQ= Roland Morris Disability Questionnaire; SF-36= Short Form 36; SF-MPQ= short form McGill pain questionnaire; TSQM= Treatment Satisfaction Questionnaire for Medication; WOMAC = Western Ontario and McMasters Universities OA Index;

APPENDIX 3: Summary of Critical Appraisal

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using buprenorphine

Strengths	Limitations
da Costa 2014[8]	
• Comprehensive literature search was performed. • Focused indication (osteoarthritis of knee or hip). • Publication bias was assessed using a funnel plot. • Duplicate data extraction	• Unclear whether gray literature was included in the literature search. • The only comparisons performed were buprenorphine versus placebo. There were no indirect comparison analyses.
Chaparro 2014[9,10]	
• Comprehensive literature search was performed, including unpublished sources. • Quality assessment of included studies was performed. • Duplicate data extraction	• The only comparisons performed were buprenorphine versus placebo. There were no indirect comparison analyses. • There were no separate pooled estimates for risk of adverse events for buprenorphine.
Manchikanti 2011[11]	
• The comprehensive literature search included studies comparing active treatments or using placebo as a control • Quality assessment of included studies was performed. • Duplicate data extraction	• Only one study used buprenorphine (compared to tramadol).
Bekkering 2011[12]	
• Comprehensive literature search was performed • Network meta-analysis was performed to compare morphine to other opioids.	• Included mixed populations of cancer and non-cancer pain. Only one relevant analysis for this report. • It was not stated how quality of the individual trials was accounted for in the network meta-analysis. • Did not use duplicate data extraction

Table A4: Strengths and Limitations of Randomized Controlled Trials using buprenorphine	
Strengths	**Limitations**
Rauck 2016[13]	
• Double blind methods were applied. • Power calculations were performed to estimate sample size.	• Study was sponsored by a manufacturer of buprenorphine patches.
Gimbel 2016[14]	
• Double blind methods were applied. • Power calculations were performed to estimate sample size.	• Study was sponsored by a manufacturer of buprenorphine patches. • Generalizability may be limited to opioid experienced patients who were willing to taper their pre-existing opioid treatment.
Simpson 2016[15]	
• Patients and investigators were blinded to treatment status. • Intent to treat and per protocol analyses were provided for the main outcomes. • Conservative data imputations were applied for the main analyses (e.g. patients who withdrew were considered treatment failures).	• A higher proportion of patients withdrew and this was higher in the buprenorphine group (40%) compared to the placebo group (26%). • Study was sponsored by a manufacturer of buprenorphine patches
Leng 2015[16]	
• Double-dummy methods were used maintain blinding. • Sample size and non-inferiority boundary justification was provided. • Study used an active comparator (tramadol) • Trial design and results were clearly reported.	• Trial was conducted exclusively in China, and perceptions of pain and usage of breakthrough medication may differ in other clinical contexts. • Most patients in the buprenorphine group were using the lowest dose (57% used 5 mcg/hr), indicating that the results may not be generalizable to patients with more severe chronic pain. • Study was sponsored by a manufacturer of buprenorphine patches
Canneti 2013[23]	
• Authors selected a focused patient population (AIDS patients with neuropathic pain). • Authors state that they have no conflict of interest	• Poorly reported results, incomplete data presentation. • Very small sample size. Not powered to test non-inferiority or superiority of buprenorphine and fentanyl. • Open label assessment of subjectively measured outcomes (e.g. pain) has risk of bias.

Table A4: Strengths and Limitations of Randomized Controlled Trials using buprenorphine	
Strengths	**Limitations**
Mitra 2011[24]	
• Authors used a relevant active control group (transdermal fentanyl) • Source of study funding was local government.	• No description of sample size estimation was provided. Not designed to test non-inferiority or superiority of buprenorphine and fentanyl. • Authors provided very little information about the validity and reliability of the new scale used in the trial to measure the main outcomes. • The study was poorly reported with very few estimates and measures of variance reported for the results. • No clear description of how missing data were handled in the analyses.
Conaghan 2011[25]	
• An explanation was given for the selection of the non-inferiority boundary (-1.5 points on a scale of 0-11). • Clear sample size estimations were provided.	• Sustained release codeine would have been a more relevant comparator. • Open label assessment of subjectively measured outcomes has risk of bias. • >45% of patients withdrew from the study • Results may not be generalizable to younger patients. • Some authors were from a manufacturer of buprenorphine patches
Steiner [Opioid Naïve] 2011[17-20]	
• Double blind methods were applied • Investigators attempted to assess several clinically relevant outcomes (e.g. disability, quality of life, pain)	• Population was opioid naïve or had limited exposure to opioids. • Comparison was with placebo (no active comparator group). • The enriched study design only included patients who responded to and were tolerant of buprenorphine. • Some authors were from a manufacturer of buprenorphine patches
Steiner [Opioid Experienced] 2011[21,22]	
• Double blind methods were applied • Investigators attempted to assess several clinically relevant outcomes (e.g. disability, quality of life, pain)	• Oxycodone sustained release would have been a more relevant comparator. • The study was not designed to detect differences in pain scores between buprenorphine 20 mcg/day and oxycodone. • Some authors were from a manufacturer of buprenorphine patches.

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A5: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Systematic Reviews	
da Costa 2014[8]	
Four included trials compared transdermal buprenorphine (5-20 mcg/hr) with placebo in patients with osteoarthritis of the knee or hip. Data were pooled for some outcomes. Statistically significant improvements were shown using SMD, favouring buprenorphine over placebo for pain (4 trials; SMD -0.19, 95%CI: -0.30 to -0.09) and function (2 trials). Statistically significant differences favouring the placebo group were shown for adverse events (1 trial) and withdrawals due to adverse events (4 trials).	The small mean benefit of non-tramadol opioids are contrasted by significant increases in the risk of adverse events. For the pain outcome in particular, observed effects were of questionable clinical relevance since the 95% CI did not include the minimal clinically important difference of 0.37 SMDs, which corresponds to 0.9 cm on a 10-cm VAS.
Chaparro 2014[9,10]	
Two blinded RCTs were included in the systematic review. These compared transdermal buprenorphine (up to 40 mcg/hr) with placebo. Meta-analysis was used to combine the results of these studies for some outcomes. Quality of both studies was ranked as "low". There was a small statistically significant difference in pain improvement, favouring buprenorphine (SMD, − 2.47; 95% CI, − 2.69 to − 2.25). However, for the outcome "At least 30% pain relief", there was a statistically significant difference favouring placebo (odds ratio 1.49, 95%CI: 1.08, 2.06). There was no statistically significant difference in one trial for functionality (SMD, − 0.14; 95% CI, − 0.53 to 0.25).	There is "very low-quality evidence" that transdermal buprenorphine is better than placebo in improving pain and very low-quality evidence of no difference on functionality outcomes.
Manchikanti 2011[11]	
Mean change in pain scores at 12 weeks was 2.26 in buprenorphine patients vs 2.09 in tramadol patients. WDAEs were 14.5% in the buprenorphine group vs 29.2% in the tramadol group. Most common AEs (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%. No statistical test results were provided.	The efficacy of buprenorphine relative to tramadol on pain was "indeterminate". The evidence was poor for transdermal buprenorphine for managing osteoarthritis based upon a single RCT.

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
Bekkering 2011[12]	
A statistically significant difference was found in the network meta-analysis for the comparison of morphine to buprenorphine in studies of non-cancer pain, favouring morphine (WMD 8.0, 95%CI: 0.6-15.4; N=19 studies, 3 of which used buprenorphine exclusively for non-cancer pain).	The network analysis found no difference between morphine and buprenorphine for change in pain intensity or serious adverse events (in a population of cancer and non-cancer pain). The network analysis also found that patients using buprenorphine have a lower risk of WDAE and a higher risk of withdrawal due to lack of efficacy, relative to morphine in a mixed cancer/non-cancer population).
Randomized Controlled Trials	
Rauck 2016[13]	
Mean pain score change from baseline at week 12 (SD): Buccal buprenorphine: 0.94(1.85) Placebo: 1.59(2.04) Difference: -0.67(95%CI: -1.07,-0.26); p=0.001 Patients with ≥30% pain reduction, week 12 Transdermal buprenorphine: 41% Placebo: 33% P=0.08 There were no statistically significant differences between buprenorphine and placebo for RMDQ or MOS.	"This study demonstrates the analgesic efficacy of buccal buprenorphine doses of 150–450 µg administered twice daily in the treatment of opioid-naive patients with moderate to severe chronic lower back pain requiring around-the-clock analgesia for an extended period of time."
Gimbel 2016[14]	
Mean pain score change from baseline at week 12 (SD): Buccal buprenorphine: 0.88(1.79) Placebo: 1.92(1.87) Difference: -0.98(95%CI: -1.32,-0.64); p<0.001 Mean RMDQ disability score change from baseline (SD): Buccal buprenorphine: 0.5(5.03) Placebo: 1.6(5.63) Difference: -1.20(95%CI: -2.08,-0.31)); p=0.008	"In opioid-experienced patients (requiring 30-160 mg/d MSE), [transdermal buprenorphine] (with approximately 50% bioavailability) at doses up to 900 mg twice daily produced analgesia superior to placebo over the 12-week, double-blind period with significant differences in PGIC, as well as percentages of patients with ≥30% or ≥50% reductions in pain. There were few differences between [transdermal buprenorphine] and placebo in the incidence of AEs including constipation, and there were no reports of respiratory depression." p.2524
Simpson 2016[15]	
Patients with ≥30% pain reduction, week 12 (intention to treat population) Transdermal buprenorphine: 52% Placebo: 41% Odds ratio: 1.56 (95%CI: 0.82,2.97); p=0.18	"…when tolerated, buprenorphine patches are an effective therapy for DPNP and provide another option to manage this challenging chronic condition. Common opioid related adverse effects, such as nausea and

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
Patients with ≥30% pain reduction, week 12 (per protocol/completers population) Transdermal buprenorphine: 86% Placebo: 56% Odds ratio: 6.88 (95%CI: 2.2,21.47); p<0.001 Withdrawal due to adverse events, % Transdermal buprenorphine: 30% Placebo: 6%	constipation, need to be anticipated and proactively managed with both patient education and coprescription of antiemetics and aperients to optimize tolerability and to facilitate an adequate trial of buprenorphine patch therapy." p.1500 "Buprenorphine was associated with improvements in quality of sleep." p. 1499
Leng 2015[16]	
Mean change from baseline in VAS score at week 8 (SD): Transdermal buprenorphine: -3.30(2.29) tramadol: -3.75(2.15) Difference of change: 0.45(95%CI:-0.08,0.99) No statistically significant differences were observed between buprenorphine and tramadol for: pain related waking at night, proportion of patients with good sleep, number of rescue doses of paracetamol. Adverse events (buprenorphine/tramadol), % SAE: 0%/2% AE during titration period: 44%/51% AE during maintenance period: 20%/17% Dizziness: 24%/17% Nausea: 21%/22% Vomiting: 10%/11% Erythema: 15%/13%	"Our data confirmed that [transdermal buprenorphine] was effective in pain relieving, and that it was well tolerated in Chinese patients with moderate to severe musculoskeletal pain insufficiently controlled under NSAIDs treatment. Furthermore, [transdermal buprenorphine] treatment was noninferior to sustained-release tramadol tablets." p. 619
Canneti 2013[23]	
Authors reported improvements from baseline for total neuropathic pain score, SF-12 and sleep quality but the data were poorly and incompletely reported. The data referring to comparisons of buprenorphine versus fentanyl are incomplete and not interpretable. Buprenorphine/Fentanyl AEs, n/n Nausea: 1/4 Constipation: 0/1 Skin reaction: 0/2	"High efficacy, good tolerability and convenient administration route of transdermal buprenorphine and fentanyl make these treatments valid therapeutic options for the therapy of neuropathic pain in AIDS patients." p. 883
Mitra 2013[24]	
Proportion of patients reporting pain reduction of 3 points (scale range 0-10), n/N(%) *At month 3:*	"Fifty percent of the [transdermal buprenorphine] and 43% of [transdermal fentanyl] groups had significant relief in 3

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
Transdermal buprenorphine: 8/16(50%) Transdermal fentanyl: 6/14(43%) *At month 6:* "8% in both groups" *At month 12:* "11% in both groups" No differences observed between treatment groups for physical activity, rescue medication, doctor visits, sleep, mood or adverse events	months, which persisted up to 6 months. Only 11% and 13% of patients, respectively, had sustained relief after 6 months." p. 75 "The clinical observations noted in this study found that switching of patches could benefit nonmalignant pain patients in terms of side effects and tolerance." p. 81
Conaghan 2011[25]	
Mean pain score (scale of 0-11), weeks 11 and 12, (SD) Transdermal buprenorphine + paracetamol: 3.0(1.85) Codeine + paracetamol: 3.0(2.12) Difference -0.02(95%CI: -0.64,0.60) MOS sleep disturbance scale at discontinuation: Transdermal buprenorphine + paracetamol: Median (IQR): 15.6(5.6-31.3) Codeine + paracetamol: Median (IQR): 27.5(11.3-47.5) Adverse events (buprenorphine/codeine), % Constipation: 26%/32% Nausea: 40%/25% Vomiting: 11%/8% Erythema: 27%/0% Pruritus: 17%/0% Dizziness: 14%/6% Patients receiving buprenorphine required one less dose of rescue ibuprofen per day (p=0.002)	"7-day buprenorphine patches plus oral paracetamol were non-inferior to [codeine plus paracetamol] tablets with respect to analgesic efficacy in older adults with OA pain in the hip/knee." p.930
Steiner 2011 [Opioid Naïve][17-20]	
Average pain over 24 hours, at week 12 (SD): Transdermal buprenorphine: 3.81 (0.17) Placebo: 4.39 (0.15) Mean difference: -0.58 (95%CI: -1.02,-0.14) P=0.01 Sleep disturbance subscale of MOS, LSM Transdermal buprenorphine: 35.1 Placebo: 39.5 Mean difference: -4.4 (95%CI: -7.5,-1.3)	"[Transdermal buprenorphine - Butrans] was effective in treating opioid-naive patients with moderate to severe chronic lower back pain compared with placebo transdermal systems."[17] p.916 "[Transdermal buprenorphine - Butrans] led to greater improvement than placebo in all aspects of Health Related Quality of Life for patients with moderate-to-severe chronic lower

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
p=0.006 (favouring buprenorphine) Proportion with ≥30% improvement in pain Transdermal buprenorphine: 53% Placebo: 46% p=0.11 No statistically significant difference in the number of supplemental analgesics taken (p=0.16) Means for buprenorphine patients, for all domains of the SF-36 score at week 12 were higher compared to placebo. (all p<0.01) For all items and both subscales of the Brief Pain Inventory interference score, the mean week 12 scores for the buprenorphine group were lower compared to placebo (all p < 0.001), indicating less intensity and less impact of pain on functioning.	back pain."[17] p. 21 Transdermal buprenorphine (Butrans) reduces the "impact of pain on several domains of functioning in patients with moderate to severe chronic lower back pain."[19] p. 44 Post hoc analyses "suggest that for patients with moderate to severe chronic lower back pain, 12 weeks use of transdermal buprenorphine improves the ability to carry out certain activities of daily living related to sleeping, lifting, bending, and working."[20] p. 1015
Steiner 2011[Opioid Experienced],[21,22]	
Average pain at week 4/8/12: Transdermal buprenorphine 5 mcg/hr: 3.79/3.83/4.02 Transdermal buprenorphine 20mcg/hr: 3.40/3.35/3.35 (p<0.001 vs buprenorphine 5 mcg/hr) Oxycodone 40mg/day: 3.14/3.24/3.26 (p<0.001 vs buprenorphine 5 mcg/hr) Transdermal buprenorphine 20mcg/hr resulted in larger improvements in SF-36 domains of physical health, bodily pain and overall physical, compared to 5 mcg/hr (all p<0.01), but there were no statistically significant differences between buprenorphine groups for physical functioning, general health, vitality, social functioning, emotional role or mental health.	Transdermal buprenorphine 20 mcg/hr was superior to 5 mcg/hr "in providing statistically significant and clinically meaningful pain management in patients previously requiring opioids for moderate to severe, chronic low back pain." "Patients in the oxycodone 40 mg/day treatment group had results similar to the [transdermal buprenorphine] 20 treatment group." (no statistical comparisons were provided)

AE= adverse events; LSM= least square means; MOS= Medical Outcomes Sleep scale RCT= randomized controlled trial; SD= standard deviation; SMD=standardized mean difference; WDAE= withdrawals due to adverse events