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SUMMARY WITH CRITICAL APPRAISAL

Tramadol for the Management of Pain in Adult Patients: A Review of Clinical Effectiveness – An Update

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Abbreviations

AAP	acetaminophen
AE	adverse event
LBP	low back pain
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
RCT	randomized controlled trial
SR	systematic review
VAS	visual analogue scale
WOMAC	Western Ontario and McMaster Universities Arthritis Index

Context and Policy Issues

Pain can be of two types, acute or chronic. Acute pain usually results from disease, inflammation or tissue injury and generally occurs suddenly.[1] Chronic pain is persistent pain, which can be continuous or recurrent and it adversely impacts an individual's well-being, and functional ability.[1] Estimates of prevalence rates for chronic pain in adults from epidemiological studies were quite varied, ranging from 5% to 40%.[2] In Canada, the 2007 to 2008 estimate of prevalence of chronic pain was 18.9%.[2,3]

Treatment options for chronic pain include pharmacological and non-pharmacologic approaches. Pharmacological options include a variety of drug types such as non-opioid analgesics (acetaminophen [AAP], non-steroidal anti-inflammatory drug [NSAID], COX-2 inhibitors, etc.), opioids, antidepressants, antiepileptic drugs, muscle relaxants and topical analgesic drugs.[4] Combinations of drugs with different mechanism of action may result in improved analgesia and fewer side effects due to the reduced doses of each drug in the treatment regimen.[4] Opioids are widely used for management of pain related to cancer.[5] The treatment goal for acute low back pain is short-term pain relief, typically with non pharmacologic methods, such as superficial heat, massage, acupuncture or spinal manipulation. Recommended pharmacotherapies for acute low back pain include NSAID with or without a skeletal muscle relaxant.[6]

Tramadol is a centrally acting synthetic opioid analgesic, and is considered a weak opioid due to its relatively low affinity for μ-opioid receptor, the main target for traditional opioids.[1,7] Its analgesic potency is claimed to be about one tenth that of morphine.[8] Tramadol and its active metabolite bind to μ-opioid receptors in the central nervous system and also inhibit the reuptake of norepinephrine and serotonin associated with pain relief.[7,8] Tramadol is available in various formulations and also in combination with other drugs such as acetaminophen and paracetamol.[1] Despite a relatively safe analgesic with low potential for dependence relative to morphine, tramadol dependence may occur when used for prolonged periods of time, such as longer then several weeks to months. Abuse of tramadol is commonly reported in many countries.[8]

This report is an update of a previous Rapid Response Report (Summary with Critical appraisal).[9] The purpose of this report is to summarize the new evidence regarding the clinical effectiveness of tramadol or tramadol combinations for the management of pain in adults, after the publication of the previous CADTH rapid response report.

Research Question

What is the clinical effectiveness of tramadol for the management of pain in adult patients?

Key Findings

Results of six systematic reviews (including one conventional meta-analysis and three network meta-analyses) and three individual RCTs suggest greater pain reduction and more adverse events with tramadol and tramadol combination products compared with placebo. The differences, however, were not always statistically significant. A network meta-analysis between tramadol and other active treatments suggests similar efficacy on pain relief between tramadol and NSAIDs, acetaminophen and other opioids. The results, however, need to be interpreted with caution as significant heterogeneity was observed across the individual studies included in the systematic reviews and meta-analyses. Results of individual RCTs showed similar pain relief and safety for tramadol compared with acetaminophen and NSAIDs in patients with acute pancreatitis, but tramadol was superior to desmopressin or indomethacin in patients with acute renal colic. For patients with osteoarthritis, transdermal fentanyl was superior to a tramadol plus acetaminophen combination in pain control. However, the quality of these trials may have been compromised and it remains uncertain whether the findings are generalizable to the Canadian population.

Methods

Literature Search Methods

This report makes use of a literature search developed for a previous CADTH report. The original literature search was conducted in December 2015 on key resources including Medline, EMBASE, 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. Filters were applied to limit retrieval to health technology assessments, systematic reviews, and meta-analyses, and randomized controlled trials. Where possible, retrieval was limited to the human population. The initial search was also limited to English-language documents published between January 1, 2012 and December 31, 2015. For the current report, database searches were rerun on October 17, 2018 to capture any articles published since January 2014. The search of major health technology agencies was also updated to include documents published since January 2014.

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.

Table 1: Selection Criteria

Population	Adult patients requiring management of acute or chronic pain
Intervention	Tramadol or tramadol products (combinations)
Comparator	Other analgesics (e.g., narcotics, NSAIDs) Placebo

Outcomes	Clinical effectiveness (e.g., reduction in pain, pain relief, patient satisfaction) and safety (e.g., harms, adverse events, abuse and misuse)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria, if they were duplicate publications, or were published prior to 2014. Systematic reviews (SRs) or meta-analyses (MAs) were excluded if they had included studies fully captured in other more recent and/or comprehensive SRs. Randomized controlled trials (RCTs) were excluded if they have been reported in the included SRs. Studies on surgical patients or women in labour were excluded.

Critical Appraisal of Individual Studies

The included SRs were critically appraised by one reviewer using the AMSTAR 2 tool,[10] and the included RCTs were critically appraised using the Downs and Black checklist.[11] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 545 citations were identified in the updated literature search. Following screening of titles and abstracts, 515 citations were excluded and 30 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 23 publications were excluded for various reasons, while nine publications met the inclusion criteria and were included in this report. These comprised six SRs[12-17] and three RCTs.[18-20] Appendix 1 presents the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Characteristics of the included SRs and RCTs are summarized below and details are provided in Appendix 2, Tables 2 and 3.

Study Design

Six SRs[12-17] published from 2014 to 2018 and three RCTs[18-20] published from 2014 to 2016 were included in this review. Among the six SRs, data synthesis was planned in five using conventional meta-analysis[13,15] or network meta-analysis methods.[12,14,17] The number of included studies in the SRs ranged from 10 to 156, and the number of trials of tramadol or tramadol products ranged from two to 10. For all trials included in the SRs (including those involving tramadol or tramadol products), the total number of participants in the SRs ranged from 438 to 19,045. The duration of follow up varied between 2 and ≥ 12 weeks. The number of participants in the RCTs ranged from 90 to 200.

Country of Origin

The SRs were published by authors in the United Kingdom,[13,15] China,[14] South Korea,[12] and the United States[16,17]. The three RCTs were conducted in Iran,[19] Turkey[18] and Japan.[20]

Patient Population

The studies enrolled adult patients with chronic conditions such as low back pain,[16] osteoarthritis (OA),[12,17,20] neuropathic pain,[13] and cancer[15]. One study included mixed patient populations with chronic cancer pain or non-cancer pain.[14] Studies of patients with acute pain related to acute renal colic[19] and acute pancreatitis[18] were also evaluated in this report.

Interventions and Comparators

In the included SRs, clinical effectiveness and safety of tramadol alone (all SRs) or tramadol combined with AAP (two SRs[15,16]) were examined. In all of the SRs, the active comparators for tramadol or tramadol products were NSAIDs, AAP, other opioids and a selective serotonin and norepinephrine reuptake inhibitor (duloxetine). Four of the SRs contained a placebo or no treatment arm.[13,15-17] The doses of tramadol ranged from 100 mg/day to 400 mg/day.

In the included RCTs, tramadol was administered intravenously,[18] intramuscularly,[19] or orally.[20] In a Japanese study, treatment effect of the combination product of tramadol and acetaminophen was evaluated in patients with OA.[20] In studies that enrolled patients with acute pain, the study drugs were administered once. Patients with inadequate pain relief at 30 minutes received morphine sulfate as a rescue drug,[18] or received a second dose of the same drug.[19] The comparators included paracetamol, dexketoprofen,[18] desmopressin, indomethacin,[19], loxoprofen and transdermal fentanyl.[20]

Outcomes

All SRs reported on pain assessment measured with pain intensity scales, except for the Meng study,[14] which evaluated the safety outcomes and patient satisfaction. Four SRs reported on adverse events (AEs) or side effects.[13-16]

For the RCTs of patients with acute pancreatitis or renal colic, reduction in pain intensity was measured 30 minutes after the treatment.[18,19]

Summary of Critical Appraisal

Critical appraisal of the included SRs, and RCTs are summarized below and additional details for the SRs and RCTs are provided in Appendix 3.

Systematic reviews

All the included SRs[12-17] stated the objectives, inclusion and exclusion criteria, searched multiple databases, described study selection and provided lists of included studies. A list of excluded studies was provided in three SRs,[13,15,16] but not in the other three SRs.[12,14,17] Article selection was done in duplicate in all SRs, and data extraction and quality assessment of the included primary studies were done in duplicate in all SRs but one.[17] All SRs reported key trial and patient characteristics of the included individual trials, such as demographic characteristics, baseline pain status and treatment regimens. Publication bias was explored in three SRs[12,13,17] and not in the other three SRs.[14-16] Conflicts of interest were stated in all SRs. Although the risk of bias was assessed in all SRs, four of them addressed the impact of risk of bias on study findings.[13,15-17]

Meta-analyses or network meta-analyses were planned for five SRs[12-15,17] but actually conducted in four.[12-14,17] Statistical methods for data synthesis were appropriate and described in detail. Heterogeneity across the included individual trials were estimated in

using various approaches, such as I^2 and random-effect model in conventional meta-analysis, or between-trial variance of the posterior distribution in a network meta-analysis. Subgroup analysis or sensitivity analysis was conducted in two SRs to explore the treatment effect of the study drugs on various scenarios or various patient groups.[12,17] Data pooling was not possible in the Wiffen review, and the authors noted that this was because of the small amount of information available for tramadol, alone or combined with AAP, for any outcomes of interest; in addition, the authors judged the evidence from the included trials to be of poor quality due to a lack of blinding of outcome assessment, unclear methods of sequence generation and allocation concealment, and the poor reporting of the study results.[15]

Pain outcomes were measured using different instruments among the SRs, for example, pain intensity scores, Western Ontario and McMaster Universities Arthritis Index (WOMAC), visual analogue scale (VAS) and Patient Global Impression of Change (PGIC). It is challenging to compare the results from different SRs and MAs due to the diverse outcome measures.

In all three RCTs, the objectives, inclusion and exclusion criteria, description of patient characteristics, interventions and outcomes were provided. Two of the RCTs were single-blinded, as either patients[18] or outcome assessors[19] were blinded for the treatment allocation. Sample size calculations were not provided in any of these trials. Patient disposition was described in all trials. In the Japanese study involving patients with knee or hip OA, 13% to 18% of participants withdrew the study by the end of the 12-week treatment period. The authors of all the RCT stated there was no conflict of interest. Generalizability was limited as the RCTs were either conducted in a specific country or a single centre.

Summary of Findings

The overall findings are summarized below and details of the findings of included systematic reviews and RCTs are provided in Appendix 4.

What is the clinical effectiveness of tramadol for the management of pain in adult patients?

Systematic reviews

Six relevant SRs[12-17] comparing tramadol or tramadol combination product with placebo or active control were identified. Conventional meta-analysis[13] or network meta-analysis methods[12,14,17] were used to pool the data in four SRs. Among these SRs where a placebo arm was presented, greater pain reduction with tramadol or tramadol combination when compared with placebo was observed; however, the between-group differences were statistically significant in one meta-analysis[13] and one network meta-analysis[17] but statistically nonsignificant in another network meta-analysis.[12] In an SR which included previously published SR and/or MA for patients with LBP, the authors indicated that tramadol was associated with statistically greater short-term pain relief and function improvement versus placebo, based on the results from previous MAs.[16] Compared to other active treatments (i.e. NSAIDs, AAP and duloxetine), the differences in pain intensity reduction from baseline between tramadol or tramadol product were not statistically significant, for patients with chronic osteoarthritis. Treatment with tramadol was reported to be inferior to morphine in pain relief (reduction of ≥ 50% or 30% from baseline) in one SR of cancer-related pain; however the results were derived from one single clinical trial and the statistical significance of the between-group comparison cannot be determined.[15]

In terms of adverse events, tramadol therapy was associated with higher rates of adverse event compared with placebo.[13] There was no statistically significant difference in the risk of adverse events between tramadol and other opioids, in patients experiencing chronic pain.[14] In an SR of patients experiencing cancer pain, the risk of serious adverse events was similar between tramadol (3/142 patients) and morphine (3/138 patients), based on the results of a single individual trial.[15]

Randomized controlled trials

In three RCTs, the treatment effects of tramadol were compared with other active treatments in patients with acute pancreatitis, acute renal colic and OA. Tramadol showed similar effects on pain relief, measured with VAS and was associated with less rescue medication use (10% with tramadol, 13% with AAP and 20% with NSAID), as compared with AAP and NSAID (dexketoprofen) in patients with acute pancreatitis; similar incidence of AEs was reported in the three treatment groups.[18,19] In the trial of patients with acute renal colic secondary to urolithiasis, intramuscular tramadol was statistically significantly superior to rectal indomethacin or intranasal desmopressin in pain relief measured at 30 minutes after the treatment, and was associated with less rescue medication use compared with the other two treatment groups.[19] Transdermal fentanyl was superior to the tramadol combination product (tramadol plus AAP) in reducing pain intensity for patients with OA.[20]

Limitations

There was variability in the pain conditions assessed across the studies, for example, osteoarthritis,[12,17] neuropathic pain,[13] chronic pain,[14] chronic low back pain,[16] and cancer pain.[15] As some of the same studies were included in different SRs, there was overlap in the RCTs included in the SRs, hence the results were not mutually exclusive. Different pain conditions may influence patients' response to the same drug and may influence pooled estimates of treatment effect size. Heterogeneity was present among the studies pooled. Moreover, not all outcomes were reported in all RCTs.

Follow up times in the studies ranged from one single dose to 12 weeks, hence conclusions on long term effects of tramadol or tramadol products are not possible.

Except for the SR which reported safety data exclusively,[14] harm outcomes were sparsely presented in the included SRs and RCTs in our report. Therefore, it is challenging to explore the safety profile of tramadol and tramadol products. In addition, there is a lack of data with respect to drug abuse for tramadol, so we are not able to assess the abuse potential for the treatment of interest.

All three RCTs were conducted in countries other than Canada. The study findings, therefore, may not be generalizable to a Canadian setting.

Conclusions and Implications for Decision or Policy Making

Six systematic reviews, including one conventional meta-analyses and three network meta-analyses, and three RCTs compared tramadol or tramadol products with placebo or other active treatments such as NSAIDs, acetaminophen or other opioids were identified for this report. Systematic reviews and individual RCTs suggest greater pain reduction and more adverse events with tramadol and tramadol combination products compared with placebo, however the differences were not always statistically significant. Network meta-analysis between tramadol and other active treatments for pain relief suggests similar efficacy between tramadol and NSAIDs, acetaminophen and other opioids. The results, however,

need to be interpreted with caution as significant heterogeneity was observed across the individual studies included in the systematic reviews and meta-analyses. Results of an RCT of patients with acute pancreatitis suggest comparable clinical efficacy and safety of tramadol to other active treatments. In an RCT of patients with acute renal colic, tramadol was statistically significantly superior to desmopressin or indomethacin in pain relief. Another individual RCT indicated that in patients with osteoarthritis, transdermal fentanyl was superior to a tramadol plus acetaminophen combination product in pain intensity reduction. However the quality of these trials may have been compromised due to small sample sizes, lack of rigorous statistical analyses and short study duration. The generalizability of the findings may be limited to Canadian population. Therefore, the results should be interpreted with caution.

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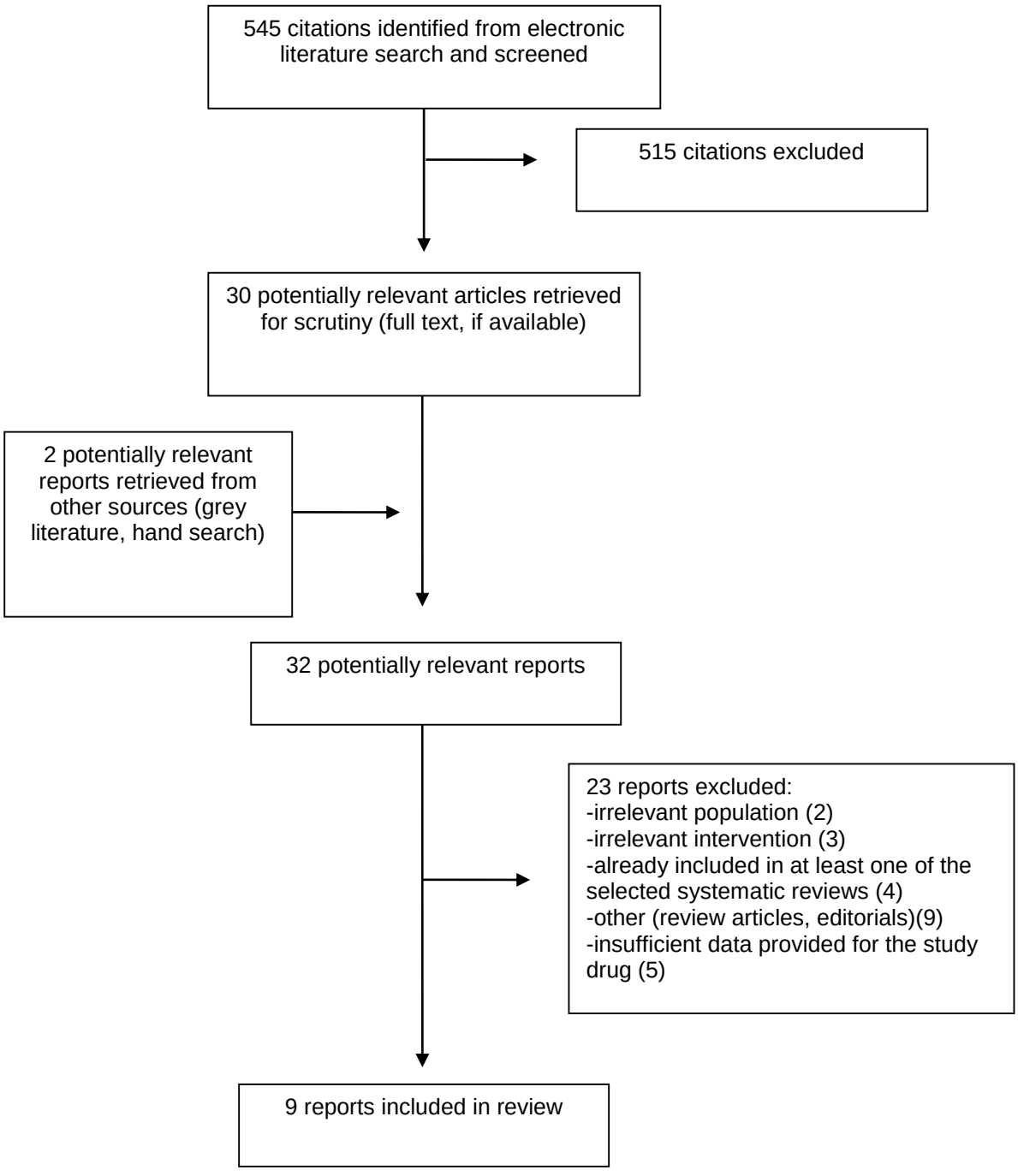
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Jung et al., 2018[12] South Korea	44 RCTs, including 6 RCTs containing a treatment arm of tramadol. ≥ 6 weeks treatment with the study drugs ≥ 6 weeks follow-up Multiple databases were searched up to June 2016	Adults with knee OA Number of participants: 19,045	Oral pharmacologic interventions: -NSAIDs i.e. diclofenac, ibuprofen, naproxen and celecoxib -AAP -tramadol (doses ranged 100-400 mg/day)	Change from baseline in pain assessed by WOMAC, VAS or NRS Change in physical function assessed by WOMAC subscales
Duehmke et al., 2017[13] United Kingdom	6 double-blind RCTs of tramadol ≥ 2 weeks study duration Multiple databases were searched up to January 2017	Adults with chronic moderate or severe neuropathic pain for at least three months due to cancer, cancer treatment, postherpetic neuralgia, peripheral diabetic neuropathy, spinal cord injury, or polyneuropathy. Number of participants: 438	-Tramadol (doses ranged 100-400 mg/day, or maximum tolerated dose; any routes of administration) -Other active interventions -placebo	Pain relief measured with PGIC scale AEs
Meng et al., 2017[14] China	32 RCTs, including 2 RCTs containing a treatment arm of tramadol. Study duration ranged from 2 to 56 weeks. Multiple databases were searched up to June 2016	Adults with cancer or non-cancer chronic pain Number of participants: not reported	Opioid drug either alone or in combination with NMDA receptor antagonist. Comparisons were made between these regimens: buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone, oxycodone-naloxone, oxymorphone, tapentadol and tramadol.	AEs Incidence of constipation Trial withdrawal rate Patient satisfaction
Wiffen et al., 2017[15] United Kingdom	10 RCTs of tramadol with or without AAP Study duration ranged from 1 day to 6 months.	Adult patients with chronic malignant tumor-related pain who were experiencing pain intensities described	-Tramadol with or without -AAP -morphine -buprenorphine -dihydrocodeine -flupirtine	Pain reduction from baseline: ≥ 30%, ≥ 50% AEs

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Multiple databases were searched up to November 2016.	as moderate to severe. Number of participants: 958	-hydrocodeine -paracetamol plus codeine -cobrotoxin plus tramadol plus ibuprofen -rectal formulation of tramadol -placebo	
Chou et al., 2016[16] United States	156 SRs, RCTs and cohort studies; 7 RCTs containing a treatment arm of tramadol were included. Multiple databases were searched up to April 2015.	Patients with LBP of any duration. Number of participants: not reported	Pharmacological therapies for LBP: AAP, NSAIDs, opioids, skeletal muscle relaxants, benzodiazepines, antidepressants, antiseizure medications and systemic corticosteroids. Non-pharmacological therapies for LBP Placebo or sham treatments, no treatment, wait list or usual care.	Change in pain intensity Function improvement Improvement in HRQoL AEs
Myers et al., 2014[17] United States	34 RCTs, including 5 RCTs containing a treatment arm of tramadol were included. ≥ 12 weeks study duration Multiple databases were searched up to March 2013.	Patients with OA, after failure of AAP therapy Number of participants: 17,442	Duloxetine NSAIDs opioids placebo	Change in total WOMAC score at 12 or more weeks from baseline

AAP = acetaminophen; HRQoL = health-related quality of life; LBP = low back pain; NMDA = N-methyl D-aspartic acid; NRS = numerical rating scale; NSAID = non-steroidal anti-inflammatory drug; OA = osteoarthritis; PGIC = Patient Global Impression of Change scale; RCT = randomized controlled trial; SR = systematic review; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Arthritis Index;

Table 3: Characteristics of Included Randomized Controlled Trials

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Gulen et al., 2016[18] Turkey	Single-centre, single-blind (patients) RCT	Adult patients with acute pancreatitis enrolled between January and June 2014	Tramadol, intravenous, 1 mg/kg: 30 patients Paracetamol,	Pain intensity measured with a 100-mm VAS

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Number of participants: 90	intravenous, 1000 mg: 30 Dexketoprofen, intravenous, 50 mg: 30 Rescue medication was allowed if inadequate response were reported 30 minutes after the treatment.	AEs Outcomes were assessed 30 minutes after the treatment.
Shirazi et al., 2015[19] Iran	Single-centre, single-blind (outcome assessor) RCT	Patients with acute renal colic caused by urolithiasis, and enrolled between July 2005 and July 2006. Number of participants: 120	Tramadol, intramuscular, 50 mg: 40 Desmopressin, intranasally, 40 mcg: 40 Indomethacin, rectally, 100 mg: 40 A second treatment was administered if inadequate response was reported 30 minutes after the treatment.	Pain intensity measured with a 10-cm VAS AEs Outcomes were assessed 30 minutes after the treatment.
Fujii et al., 2014[20] Japan	Single-centre RCT Treatment duration: 12 weeks	Patients with knee or hip OA for at least one month Number of participants: 200	Tramadol 37.5 mg/AAP 325 mg combination, 2-8 tablets/day: 65 Loxoprofen, 180 mg/day: 70 Transdermal fentanyl: 65	Pain intensity measured with a VAS at baseline, and after 1, 4, and 12 weeks of treatment AEs

AAP = acetaminophen; AE = adverse event; OA = osteoarthritis; RCT = randomized controlled trial; VAS = visual analogue scale;

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[10]

Strengths	Limitations
Jung et al., 2018[12]	
• The population, intervention, comparators, and outcomes were described • Study selection, data extraction and quality assessment processes were performed in duplicate • Statistical methods for data syntheses were appropriate and provided in details • The review authors provided adequate details regarding the characteristics of the included studies • Heterogeneity was assessed; subgroup analysis/sensitivity analysis were performed • The likelihood of publication bias was assessed, and the review authors suggested that the study results were unlikely subject to publication bias • Conflicts of interest was declared	• The literature search was restricted to English-language articles • A list of excluded studies was not provided • The potential impact of risk of bias on study findings was not adequately assessed • Safety of the study drugs was not assessed.
Duehmke et al., 2017[13]	
• The population, intervention, comparators, and outcomes were described • A list of excluded studies along with reasons for exclusion was provided • The review used a comprehensive literature search strategy and keywords were provided, no language restrictions • Study selection and data extraction were performed in duplicate • The review authors provided adequate details of the included studies. All included studies were double-blind RCTs. • Heterogeneity was assessed visually, as well as with the use of I^2 statistic • The review authors accounted for risk of bias when discussing the results • Heterogeneity was satisfactorily discussed • The review authors adequately investigated publication bias • The review authors declared that there were no conflicts of interest • Source of funding was described	• Sources of funding for the individual studies were not included • all included studies were with low to very low quality, according to the review authors • Study duration of the included studies ranged from 4 to 6 weeks, which is inadequate for long-term chronic pain condition • Subgroup analysis or sensitivity analysis was not performed due to the small sample size of the included studies (number of study participants ranged from 35 to 131)
Meng et al., 2017[14]	
• The population, intervention, comparators, and outcomes were described • The review used a comprehensive literature search strategy and keywords were provided. • Study selection and data extraction were performed in duplicate • The review authors provided adequate details of the included studies. • Heterogeneity was estimated from between-trial variance of the posterior distribution	• A list of excluded studies along with the reasons for exclusion was not provided • Unclear whether the literature search was restricted by language • The review authors did not explain their selection of the study designs for inclusion • The potential impact of risk of bias on study findings was not adequately assessed • Sources of funding for the individual studies were not included

Strengths	Limitations
• The review authors accounted for risk of bias when discussing the results • Risk of bias was adequately assessed • The study was not sponsored by the industry	• Potential publication bias among the included studies was not assessed • Subgroup analysis or sensitivity analysis was not performed
Wiffen et al., 2017[15]	
• The population, intervention, comparators, and outcomes were described • The review methods were established *a priori* • A list of excluded studies along with reasons for exclusion was provided • The review used a comprehensive literature search strategy and keywords were provided. • Study selection and data extraction were performed in duplicate • The review authors provided adequate details of the included studies. • A quality assessment of the individual studies was performed; The review authors accounted for risk of bias when discussing the results • The review authors adequately assessed heterogeneity • Funding source was disclosed	• Sources of funding for the individual studies was not provided • publication bias was not assessed due to the insufficient data • all included studies were with very low quality, according to the review authors • the results were poorly reported; data synthesis was not able to be performed due to the lack of data. • Sensitivity analysis or subgroup analysis was not able to conduct
Chou et al., 2016[16]	
• The population, intervention, comparators, and outcomes were described • The review methods were established a priori • Study selection and data extraction were performed in duplicate; a list of excluded studies was provided • Different types of studies were included. Cohort studies were included for safety data assessment. • The review authors provided adequate details of the included studies. • Reasons for heterogeneity were explored • Sources of funding for the individual studies were included • The review authors accounted for risk of bias when discussing the results • Funding sources of this review were disclosed.	• Non-English language articles were excluded • Data was qualitatively reviewed; data synthesis was not performed • A number of interventions were evaluated in small numbers of trials or in trials that had important methodological limitations • Sensitivity analysis or subgroup analysis was not performed
Myers et al., 2014[17]	
• The population, intervention, comparators, and outcomes were described • The review used a comprehensive literature search strategy and keywords were provided. • Study selection was performed in duplicate • The review authors provided adequate details of the included studies. • Quality of the included studies was assessed; risk of bias was accounted for when discussing the results • Heterogeneity was assessed and discussed • Appropriate statistical methods were used for data synthesis • Sensitivity analyses were conducted on various scenarios • The review authors adequately investigated publication bias	• Literature search was limited to English-language articles • Data extraction and quality assessment was conducted by one reviewer and checked by the second reviewer. • A list of excluded studies was not provided although the reasons for exclusion were described • Sources of funding for the individual studies not reported

Strengths	Limitations
• Conflict of interest was declared by the review authors	

Table 5: Strengths and Limitations of Clinical Studies using Downs and Black checklist[11]

Strengths	Limitations
Gulen et al., 2016[18]	
• Objectives were stated. • Inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Patient disposition was described, no lost to follow up • All patients were included in data analysis • Randomization was conducted using random number table; patients were blinded • The authors stated that there was no conflict of interest.	• Methods of sample size calculation was not described • Baseline characteristics were presented for all patients, no data for each treatment group • Generalizability limited; single centre in Turkey
Shirazi et al., 2015[19]	
• Objectives were stated. • Inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Computer-generated random scheme; single blinded study • Patient disposition was reported • All patients were included in data analysis • Sample size calculation was provided • P-values were provided in some instances but not always • The authors disclosed conflict of interest.	• Generalizability limited; single centre in Iran • No methods of sample size calculation were provided
Fujii et al., 2014[20]	
• Objectives were stated. • Inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Randomized (details not provided); not blinded • Patient disposition was described • *P*-values were provided • No conflict of interest was declared.	• At the end of the treatment period, 13%-18% of study participants withdrew the study • Sample size calculation was not provided • Generalizability limited; single centre in Japan • 12 weeks treatment duration is not considered sufficient for the chronic condition such as OA

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Jung et al., 2018[12]	
Change of SMD in WOMAC pain scale at week 6 from baseline Tramadol vs. placebo: -0.69 (95% CrI -2.60 to 1.21) – least efficacious AAP vs. tramadol: -0.39 (95% CrI -2.91 to 2.15) Aceclofenac vs. tramadol: -0.28 (95% CrI -4.61 to 4.04) Naproxen vs. tramadol: -1.04 (95% CrI -3.21 to 1.14) Diclofenac vs. tramadol: -0.27 (95% CrI -3.08 to 2.55) Meloxicam or Aceclofenac vs. tramadol: -0.11 (95% CrI -3.41 to 3.18) Etoricoxib vs. tramadol: -1.60 (95% CrI -4.65 to 1.41) – most efficacious Subgroup analysis based on baseline pain status High baseline pain group: top 4 ranked interventions were etoricoxib, celecoxib, aceclofenac and meloxicam/aceclofenac; Low baseline pain group: top 4 ranked interventions were tramadol, celecoxib, diclofenac and AAP.	*"In this network meta-analysis, there was a trend towards superiority of many of the treatments compared with placebo in controlling knee OA symptoms… in our analysis the extent of improvement of knee OA symptoms by AAP or tramadol was similar to that of NSAIDs. It is notable that the ranking of treatments differed according to the baseline severity of the knee OA in terms of pain and radiographic status… tramadol was ranked high in the lower pain subgroup but low in the higher pain subgroup"* (p5-6)
Duehmke et al., 2017[13]	
At least 50% pain intensity reduction from baseline in PGIC Tramadol (70/132, 53%) vs. placebo (40/133, 30%), RR 2.2 (95% CI 1.02 to 4.6) % of AEs Tramadol (58%) vs. placebo (34%), RR 1.6 (95% CI 1.2 to 2.1) % of WDAEs Tramadol (16%) vs. placebo (3%), RR 4.1 (95% CI 2.0 to 8.4) Death No cases of death were reported in the included studies. * No pooled results available for tramadol vs. active comparators	"*There is only modest information about the use of tramadol in neuropathic pain, coming from small, largely inadequate studies with potential risk of bias. That bias would normally increase the apparent benefits of tramadol. The evidence of benefit from tramadol was of low or very low quality, meaning that it does not provide a reliable indication of the likely effect, and the likelihood is very high that the effect will be substantially different from the estimate in this systematic review*." (p2)
Meng et al., 2017[14]	
% of any AEs, OR for tramadol vs. other opioids 0.87 (95% CI 0.65 to 1.17) % of constipation, OR for tramadol vs. other opioids 0.75 (95% CI 0.31 to 1.79) % of WDAE or patient satisfaction was not assessed in the trials of tramadol. OR of various opioids in achieving patient satisfaction in pain relief Oxycodone-naloxone vs. tramadol: 5.44 (95% CI 2.15 to 15.13) Fentanyl vs. tramadol: 2.90 (95% CI 0.79 to 11.07) Tapentadol vs. tramadol: 1.58 (95% CI 0.64 to 3.99)	"*There was no significant difference in the incidence between oxycodone or tramadol and their comparator opioids*" (p9)

Main Study Findings	Authors' Conclusion
Oxycodone vs. tramadol: 1.29 (95% CI 0.55 to 3.06) Buprenorphine vs. tramadol: 1.24 (95% CI 0.70 to 2.23) Morphine vs. tramadol: 1.20 (95% CI 0.49 to 3.15) Hydromorphone vs. tramadol: 1.18 (95% CI 0.48 to 3.17)	
Wiffen et al., 2017[15]	
<u>Participants with pain reduction of ≥ 30% from baseline (from 1 study)</u> Weak opioid group 55/117 (47%) vs. morphine 91/110 (82%), relative effect not calculated; <u>Participants with pain reduction of ≥ 50% from baseline (from 1 study)</u> Weak opioid group 49/117 (42%) vs. morphine 83/110 (75%), relative effect not calculated; <u>Serious adverse events including death (from 1 study)</u> Tramadol 3/142 vs. morphine 3/ 138; No data were available for data synthesis for other outcome assessment. * weak opioid group: tramadol, tramadol plus AAP, and AAP plus codeine were combined as a single weak opioid group	*"There is limited, very low quality, evidence from randomised controlled trials that tramadol produced pain relief in some adults with pain due to cancer and no evidence at all for children. There is very low quality evidence that it is not as effective as morphine. This review does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different is very high. The place of tramadol in managing cancer pain and its role as step 2 of the WHO analgesic ladder is unclear"* (p2)
Chou et al., 2016[16]	
For chronic low back pain, tramadol were associated with moderate effects on pain intensity reduction, and small effects on function versus placebo (based on data from 1 SR of 5 RCTs and 2 additional RCTs). Data were qualitatively reviewed for tramadol: A systematic review found tramadol to be associated with greater short-term pain relief vs. placebo (5 trials; SMD, −0.55; 95% CI −0.66 to −0.44; I^2 = 86%, for a mean difference of 1 point or less on a 0–10 pain scale) and function (5 trials; SMD, −0.18; 95% CI −0.29 to −0.07; I^2 = 0%, for a mean difference of ~1 point on the RDQ); 2 trials not included in the systematic review reported results consistent with the systematic review findings. No data regarding the comparisons between tramadol and other active treatments are available.	"*For acute or subacute low back pain, NSAIDs, opioids (buprenorphine patch), and skeletal muscle relaxants were associated with small effects on pain versus placebo, and NSAIDs were associated with small effects on function. Acetaminophen and systemic corticosteroids were associated with no beneficial effects versus placebo*." (pES-6) "*For chronic low back pain, NSAIDs and tramadol were associated with moderate effects on pain versus placebo, and opioids, duloxetine, and benzodiazepines were associated with small effects*." (pES-6) "*Pharmacological therapies were associated with an increased risk of adverse events versus placebo*." (pES-7)
Myers et al., 2014[17]	
<u>Change in WOMAC total score from baseline</u> Tramadol vs. placebo: -2.89 (95% CI -5.41 to -0.54) Tramadol vs. duloxetine: 3.57 (95% CI -0.17 to 7.19) *****a positive result indicates that the compared treatment is worse than duloxetine	"*No difference between duloxetine and other post-first line oral treatmentsfor osteoarthritis (OA) in total WOMAC score after approximately 12 weeks of treatment*" (p1)

AAP = acetaminophen; AE = adverse event; CI = confidence interval; CrI = credible interval; NSAID = non-steroidal anti-inflammatory drug; OR = odds ratio; PGIC = Patient Global Impression of Change scale; RR = risk ratio; SMD = standardized mean difference; WDAE = withdrawal due to adverse event; WOMAC = Western Ontario and McMaster Universities Arthritis Index;

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Gulen et al., 2016[18]	
Change in pain intensity scores from baseline to 30 minutes after treatment Tramadol: 45.4 (95% CI 30 to 54) Paracetamol: 41.5 (95% CI 34 to 50) Dexketoprofen: 40.5 (95% CI 30 to 47) Between-group comparisons for tramadol vs. comparators Dexketoprofen vs. tramadol: 5 (95% CI -3 to 13) Paracetamol vs. tramadol: 2 (95% CI -7 to 10) P=0.38 for three-group comparison. Rescue medication use Dexketoprofen: 6 patients (20%) Paracetamol: 4 patients (13.3%) Tramadol: 3 patients (10%) AEs Dexketoprofen: 2 nausea/vomiting Paracetamol: 1 nausea/vomiting Tramadol: 2 nausea/vomiting, 1 hypotensive episode	*"intravenous paracetamol, dexketoprofen and tramadol are not superior to each other in the management of pain caused by nontraumatic acute pancreatitis."* (p192)
Shirazi et al., 2015[19]	
Change in pain intensity from baseline to 30 minutes after treatment (VAS) Tramadol: changed from 8.3 (SD 1.2) to 3.6 (SD 0.6) Desmopressin: changed from 8.4 (SD 0.7) to 5.3 (SD 0.5) Indomethacin: changed from 8.3 (SD 0.9) to 4.7 (SD 0.4) The pain intensity was lower in the tramadol group when compared to desmopressin group at 30 minutes after the treatment (p=0.01) or indomethacin (p=0.01). Rescue medication use Tramadol: 10 (25%) Desmopressin: 25 (62.5%) Indomethacin: 21 (52.2%) Significantly higher in desmopressin (p=0.02) and indomethacin (p=0.01) groups when compared to tramadol.	"*rectal indomethacin, intramuscular tramadol and intranasal desmopressin are effective and safe routes of controlling pin in acute renal colic secondary to urolithiasis. Tramadol was the most effective agent in controlling the pain"* (p41)
Fujii et al., 2014[20]	
Change in pain intensity from baseline Tramadol + AAP: changed from 5.4 (SEM 2.1) to 2.7 (SEM 2.0) Transdermal fentanyl: changed from 6.4 (SEM 4.2) to 2.0 (SEM 1.0) Loxoprefen: changed from 5.2 (SEM 2.3) to 3.3 (SEM 2.0) Significant difference in all scores in the tramadol/AAP group compared with loxoprofen group, p< 0.05; Significant difference in all scores in the transdermal fentanyl group, compared with the loxoprofen or tramadol/AAP groups, p< 0.05.	"*fentanyl may induce progressive changes in knee or hip OA during a relatively short period, compared with oral non-steroidal anti-inflammatory drugs or tramadol*" (p1379)

AAP = acetaminophen; AE = adverse event; CI = confidence interval; VAS = visual analogue scale; SD = standard deviation; SEM = standard error of the mean.

Appendix 5: Additional References of Potential Interest

Adverse Events related to use of opioids

Els C, Jackson TD, Kunyk D, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database Syst Rev*. 2017 Oct 30;10:CD012509.

Consensus statement from the Canadian Pain Society

Moulin D, Boulanger A, Clark AJ, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain Res Manag*. 2014 Nov-Dec;19(6):328-335.