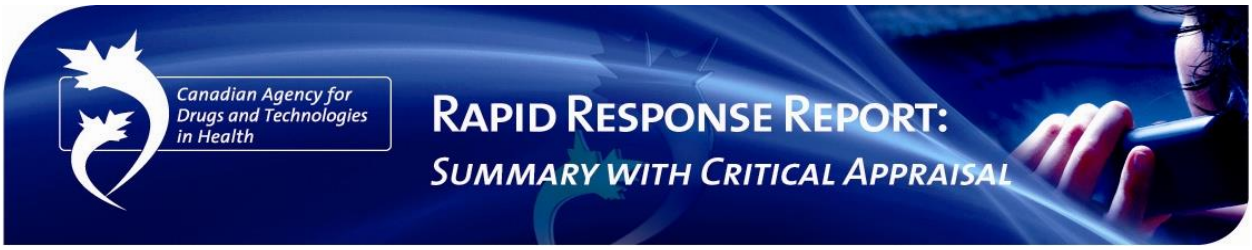


TITLE: Tramadol for the Management of Pain in Adult Patients: A Review of the Clinical Effectiveness

DATE: 02 February 2015

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]

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, non-steroidal anti-inflammatory drug [NSAID]), opioids, antidepressants, antiepileptic drugs and muscle relaxants.[3]

Tramadol is considered a weak opioid due to its relatively low affinity for μ-opioid receptor, the main target for traditional opioids.[1] Tramadol and its active metabolite bind to μ-opioid receptors in the central nervous system resulting in inhibition of ascending pain pathways and also inhibits the reuptake of norepinephrine and serotonin involved in the descending inhibitory pain pathway associated with pain relief.[4] Tramadol is available in various formulations and also in combination with other drugs such as acetaminophen and paracetamol. There appears to be some concern regarding the place of tramadol in the management of pain in adults.

The purpose of this report is to review the clinical effectiveness of tramadol or tramadol combinations for the management of pain in adults. This report is an update of a previous Rapid Response Report (Reference List)[5] and includes additional details.

RESEARCH QUESTION

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

KEY FINDINGS

Systematic reviews and 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 or statistical significance was not reported. Efficacy and safety results of tramadol or tramadol combinations compared with an active agent varied depending on the particular comparator agent. Results were from single RCTs or indirect comparison and need to be interpreted with caution.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Pubmed, Medline (OVID) and Embase (OVID) databases, The Cochrane Library (2015, Issue 1), University of York Centre for Reviews and Dissemination (CRD), Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses and randomized controlled trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and January 6, 2015.

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 (eg: narcotics, NSAIDs), placebo
Outcomes	Clinical benefit and harms
Study Designs	Health technology assessment (HTA), systematic review (SR), meta-analysis (MA), and randomized controlled trial (RCT)

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria, if they were duplicate publications, or were published prior to 2012. Studies on surgical patients or women in labour were excluded

Critical Appraisal of Individual Studies

Critical appraisal of a study was conducted based on an assessment tool appropriate for the particular study design. The AMSTAR checklist[6] was used for systematic reviews; the Downs and Black checklist[7] for RCTs. For the critical appraisal, a numeric score was not calculated. Instead, the strength and limitations of the study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 359 citations were identified in the updated literature search. Of these 359 citations, 315 citations had already been identified and screened for the previous Rapid Response report and so were not screened again. Of the potentially relevant citations identified for the previous report, 21 were potentially relevant for this current report and were retrieved for full text review. The remaining new 44 citations from the updated search were screened and following screening of titles and abstracts, 41 citations were excluded and 3 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publication was retrieved from the grey literature search. Of these 24 potentially relevant articles, 13 publications were excluded for various reasons, while 11 publications met the inclusion criteria and were included in this report. These 11 publications comprised of four systematic reviews[8-11] and seven RCTs.[12-18] Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Characteristics of the included systematic reviews (SRs) and randomized controlled trials (RCTs) are summarized below and details are provided in Appendix 2.

Systematic review

Four relevant SRs[8-11] comparing tramadol or tramadol combination product with placebo or active control were identified. Two SRs[8,11] were from the Cochrane collaboration and were published in 2014 and 2012. One SR[9] was published in 2014 from USA and one SR[10] was published in 2013 from China. Two SRs[8,10] included adults with low back pain, one SR[9] included adults with chronic non-malignant pain and one SR[11] included adults with painful diabetic neuropathy. The number of included studies in the SRs ranged from one to 45. Three studies overlapped in three SRs.[8-10] and one RCT overlapped in two SRs. [8,10] The number of participants in the SRs ranged from 313 to 12,985.The duration of follow up varied between 6 and 12 weeks in three SRs[9-11] and was not reported in one SR.[8] All SRs reported on pain assessment and three SRs reported on adverse events (AEs) or side effects.

Two SRs[8,10] included meta-analyses and compared tramadol or tramadol combination with placebo and also compared tramadol with celecoxib. One SR[9] was a model-based indirect comparison of tramadol with tapentadol. One SR[11] was a qualitative analysis, comparing tramadol combination with placebo.

Randomized controlled trial

Seven relevant RCTs[12-18] were identified. Four RCTs[13-16] compared tramadol combination with placebo and three RCTs[12,17,18] compared tramadol or tramadol combination with active treatment.

Tramadol combination versus placebo

Of the four RCTs in this category, three RCTs[13-15] compared tramadol combined with acetaminophen versus placebo and one RCT[16] compared tramadol combined with paracetamol versus placebo. One RCT[13] was published in 2014 from the Netherlands, two RCTs were published in 2013 from Taiwan[15] and Korea,[14] and one RCT[16] was published in 2012 from Canada. All RCTs were double blinded. Two RCTs[14,16] involved multi-centres, one RCT[13] involved two centres and one RCT[15] involved a single centre. Three RCTs[13,14,16] included adults with low back pain and one RCT[15] included adults with ankylosing spondylitis. The number of participants ranged from 50 to 277. Median age[13,15] ranged from 33 to 44 years and mean age[14,16] ranged from 42 to 60 years. Proportion of males varied between 25% and 80% in the tramadol combination groups and between 26% and 79% in the placebo groups. The duration of follow up varied between 2.5 days and 12 weeks. All RCTs reported on pain assessment and three RCTs[14-16] reported on adverse events.

Tramadol or tramadol combination versus active agent

Of the three RCTs in this category, one RCT[18] compared tramadol with buprenorphine, one RCT[12] compared tramadol with flupirtine and one RCT[17] compared tramadol combination with NSAID. One RCT[18] was published in 2014 from China and two RCTs were published in 2013 from India[12] and Korea.[17] One RCT[18] was double blind, one RCT[12] was single blind and one RCT[17] was open label. Two RCTs[17,18] involved multi-centres and one RCT[12] involved a single centre. One RCT[18] included adults with non-oncological musculoskeletal pain, one RCT[12] included adults with mechanical low back pain and one RCT[17] included adults with symptomatic knee arthritis and experiencing pain. The number of participants ranged between 97 and 280. Mean age ranged from 50 to 61 years. Proportion of males varied between 16% and 51% in the tramadol or tramadol combination groups and between 13% and 50% in the placebo groups. The duration of follow up varied between 4 and 8 weeks. All RCTs reported on pain assessment and adverse events.

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 review

All the included systematic reviews[8-11] stated objective, inclusion and exclusion criteria, searched multiple databases, described study selection and provided lists of included studies. One SR[11] provided a list of excluded studies as well. Article selection was done in duplicate in three SRs,[8,10,11] data extraction was done in duplicate in two SRs[8,10] and one SR[9] did not mention if article selection or data extraction were done in duplicate. Quality assessment of studies were conducted in three SRs.[8,10,11] and was unclear in one SR.[9] Publication bias was

explored in one SR[8] and not in three SRs.[9-11] Conflict of interest was stated in three SRs[9-11] and not in one SR.[8]

Randomized controlled trial

Seven relevant RCTs[12-18] were identified. Four RCTs[13-16] compared tramadol combination with placebo and three RCTs[12,17,18] compared tramadol or tramadol combination with active treatment.

Tramadol combination versus placebo

In all four RCTs[13-16] the objectives, inclusion and exclusion criteria, description of patient characteristics, interventions and outcomes were provided. In the majority of the RCTs the method of randomization was not described. All the RCTs were double blind. Sample size calculations were provided in three RCTs.[14-16] *P* values were provided though not for all outcomes and the number of withdrawals or lost to follow up were reported in all the RCTs. The authors in all RCTs declared conflict of interest. Majority of the RCTs[13,14,16] were funded by industry. Generalizability was limited as the RCTs were either conducted in a specific country or a single centre.

Tramadol or tramadol combination versus active agent

In all three RCTs[12,17,18] the objectives, inclusion and exclusion criteria, description of patient characteristics, interventions and outcomes were provided. In the majority of the RCTs the method of randomization was not described. One RCT[18] was double blind, one RCT[12] was single blind and one RCT[17] was not blinded. Sample size calculations were provided in two RCTs.[17,18] *P* values were provided in most instances in one RCT[18], but not in two RCTs.[12,17] The number of withdrawals or lost to follow up were reported in two RCTs.[17,18] The authors of all the RCT stated there was no conflict of interest. Two RCTs[17,18] were funded by industry. 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. Infrequently reported outcomes are not presented here but are provided in Appendix 4.

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

Systematic review

Four relevant SRs[8-11] comparing tramadol or tramadol combination product with placebo or active control were identified. Three SRs[8,10,11] showed greater pain reduction with tramadol or tramadol combination when compared with placebo. However, differences were statistically significant in one SR[8], not statistically significant in one SR[10] and statistical significance was not reported in another SR[11] (Table 2). Of these three SRs, two SRs[10,11] reported on adverse events or side effects. One SR[10] considering 3 RCTs reported for side effects, the relative risk (RR) and 95% confidence interval (CI) for tramadol compared with placebo as RR (95% CI) = 1.74 (1.20 to 2.52), favoring placebo. One SR[11] considering one RCT, showed that adverse events were

higher in the tramadol combination group compared with placebo (nausea: 11.9% versus 3.3%, dizziness: 6.3% versus 1.3%, and somnolence: 6.3% versus 1.3%)

Table 2: Assessment of pain for treatment with tramadol or tramadol combination versus placebo

Study	Population	Outcome	No. of RCTs	No. of patients	Effect size
Chaparro,[8] 2014	Chronic low back pain	Pain intensity change	5	1378	SMD (95% CI) = -0.55 (-0.66 to -0.44) Favours tramadol or tramadol combination
Chung,[10] 2013	Chronic non-specific low back pain	Pain intensity change	3	613	SMD (95% CI) = -1.72 (-3.45 to 0.01) NS
Chaparro,[11] 2012	Painful diabetic neuropathy	≥30% pain reduction	1	313	56.2% of patients versus 37.9% of patients. Favours tramadol combination

NS = not significant; SMD = standardized mean difference

One SR[10] including one RCT comparing tramadol with celecoxib showed that improvement in pain intensity was numerically greater with tramadol compared with celecoxib (63.2% versus 49.9%) and adverse events were numerically greater with tramadol compared with celecoxib (30.4% versus 14.4%). One SR[8] including two RCTs assessing pain intensity with tramadol compared with celecoxib showed that the RR (95% CI) was 0.82 (0.76 to 0.90) favoring tramadol.

One SR[9] presented results of indirect comparison. The estimates for reduction in pain intensity compared with baseline were 46% (95% CI: 41% to 51%) for tramadol, 36% (95% CI: 35 to 37%) for tapentadol and 28% (95% CI: 23 to 33%) for placebo. Adverse events were reported as percentage of events and were higher with tramadol or tapentadol in comparison with placebo. Some common adverse events with tramadol, tapentadol, and placebo respectively were nausea: 22.2%, 21.7% and 8.0%; constipation: 18.0%, 15.1% and 5.3%; dizziness: 13.2%, 15.7%, and 4.6% and somnolence: 13.2%, 12.6% and 3.8%.

Randomized controlled trial

Tramadol combination versus placebo:

All four RCTs[13-16] reported on assessment of pain using a variety of tools and formats. They included but were not limited to global pain change, pain relief success rate, visual analog scale (VAS) score, total pain relief score (TOTPAR), and sum of pain intensity difference (SPID). Some RCTs used multiple tools. Generally there were greater improvements with tramadol combination compared with placebo but the results were not always statistically significant. As most studies used VAS, results using VAS when available are presented in Table 3. Results with other tools are provided in Appendix 4.

Table 3: Assessment of pain for treatment with tramadol combination versus placebo					
Study	Condition	Outcome	Tramadol combination	Placebo	*P* value
Schiphorst Preuper, [13] 2014	Chronic low back pain	VAS score, median (IQR)	Before Tx: 6.1 (3.0 to 7.2)	Before Tx: 4.7 (2.7 to 7.2)	NR
			After Tx: 5.1 (3.3 to 7.1)	After Tx: 4.5 (2.9 to 6.9)	
Chang,[15]	Ankylosing spondylitis	Change in VAS pain score, %	45.6	25.7	0.087
Lee,[14] 2013	Chronic low back pain	Pain intensity change ≥30%, (using VAS), %	57.7	41.1	0.037
Lasko,[16] 2012	Acute low back pain	SPID50, median (IQR)	-6.0 (-22 to 3)	-4.0 (-23 to 10)	0.038
IQR = interquartile range; SPID50 = sum of pain intensity difference over 50 hours; Tx = treatment; VAS = visual analog scale					

Adverse events were reported in 3 RCTs[14-16] and appeared higher in the tramadol combination group compared to placebo group. In one RCT[15] the proportions of adverse event experienced were 64.2 % in the tramadol combination group and 35.8% in placebo group. In one RCT[14] the proportion of patients experiencing adverse events were 83.2 % and 54.2% in the tramadol combination group and placebo group, respectively. In one RCT[16] proportion of patients experiencing adverse events were higher in the tramadol combination group compared to placebo group (nausea: 24.1% versus 2.2%, dizziness: 14.9% versus 1.5%, and somnolence: 9.2% versus 3.7%).

Tramadol or tramadol combination versus active agent:

Three RCTs[12,17,18] compared tramadol or tramadol combination with various active agents and reported on pain assessment and adverse events..

One RCT[18] compared sustained release tramadol (T-SR) with transdermal buprenorphine (BTDS) in patients with musculoskeletal pain. Change in VAS score was not statistically significantly different between the two groups (T-SR versus BTDS: -3.75 versus -3.3, $P = 0.095$). Proportion of patients reporting at least one adverse event was 61.6 % in T-SR and 56.7% in BTDS. Three serious adverse events were reported in the T-SR group but were considered by the authors to be unrelated or unlikely related to the treatment.

One RCT[12] compared tramadol with flupirtine in patients with mechanical low back pain. VAS scores at the end of treatment in the two groups were 1.45 for tramadol and 1.26 for flupirtine, statistical significance was not reported. The pain relief rate measurement showed that the proportion of patients experiencing significant to complete pain relief was less in the tramadol group compared with the flupirtine group (39.8% versus 55.1%, $P < 0.05$). Proportion of patients experiencing adverse events were higher in the tramadol group compared with the flupirtine group (39.8% versus 24.3%, $P < 0.05$)

One RCT[17] compared tramadol combination (tramadol + acetaminophen [TA]) with non-steroidal anti-inflammatory drug (NSAID) as maintenance therapy in patients with knee osteoarthritis pain inadequately controlled by NSAID. All patients were treated with four weeks of add-on TA and then randomized to TA or NSAID. Pain as assessed by numerical rating scale (NRS) was reported as not significantly different in the two groups (TA versus NSAID: 4.55 versus 3.89, *P* = NS), *P* values were not provided. It was stated that prevalence and types of adverse events were not significantly different in the two groups (for TA versus NSAID, nausea: 8.5% versus12.0%, dizziness: 8.5% versus 8.0%, and constipation: 4.3% versus 2.0%).

Limitations

There was variability in the terminology used across the studies. For example, two SRs used different terminology: chronic low back pain or chronic non-specific low back pain but it was unclear if there was a real difference between the terms as some of the same studies were included in the both SRs. It, therefore, was a challenge to compare the clinical effectiveness among the selected studies. There was overlap in the RCTs included in the SRs hence the results were not mutually exclusive.

Heterogeneity was present among the studies pooled. Different pain conditions may influence patients' response to the same drug and may influence pooled estimates of treatment effect size. Comparison across various RCTs was difficult as populations varied, follow up times varied, and not all outcomes were reported in all RCTs.
Follow up times in the studies ranged from 2.5 days to 12 weeks, hence conclusions on long term effects of tramadol or tramadol combinations are not possible.
Except for one RCT, most 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

Three systematic reviews and four RCTs compared tramadol or tramadol combination with placebo. One systematic review included an indirect comparison between tramadol and tapentadol. A single RCT was identified for each comparison between tramadol or tramadol combination and a particular active agent. 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 or statistical significance was not reported. Indirect comparison analysis between tramadol and tapentadol suggests greater efficacy with tramadol and better safety profile with tapentadol. The results, however, need to be interpreted with caution as details of the individual studies were lacking. A single RCT suggests that efficacy with tramadol and flupirtin was comparable and safety profile of flupirtine was better. A single RCT suggests that efficacy and safety with tramadol and buprenorphine were comparable. A single RCT suggests that the efficacy and safety with tramadol combination and NSAID were comparable during the maintenance phase in patients who had responded favourably to previous add-on tramadol combination treatment. Results were from single studies of sizes ranging from 97 to 280 patients and also need to be interpreted with caution.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES

1. Kizilbash A, Ngo-Minh CT. Review of extended-release formulations of Tramadol for the management of chronic non-cancer pain: focus on marketed formulations. J Pain Res. 2014;7:149-61. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3968086

2. Schopflocher D, Taenzer P, Jovey R. The prevalence of chronic pain in Canada. Pain Res Manag [Internet]. 2011 Nov [cited 2015 Jan 26];16(6):445-50. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3298051

3. Rosenquist EWK. Overview of the treatment of chronic pain. 1800 Jan 1 [cited 2015 Jan 30]. In: UpToDate [Internet]. Waltham (MA): UpToDate; c2005 - . Available from: www.uptodate.com Subscription required.

4. Tramadol. 2015 [cited 2015 Jan 26]. In: UpToDate [Internet]. Waltham (MA): UpToDate; c2005 - . Available from: www.uptodate.com Subscription required.

5. The Canadian Agency for Drugs and Technologies in Health. Tramadol for the management of pain in adult patients: clinical effectiveness and guidelines [Internet]. Ottawa: The Agency; 2014 Oct 24. [cited 2015 Jan 26]. Available from: http://www.cadth.ca/media/pdf/htis/nov-2014/RA0707%20Tramadol%20Final.pdf

6. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007;7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

7. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun;52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

8. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared with placebo or other treatments for chronic low back pain: an update of the Cochrane Review. Spine. 2014 Apr 1;39(7):556-63.

9. Mercier F, Claret L, Prins K, Bruno R. A Model-Based Meta-analysis to Compare Efficacy and Tolerability of Tramadol and Tapentadol for the Treatment of Chronic Non-Malignant Pain. Pain Ther [Internet]. 2014 Jun [cited 2015 Jan 9];3(1):31-44. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4108025

10. Chung JW, Zeng Y, Wong TK. Drug therapy for the treatment of chronic nonspecific low back pain: systematic review and meta-analysis. Pain Physician [Internet]. 2013 Nov [cited 2015 Jan 9];16(6):E685-E704. Available from: http://www.painphysicianjournal.com/2013/november/2013;16;E685-E704.pdf

11. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. Cochrane Database Syst Rev. 2012;7:CD008943.

12. Banerjee M, Bhattacharyya K, Sarkar RN, Ghosh B. Comparative study of efficacy and tolerability of flupirtine versus tramadol in non-steroidal anti-inflammatory drug intolerant mechanical low back pain. Indian Journal of Rheumatology. 2012;7(3):135-40.

13. Schiphorst Preuper HR, Geertzen JH, van Wijhe M, Boonstra AM, Molmans BH, Dijkstra PU, et al. Do analgesics improve functioning in patients with chronic low back pain? An explorative triple-blinded RCT. Eur Spine J. 2014 Apr;23(4):800-6.

14. Lee JH, Lee CS, Ultracet ER Study Group. A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of the extended-release tramadol hydrochloride/acetaminophen fixed-dose combination tablet for the treatment of chronic low back pain. Clin Ther. 2013 Nov;35(11):1830-40.

15. Chang JK, Yu CT, Lee MY, Yeo K, Chang IC, Tsou HK, et al. Tramadol/acetaminophen combination as add-on therapy in the treatment of patients with ankylosing spondylitis. Clin Rheumatol. 2013 Mar;32(3):341-7.

16. Lasko B, Levitt RJ, Rainsford KD, Bouchard S, Rozova A, Robertson S. Extended-release tramadol/paracetamol in moderate-to-severe pain: a randomized, placebo-controlled study in patients with acute low back pain. Curr Med Res Opin. 2012 May;28(5):847-57.

17. Park KS, Choi JJ, Kim WU, Min JK, Park SH, Cho CS. The efficacy of tramadol/acetaminophen combination tablets (Ultracet®) as add-on and maintenance therapy in knee osteoarthritis pain inadequately controlled by nonsteroidal anti-inflammatory drug (NSAID). Clin Rheumatol. 2012 Feb;31(2):317-23.

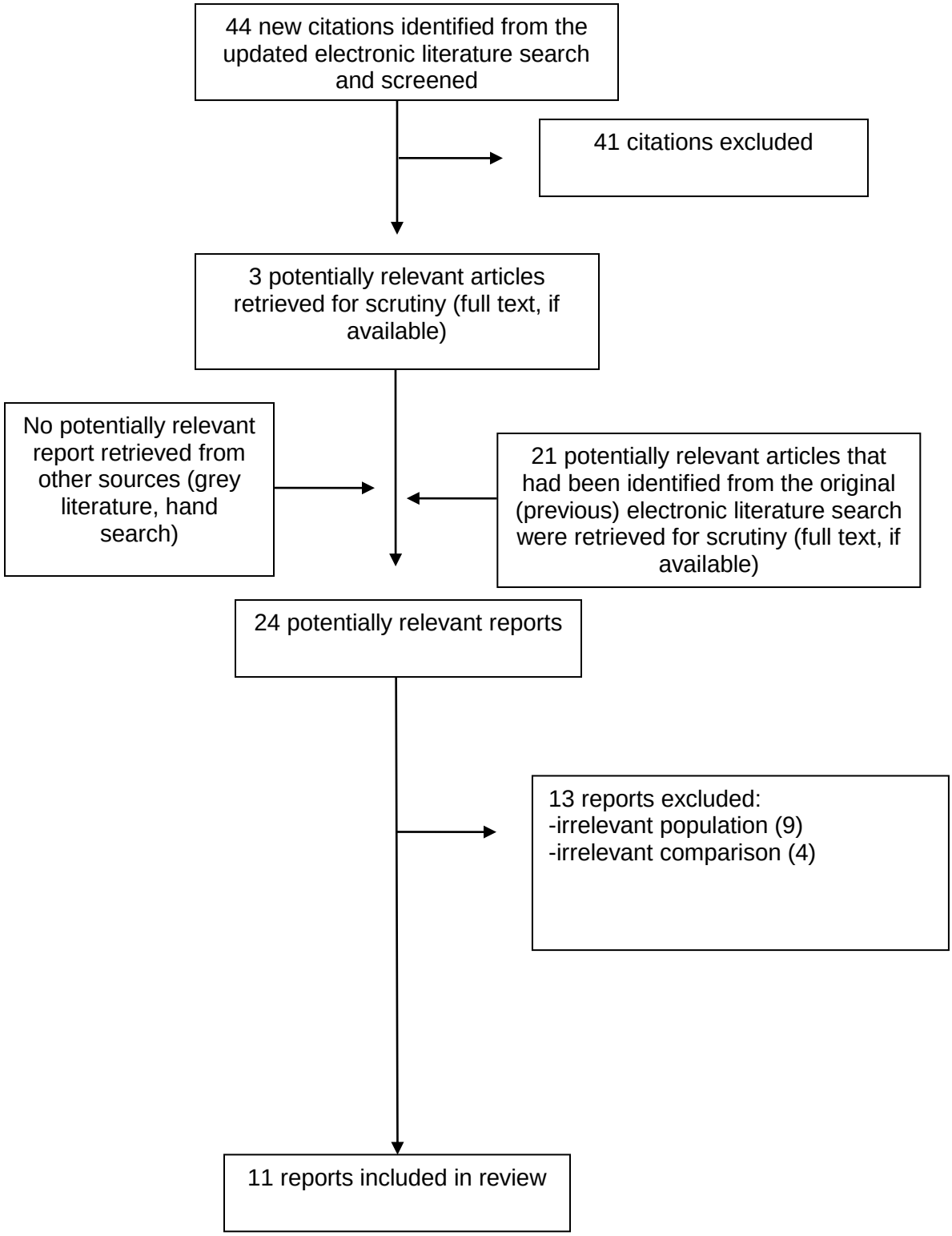
18. Leng X, Li Z, Lv H, Zheng Y, Liu Y, Dai K, et al. Effectiveness and Safety of Transdermal Buprenorphine Versus Sustained-Release Tramadol in Patients with Moderate to Severe Musculoskeletal Pain: An 8-Week, Randomized, Double Blind, Double Dummy, Multi-Center, Active-controlled, Non-inferiority Study. Clin J Pain. 2014 Dec 11.

ABBREVIATIONS

AE	adverse event
ASAS20	assessment in ankylosing spondylitis criteria
ASQoL	ankylosing spondylitis quality of life
BASDAI	Bath ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functional index
BASG	Bath ankylosing spondylitis global index
BTDS	buprenorphine
bid	twice daily
CI	confidence interval
CLBP	chronic low back pain
CNLBP	chronic non-specific low back pain
d	day
DDS-06C	75 mg tramadol + 650 mg paracetamol
F	flupiritine
FAS	full set analysis
FU	follow up
h	hour
HAQ	health assessment questionnaire
IQR	interquartile range
ITT	intent-to-treat
K-ODI	Korean Oswestry disability index
K-SF-36	Korean short-form 36 questionnaire for quality of life
LBP	low back pain
MA	meta-analysis
mg	milligram
NR	not reported
NRS	numerical rating scale
NS	not significant
NSAID	non-steroidal anti-inflammatory drug
PGA	physician global assessment
PGI-I	patients' global impression of improvement – index
PIRS	pain intensity rating scale
plb	placebo
qd	once daily
QoL	quality of life
RCT	randomized controlled trial
RMDQ	Rolland Morris disability questionnaire
RR	relative risk
SD	standard deviation
SF-36	short-form 36 questionnaire for quality of life
SMD	standardized mean difference
SPID	sum of pain intensity difference
SPID4	sum of pain intensity difference over first 4 hours
SPID50	sum of pain intensity difference over 50 hours
SPIDW50	weighted SPID50
SR	systematic review
SS	safety set
T	tramadol

TOTPAR	total pain relief score
TOTPAR50	total pain relief score over 50 hours
TOTPARW50	weighted TOTPAR50
Tx	treatment
VAS	visual analog scale
WOMAC	Western Ontario and McMaster Universities

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size[a] (N)	Comparison[a]	Outcomes[a] Measured
Systematic review				
Chaparro,[8] 2014, Cochrane Collaboration (Columbia, Canada, USA)	SR including MA SR included 7 relevant RCTs FU: NR (The SR was on assessment of opioids for the treatment of chronic low back pain. It included a total of 15 RCTs of which 5 RCTs comparing tramadol [or tramadol combination] with placebo and 1 RCT comparing tramadol with celecoxib were relevant for this review and are reported here)	Adults with persistent low back pain (LBP) for ≥ 12 weeks. (LBP defined as pain occurring below the lower ribs and above gluteal folds) N = 1378 in 5 RCTs with placebo as comparator N = 1583 in 2 RCTs (described in1 report) with celecoxib as comparator	1. Tramadol or tramadol combined with acetaminophen versus placebo. The average dose of tramadol was ~ 150 to 300 mg/day. 2. Tramadol vs celecoxib	Pain assessment, disability
Mercier,[9] 2014, USA	SR including model based MA, indirect comparison. FU (mean ± SD) = 9.0 ± 6.8 weeks 45 Phase II and Phase III studies were included. The included studies were RCTs with parallel group or cross-over design	Adults with chronic non-malignant pain (osteoarthritis pain, back pain, neuropathic pain and other chronic non-malignant pain) N = 12,985 (from 81 treatment arms)	(Tramadol or tramadol combinations) versus tapentadol versus placebo Tramadol 300 mg once daily and tapentadol 100 to 250 mg twice daily	Pain assessment, AE
Chung,[10] 2013, China	SR including MA SR included 4 relevant RCTs FU = 6 to 12 weeks (The SR was on assessment of drug therapy for the	Adults with chronic non-specific low back pain (CNLBP) for ≥ 12 weeks. (CNLBP defined as pain for ≥ 12 weeks, occurring specifically in the lower back)	1. Tramadol or tramadol combined with acetaminophen versus placebo. 2. Tramadol vs celecoxib	Pain assessment, global improvement, side effects

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size[a] (N)	Comparison[a]	Outcomes[a] Measured
	treatment of chronic low back pain. It included a total of 25 RCTs of which 3 RCTs comparing tramadol [or tramadol combination] with placebo and 1 RCT comparing tramadol with celecoxib were relevant for this review and are reported here)	N = 613 in 3 RCTs with placebo as comparator N = 796 in 1 RCT with celecoxib as comparator		
Chaparro,[11] 2012, Cochrane Collaboration (Canada)	SR with qualitative analysis SR included 1 relevant RCT FU = 8 weeks (The SR was an assessment of combination pharmacotherapy for the treatment of neuropathic pain. It included a total of 21 RCTs of which 1 RCT comparing tramadol combination with placebo was relevant for this review and is reported here)	Adults with painful diabetic neuropathy N = 313	(Tramadol 37.5 mg + acetaminophen 325 mg) versus placebo	Pain assessment, AE
Randomized controlled trial				
Tramadol (or Tramadol product) versus placebo				
Schiphorst Preuper,[13] 2014, Netherlands	RCT, triple blinded, 2- centre trial FU = 2 weeks	Adults with chronic low back pain lasting > 3 months (VAS score in past week ≥ 4.0 cm) N = 50 Age (years) (median [IQR]): 42.0 (35.5 to 50.5) in TA, 44.0 (32.5 to 48.0) in plb Male (%): 28 in TA,	TA (37.5 mg tramadol + 325 mg acetaminophen) versus placebo	Pain assessment, functionality

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size[a] (N)	Comparison[a]	Outcomes[a] Measured
		36 in plb VAS pain (median [IQR]): 6.1 (3.2 to 7.1) in TA 4.7 (2.7 to 7.2) in plb		
Chang,[15] 2013, Taiwan	RCT, double blind, single centre FU = 12 weeks	Adults with ankylosing spondylitis (with BASDAI > 3) N = 60 (30 in each group) Age (years) (median [IQR]): 38.0 (17.0) in Ultracet, 33.0 (13.0) in plb Male: 80% in Ultracet, 79% in plb BASDAI (mean ± SD): 5.3 ± 1.3 in Ultracet, 5.7 ± 1.5 in plb	Ultracet (37.5 mg tramado + 325 mg acetaminophen) versus placebo Both groups also received aceclofenac	ASAS20, BASDAI, BASFI, BASG, PGA, QoL, biochemical parameters, AE
Lee,[14] 2013, Korea	RCT, double blind, multicentre (15 centres in Korea) FU = 29 days (visit 5)	Adults with moderate to severe chronic low back pain (average pain intensity ≥ 4.0 cm on VAS) N = 248 were randomized and 245 received at least one dose of study drug Age (years) (mean ± SD): 59.9 ± 10.7 in ER-TA, 60.4± 9.9 in	ER-TA (extended release tramadol 75 mg + acetaminophen 650 mg) versus placebo	Pain assessment, QoL, functionality (K-ODI), AE

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size[a] (N)	Comparison[a]	Outcomes[a] Measured
		placebo Male (%): 25 in ER-TA, 26 in placebo		
Lasko,[16] 2012, Canada	RCT, double blind, multicentre FU = 2.5 days	Adults with moderate-to-severe acute low back pain N = 277 (141 in DDS-06C and 136 in placebo) Age (years) (mean ± SD): 42.2 ± 12.0 in DDS-06C, 42.2 ± 14.0 in placebo Male (%): 43% in DDS-06C, 52% in placebo PIRS score: 2.3 ± 0.5 in DDS-06C, 2.2 ± 0.4 in placebo	DDS-06C (75 mg tramadol + 650 mg paracetamol) versus placebo	SPID. TOTPAR, PGI, AE
Tramadol (or Tramadol product) versus active treatment				
Leng,[18] 2014, China	RCT, double blind, double dummy, non-inferiority, multicentre trial FU = 8 weeks (3 week titration period and 5 weeks maintenance period)	Adults with non-onclological moderate to severe musculoskeletal pain (intervertebral disc disease, spondylolisthesis, osteoarthritis, low back pain and other) N = 280 (139 in TA-SR and 141 in BTDS Age (years) (mean ± SD): 56.77 ± 11.60 in TA-SR 57.23 ± 10.30 in	(Tramadol + placebo) versus (Placebo + buprenorphine) Dosages of sustained release tramadol (TA-SR) tablets were 200, 300, or 400 mg/d Dosages of 7-day buprenorphine transdermal system (BTDS) were 5, 10, and 20µg/h Paracetamol was used as rescue	Pain relief, improvement in waking from pain, rescue medication use, AE

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size[a] (N)	Comparison[a]	Outcomes[a] Measured
		BTDS Male(%): 30 % in TA-SR 32% in BTDS VAS score (cm): 6.53 ± 1.29 in TA-SR, 6.44 ± 1.29 in BTDS	medication	
Banerjee,[12] 2012, India	RCT, single blind, single centre trial FU = 4 weeks	Adults mechanical low back pain of duration > 6 weeks and intolerant to NSAIDs N = 240 (ITT population = 210) Age (years) (mean ± SD): 50.44 ± 6.72 in T, 49.73 ± 7.48 in F Male (%): 51% in T, 42% in F VAS score: 8.6 ± 0.58 in T, 8.57 ± 0.53 in F	Tramadol (T) versus flupirtine (F) T 50 mg twice daily, F 100 mg twice daily	Pain assessment, AE
Park,[17] 2012, Korea	RCT, open label, multicentre trial FU = 8 weeks	Adults with symptomatic knee osteoarthritis (OA) for ≥1 year and who had experienced pain (≥5 on numeric rating scale [NRS]) despite treatment with NSAIDS (meloxicam 7.5 mg or 15 mg qd or aceclofenac 100 mg bid)	(Tramadol 37.5 mg + acetaminophen 325 mg) (TA) versus NSAID	Pain assessment, AE

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size[a] (N)	Comparison[a]	Outcomes[a] Measured
		All (143) patients received TA for 4 weeks and 97 of the 143 patients who experienced pain reduction (n< 4 on NRS) were randomized. N = 97 (47 in TA and 50 in NSAID) The ITT population was 91 and demographics for the ITT population were provided. Age (years) (mean ± SD): 60.02 ± 7.38 in TA 61.15 ± 7.52 in NSAID Male (%): 16% in TA 13% in NSAID Pain intensity (NRS): 3.61 ± 0.89 in TA 3.51 ± 0.86 in NSAID		

AE = adverse event; ASAS20 = assessment in ankylosing spondylitis criteria ; ASQoL = ankylosing spondylitis quality of life ; BASDAI = Bath ankylosing spondylitis disease activity index; BASFI = Bath ankylosing spondylitis functional index; BASG = Bath ankylosing spondylitis global index; BTDS = buprenorphine; CLBP = chronic non-specific low back pain; d = day; DDS-06C = (75 mg tramadol + 650 mg paracetamol); ER-TA = extended release tramadol + acetaminophen; F = flupirtine; FU = follow up; ; h = hour; ITT = intent-to-treat; IQR = interquartile rangeK-ODI = Korean Oswestry disability index; LBP = low back pain; MA = meta-analysis; NRS = numerical rating scale; NSAID = non-steroidal anti-inflammatory drug; PGA = physician global assessment; PIRS = pain intensity rating scale; PGI = patient global impression;, PIRS = pain intensity rating score; plb = placebo; QoL = quality of life; RCT = randomized controlled trial; SD = standard deviation; SPID = sum of pain intensity difference; SR = systematic review; T = tramadol; TA = tramadol combination; TA-SR = sustained release tramadol; TOTPAR = total pain relief score;

[a]In case of reports with multiple comparisons only comparisons of relevance for this report and the corresponding characteristics, sample size and outcomes are mentioned in the table.

APPENDIX 3: Summary of Study Strengths and Limitations

First Author, Publication Year, Country	Strengths	Limitations
Systematic review (SR)		
Chaparro,[8] 2014, Cochrane Collaboration (Columbia, Canada, USA)	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched. Trial registries were searched. Also reference list of the relevant articles were manually searched. • Study selection was described and flow chart was presented • List of included studies was provided • Article selection and data extraction were done in duplicate • Quality assessments of studies were conducted. Level of evidence was assessed • Methods used to combine the findings of studies were appropriate • Publication bias was explored using Funnel plots (Quality of evidence was downgraded by one point if funnel plot suggested publication bias.)	• List of excluded studies was not provided • Characteristics of the individual studies were not provided • Conflicts of interest of the authors were not mentioned.
Mercier,[9] 2014, USA	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched. Trial registries were searched. • Study selection was described • List of included studies was provided • Characteristics of the individual studies were provided but not in detail • As head to head trials were not available an indirect comparison was conducted and a model based meta-analysis was conducted. • Goodness-of fit plots and visual	• Flow chart for study selection was not provided • List of excluded studies was not provided • It was not stated if article selection and data extraction were done in duplicate • Publication bias was not explored • Unclear if a quality assessment of the studies was conducted; the authors mentioned that majority of the included studies were sponsored by industry. • The study was sponsored by industry

First Author, Publication Year, Country	Strengths	Limitations
	predicted checks were used to determine the appropriateness of the model • The authors stated that there was no conflict of interest.	
Chung,[10] 2013, China	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched. • Study selection was described and flow chart was presented • List of included studies was provided • Article selection and data extraction were done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies were conducted • Methods used to combine the findings of studies were appropriate • The authors stated that there was no conflict of interest.	• List of excluded studies was not provided • Publication bias was not explored
Chaparro,[11] 2012, Cochrane Collaboration	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched. Trial registries were searched. Also reference list of the relevant articles were manually searched. • Study selection was described and flow chart was presented • Lists of included and excluded studies were provided • Article selection was done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies were conducted • Authors disclosed their conflicts of interest. Two of the authors had received support from various industries but no support was received for this review.	• Unclear if data extraction was done induplicate. • Publication bias was not explored • No pooling, qualitative analysis

First Author, Publication Year, Country	Strengths	Limitations
Randomized controlled trial (RCT)		
Tramadol (or Tramadol product) versus placebo		
Schiphorst Preuper,[13] 2014, Netherlands	• Objectives were stated. • Inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Randomized (only the hospital pharmacist had access to the randomization scheme); clinicians, patients and testers were blinded • Number discontinued or lost to follow up were reported • *P*-values were provided in some instances but not always • The authors stated that there was no conflict of interest.	• Unclear if intent-to-treat analysis • Sample size calculations were not done. Authors mentioned that power analysis was not possible as no previous data on performance-based measures to establish the effect of analgesics on functional capacity, was available. • The trial was partially funded by industry • Generalizability limited; uncertain as to whether study patients were representative of all patients
Chang,[15] 2013, Taiwan	• Objectives were stated. • Inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Randomized (details not provided); double blind • Number discontinued or lost to follow up were reported • Sample size calculation was provided • *P*-values were provided in some instances but not always • The authors stated that there was no conflict of interest.	• Unclear if intent-to-treat analysis • Generalizability limited; single centre in Taiwan
Lee,[14] 2013, Korea	• Objectives were stated. • Inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Randomized (based on computer generated plan); double blind • Number discontinued or lost to follow up were reported • Intent to treat analysis but mostly full set analysis • Sample size calculation was	• Generalizability limited; though multicentre specific to a single country • All authors received research funding from industry. The trial was funded by industry

First Author, Publication Year, Country	Strengths	Limitations
	provided • *P*-values were provided in some instances but not always • The authors disclosed conflict of interest.	
Lasko,[16] 2012, Canada	• Objectives were stated. • Inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Randomized (details not provided); double blind • Number discontinued or lost to follow up were reported • Intent to treat analysis • Sample size calculation was provided • *P*-values were provided but not always • The authors disclosed conflict of interest.	• Generalizability limited to USA and Canada • Some authors were employees of industry. The trial was funded by industry
Tramadol (or Tramadol product) versus active treatment		
Leng,[18] 2014, China	• Objectives were stated. • Inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Randomized (randomization by a statistician using block randomization method); double blind • Number discontinued or lost to follow up were reported • Number discontinued or lost to follow up were reported • Intent to treat analysis but mostly full set analysis • Sample size calculation was provided • *P*-values were provided in most cases • The authors stated that there was no conflict of interest.	• Generalizability limited; multicentre but specific to China • The trial was funded by industry

First Author, Publication Year, Country	Strengths	Limitations
Banerjee,[12] 2012, India	• Objectives were stated. • Inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Randomized (details not provided); single blind • Intent to treat (ITT) analysis; ITT defined as receiving study agent and with at least one follow up visit • The authors stated that there was no conflict of interest.	• Not double blind • Number discontinued or lost to follow up were not reported • Sample size calculation was not provided • *P* values not provided • Generalizability limited; single centre and specific to single country (India)
Park,[17] 2012, Korea	• Objectives were stated. • Inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Randomized (details not provided); but not blinded • Number discontinued or lost to follow up were reported • Intent to treat (ITT) analysis; ITT defined as all patients who received at least one dose of the study agent and had available efficacy measurements • Sample size calculation was provided • The authors stated that there was no conflict of interest.	• Not blinded • *P* values not provided • Generalizability limited; multicentre but specific to single country (Korea) • The trial was funded by industry

APPENDIX 4: Main Study Findings and Authors' Conclusions

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td>Systematic review</td><td></td></tr>
<tr><td>Chaparro,[8] 2014, Cochrane Collaboration (Columbia, Canada, USA)</td><td>
Main Findings:
Outcomes with tramadol or tramadol + acetaminophen versus placebo in patients with chronic low back pain
<table>
<tr><th>Outcome</th><th>No. of RCTs</th><th>No. of patients</th><th>Effect size</th><th>Heterogeneity I^2 (%)</th></tr>
<tr><td>Pain intensity</td><td>5</td><td>1378</td><td>SMD (95% CI) = -0.55 (-0.66 to – 0.44) Favours tramadol or tramadol combination</td><td>86</td></tr>
<tr><td>Disability</td><td>5</td><td>1248</td><td>SMD (95% CI) = -0.18 (-0.29 to – 0.07) Favours tramadol or tramadol combination</td><td>NR</td></tr>
</table>
Outcomes with tramadol versus celecoxib in patients with chronic low back pain
<table>
<tr><th>Outcome</th><th>No. of RCTs</th><th>No. of patients</th><th>Effect size</th></tr>
<tr><td>Pain intensity</td><td>2 (in I report)</td><td>1583</td><td>RR (95% CI) = 0.82 (0.76 to 0.90) Favours tramadol</td></tr>
</table>
Authors' Conclusion:
"There is evidence that the use of tramadol (a weak atypical opioid) or strong opioids results in improved pain and moderate changes in function in the short term in people with CLBP when compared with placebo. However, the general applicability of this treatment to the clinical setting is questionable. Several factors, including the strict inclusion criteria of the original studies, high drop-out rates, and the poor description of the study population, concurrent treatments, work status, and compensation, limit the reported results. Notably, a number of important outcomes that capture patient function were absent (such as return-to-work outcome)……." P. 561
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td>Mercier,[9] 2014, USA</td><td>

Main Findings:

Efficacy for tramadol versus tapentadol versus placebo in participants with non-malignant pain
The model demonstrated that in a typical trial the estimated reduction in pain intensity compared to baseline value would be
46% (95% CI: 41 to 51%) for tramadol 300 mg qd,
36% (95% CI: 35 to 37%) for tapentadol 100 to 250 mg bid, and
28% (95% CI: 23 to 33%) for placebo

Adverse events and withdrawals due to adverse events for tramadol versus tapentadol versus placebo in participants with non-malignant pain

Outcome	Effect size (% of events)		
	Tramadol	Tapentadol	Placebo
Specific adverse event			
Nausea	22.2	21.7	8.0
Constipation	18.0	15.1	5.3
Dizziness	13.2	15.7	4.6
Somnolence	13.2	12.6	3.8
Vomiting	9.9	6.7	2.2
Withdrawals			
due to adverse event	20.5	18.7	7.1
due to lack of efficacy	7.8	6.1	18.5

Authors' Conclusion:
"The meta-analysis suggests that the benefit–risk ratios of tramadol (300 mg qd) and tapentadol (100–250 mg bid) are similar or not markedly different, with a slightly larger efficacy for tramadol and a slightly better safety profile in favor of tapentadol. In spite of a clinical meaningful efficacy, information from large numbers of patients exposed to these opiate analgesics confirms that one in five patients will discontinue the treatment due to intolerable adverse events, most likely constipation or nausea. As with any meta-analysis, the conclusions must be treated with a degree of caution. " P. 42

(bid = twice daily; qd = once daily)

</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td>Chung,[10] 2013, China</td><td>

Main Findings:

Outcomes with tramadol versus placebo in patients with chronic non-specific low back pain

<table>
<tr><th>Outcome</th><th>No. of RCTs</th><th>No. of patients</th><th>Effect size</th><th>Heterogeneity I^2 (%)</th></tr>
<tr><td>Pain intensity[a]</td><td>3</td><td>613</td><td>SMD (95% CI) = -1.72 (-3.45 to 0.01) NS</td><td>99</td></tr>
<tr><td>Global improvement[b]</td><td>3</td><td>613</td><td>SMD (95% CI) = -0.24 (-0.37 to -0.11) Favours tramadol</td><td>0</td></tr>
<tr><td>Side effects[c]</td><td>3</td><td>613</td><td>RR (95% CI) = 1.74 (1.20 to 2.52) Favours placebo</td><td>83</td></tr>
<tr><td colspan="5">[a]Change in pain intensity from baseline using various scales (VAS: 0 to 100; NRS: 0 to 10; FU = 12 weeks
[b]Change in patients experiencing global improvement using RMDQ and PGI-I; FU = 12 weeks
[c]Proportion of patients experiencing side effects using numbers of adverse events; FU = 12 weeks</td></tr>
</table>

Outcomes with tramadol versus celecoxib in patients with chronic non-specific low back pain

<table>
<tr><th rowspan="2">Outcome</th><th rowspan="2">No. of RCTs</th><th rowspan="2">No. of patients</th><th colspan="2">Effect size (% of patients)</th></tr>
<tr><th>Tramadol</th><th>Celecoxib</th></tr>
<tr><td>Pain intensity[a]</td><td>1</td><td>796</td><td>63.2</td><td>49.9</td></tr>
<tr><td>AE</td><td>1</td><td>796</td><td>30.4</td><td>14.4</td></tr>
<tr><td colspan="5">[a]Pain intensity assessed using NRS (11 point Likert scale) and having at least 30% improvement, FU = 6 weeks</td></tr>
</table>

Authors' Conclusion:

"…..The mild opioid tramadol shows no statistically significant effect of pain relief, but has small effect sizes in improving function……" P. E698.

</td></tr>
<tr><td>Chaparro,[11] 2012, Cochrane Collaboration</td><td>

Main Findings:

Outcomes with tramadol + acetaminophen versus placebo in patients with painful diabetic neuropathy

<table>
<tr><th rowspan="2">Outcome</th><th rowspan="2">No. of RCTs</th><th rowspan="2">No. of patients</th><th colspan="2">Effect size (% of patients)</th></tr>
<tr><th>Tramadol</th><th>Placebo</th></tr>
<tr><td>≥30% pain reduction</td><td>1</td><td>313</td><td>56.2</td><td>37.9</td></tr>
<tr><td colspan="5">AE</td></tr>
<tr><td>Nausea</td><td rowspan="4">1</td><td rowspan="4">313</td><td>11.9</td><td>3.3</td></tr>
<tr><td>Dizziness</td><td>6.3</td><td>1.3</td></tr>
<tr><td>Somnolence</td><td>6.3</td><td>1.3</td></tr>
<tr><td>Withdrawal due to AE</td><td>8.1</td><td>6.5</td></tr>
</table>

</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>Authors' Conclusion:
"…the number of available studies for any one specific combination, as well as other study factors (e.g. limited trial size and duration), preclude the recommendation of any one specific drug combination for neuropathic pain. ….." P. 2</td></tr>
<tr><td colspan="2">Randomized controlled trial (RCT)</td></tr>
<tr><td colspan="2">Tramadol (or Tramadol product) versus placebo</td></tr>
<tr><td>Schiphorst Preuper,[13] 2014, Netherlands</td><td>
Main Findings:

Outcomes with tramadol 37.5 mg and acetaminophen 325 mg combination (TA) versus placebo in patients with chronic low back pain
<table>
<tr><th>Outcome[a]</th><th>Time point</th><th>Tramadol + acetaminophen (TA)
N =24</th><th>Placebo

N = 25</th></tr>
<tr><td rowspan="2">VAS</td><td>Before Tx</td><td>6.1 (3.0 to 7.2)</td><td>4.7 (2.7 to 7.2)</td></tr>
<tr><td>After Tx</td><td>5.1 (3.3 to 7.1)</td><td>4.5 (2.9 to 6.9)</td></tr>
<tr><td rowspan="2">RMDQ (0 – 24)</td><td>Before Tx</td><td>13.0 (10.3 to 14.8)</td><td>13.0 (10.5 to 15.0)</td></tr>
<tr><td>After Tx</td><td>11.5 (9.3 to 15.0)</td><td>13.0 (8.0 to 14.5)</td></tr>
<tr><td>Global pain change – pain relief, n (%)</td><td>After Tx</td><td>10 (42)</td><td>1 (4)</td></tr>
<tr><td>Global pain change – same pain or worse, n (%)</td><td>After Tx</td><td>14 (58)</td><td>24 (96)</td></tr>
<tr><td colspan="4">[a]Outcome expressed as median (IQR) unless otherwise stated</td></tr>
</table>
Responders
Pain relief in the 10 responders in the TA group
<table>
<tr><th>Outcome[a]</th><th>Time point</th><th>Tramadol + acetaminophen (TA)
N = 10</th><th>P value</th></tr>
<tr><td rowspan="2">RMDQ (0 – 24)</td><td>Before Tx</td><td>13.0 (10.3 to14.8)</td><td rowspan="2">0.02</td></tr>
<tr><td>After TX</td><td>11.5 (9.3 to 15.0)</td></tr>
</table>
Responders showed a significantly lower score on the subscale of catastrophizing on the Pain Cognition List (PCL) compared to non-responders: median 35.5 versus 44.0, P = 0.005

Authors' Conclusion:
"Overall treatment effects were small and non-significant. A subgroup, however, reported improved functioning as a result of treatment. Responders had lower catastrophizing scores." P. 800
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td>Chang,[15] 2013, Taiwan</td><td>
Main Findings:
Outcomes with tramadol 37.5 mg and acetaminophen 325 mg combination (Ultracet) versus placebo in patients with ankylosing spondylitis
<table>
<tr><th>Outcome[a]</th><th>Time point</th><th>Tramadol + acetaminophen</th><th>Placebo</th><th>P value</th></tr>
<tr><td rowspan="2">ASAS20 (% of patients)</td><td>Week 2</td><td>36.6</td><td>27.6</td><td>NR</td></tr>
<tr><td>Week 12</td><td>53.3</td><td>31</td><td>0.047</td></tr>
<tr><td rowspan="2">ASQoL</td><td>Week 2</td><td>-1.0 (2.0)</td><td>0.0 (2.0)</td><td>NR</td></tr>
<tr><td>Week 12</td><td>-1.0 (4.0)</td><td>0.0 (2.0)</td><td>NR</td></tr>
<tr><td rowspan="2">BASDAI</td><td>Week 2</td><td>-0.8 ± 1.5</td><td>-1.2 ± 1.7</td><td>NR</td></tr>
<tr><td>Week 12</td><td>-2.2 ± 2.2</td><td>-1.5 ± 1.7</td><td>NR</td></tr>
<tr><td rowspan="2">BASFI</td><td>Week 2</td><td>-0.1 ± 1.6</td><td>-0.6 ± 1.2</td><td>NR</td></tr>
<tr><td>Week 12</td><td>-0.7± 2.5</td><td>-0.3 ± 1.5</td><td>NR</td></tr>
<tr><td rowspan="2">BASG</td><td>Week 2</td><td>-0.9 ± 2.4</td><td>-0.4 ± 1.5</td><td>NR</td></tr>
<tr><td>Week 12</td><td>-1.5 ± 2.8</td><td>-0.6 ± 2.2</td><td>NR</td></tr>
<tr><td rowspan="2">PGA</td><td>Week 2</td><td>-0.3 (1.0)</td><td>0.0 (1.0)</td><td>NR</td></tr>
<tr><td>Week 12</td><td>-1.5 (1.5)</td><td>-1.0 (1.0)</td><td>NR</td></tr>
<tr><td rowspan="2">SF-36, physical functioning</td><td>Week 2</td><td>2.5 ± 18.3</td><td>1.6 ± 14.6</td><td>NR</td></tr>
<tr><td>Week 12</td><td>3.7 ± 18.7</td><td>3.3 ± 14.7</td><td>NR</td></tr>
<tr><td rowspan="2">VAS pain score (%)</td><td>Week 2</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Week 12</td><td>45.6</td><td>25.7</td><td>0.087</td></tr>
<tr><td colspan="5">[a]Outcomes are reported as change from baseline and presented as mean± SD or median (IQR), if not otherwise stated.</td></tr>
</table>
Adverse events with tramadol and acetaminophen combination (Ultracet) versus placebo in patients with ankylosing spondylitis
<table>
<tr><th>Adverse events category[a]</th><th>Tramadol + acetaminophen N = 30</th><th>Placebo N = 30</th><th>P value</th></tr>
<tr><td>Total AE</td><td>43 (64.2)</td><td>24 (35.8)</td><td>< 0.001</td></tr>
<tr><td>Possible AS-related</td><td>12 (17.9)</td><td>10 (14.9)</td><td>0.602</td></tr>
<tr><td>CNS system</td><td>10 (14.9)</td><td>3 (4.5)</td><td>0.030</td></tr>
<tr><td>Digestive system</td><td>7 (10.4)</td><td>3 (4.5)</td><td>0.170</td></tr>
<tr><td>Urology</td><td>1 (1.5)</td><td>0 (0.0)</td><td>1.0</td></tr>
<tr><td>Infection</td><td>1 (1.5)</td><td>1 (1.5)</td><td>1.0</td></tr>
<tr><td>Other</td><td>11 (16.4)</td><td>7 (10.4)</td><td>0.269</td></tr>
<tr><td colspan="4">[a]Data presented as number of event (% events)</td></tr>
</table>
Number of withdrawals with tramadol and acetaminophen combination (Ultracet) versus placebo in patients with ankylosing spondylitis
<table>
<tr><th>Withdrawals</th><th>Tramadol + acetaminophen</th><th>Placebo</th></tr>
<tr><td>Total</td><td>6</td><td>11</td></tr>
<tr><td>due to AE</td><td>1</td><td>3</td></tr>
<tr><td>due to withdrawal of consent</td><td>2</td><td>2</td></tr>
<tr><td>due to lack of efficacy</td><td>3</td><td>5</td></tr>
<tr><td>due to protocol violation</td><td>0</td><td>1</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>Authors' Conclusion:
"The tramadol 37.5 mg/acetaminophen 325 mg combination tablet (Ultracet®) might have additional effect to nonsteroidal anti-inflammatory drugs in the treatment of patients with ankylosing spondylitis. It showed marginal benefit in pain and disease activity. However, a slight increase in minor adverse events was noted." P. 346</td></tr>
<tr><td>Lee,[14] 2013, Korea</td><td>Main Findings:

Percentage of patients with pain relief with tramadol 75 mg + acetaminophen 650 mg (ER-TA) versus placebo in patients with chronic low back pain; FAS
<table>
<tr><th>Outcome</th><th>Time point</th><th>Tramadol + acetaminophen N = 85</th><th>Placebo N = 90</th><th>P value</th></tr>
<tr><td>Pain intensity change ≥30% (using VAS)</td><td>Visit 5 or study end</td><td>57.7</td><td>41.1</td><td>0.037</td></tr>
<tr><td>Pain intensity change ≥50% (using VAS)</td><td>Visit 5 or study end</td><td>31.76</td><td>20.00</td><td>0.075</td></tr>
<tr><td rowspan="3">Pain relief success rate (using 6-point pain relief scale; success = slight pain relief and above, i.e. 1 to 4)</td><td>Visit 3</td><td>70.73</td><td>53.41</td><td>0.020</td></tr>
<tr><td>Visit 4</td><td>82.35</td><td>65.17</td><td>0.010</td></tr>
<tr><td>Visit 5 or study end</td><td>81.18</td><td>77.53</td><td>0.465</td></tr>
<tr><td colspan="5">visit 3: day 8, visit 4: day 15, visit 5: day 29</td></tr>
</table>
Quality of life (QoL) using Korean Short form-36 (K-SF-36) with tramadol 75 mg + acetaminophen 650 mg (ER-TA) versus placebo in patients with chronic low back pain; FAS
<table>
<tr><th>Outcome[a] (K-SF-36 domain)</th><th>Tramadol + acetaminophen N = 83</th><th>Placebo N = 87</th><th>P value</th></tr>
<tr><td>Physical functioning</td><td>9.82 ± 18.35</td><td>6.67 ± 15.99</td><td>0.352</td></tr>
<tr><td>Role-physical</td><td>16.04 ± 23.8</td><td>8.69 ± 22.62</td><td>0.022</td></tr>
<tr><td>Body pain</td><td>19.39 ± 18.99</td><td>17.69 ± 14.84</td><td>0.571</td></tr>
<tr><td>General health</td><td>7.36 ± 14.41</td><td>2.77 ± 12.58</td><td>0.040</td></tr>
<tr><td>Vitality</td><td>11.14 ± 20.55</td><td>5.82 ± 18.94</td><td>0.052</td></tr>
<tr><td>Social functioning</td><td>11.75 ± 25.70</td><td>6.61 ± 20.60</td><td>0.115</td></tr>
<tr><td>Role-emotional</td><td>8.13 ± 28.93</td><td>7.47 ± 28.25</td><td>0.779</td></tr>
<tr><td>Mental Health</td><td>20.48 ± (23.20</td><td>18.39 ± 24.61</td><td>0.778</td></tr>
<tr><td>Reported health transition</td><td>–18.07 ± 25.99</td><td>–6.90 ± 30.19</td><td>0.005</td></tr>
<tr><td colspan="4">[a]Data reported as mean ± SD</td></tr>
</table></td></tr>
</table>

First Author, Publication Year, Country	Main Findings and Authors' Conclusion

Functional improvement using Korean Oswestry disability index (K-ODI) with tramadol 75 mg + acetaminophen 650 mg (ER-TA) versus placebo in patients with chronic low back pain ; FAS

Outcome[a] (K-ODI domain)	Tramadol + acetaminophen N = 83	Placebo N = 87	*P* value
Pain intensity	1.012 ± 0.819	0.793 ± 0.966	0.101
Personal care	0.590 ± 1.082	0.322 ± 0.982	0.045
Lifting	0.494 ± 1.130	0.195 ± 1.256	0.080
Walking	0.337 ± 0.769	0.356 ± 0.792	0.900
Sitting	0.518 ± 1.028	0.333 ± 1.042	0.335
Standing	0.590 ± 1.048	0.299 ± 0.929	0.135
Sleeping	0.530 ± 0.941	0.322 ± 1.062	0.066
Sex life	0.612 ± 1.187	0.286 ± 1.099	0.420
Social life	0.506 ± 1.119	0.460 ± 1.265	0.773
Travelling	0.446 ± 0.978	0.161 ± 1.119	0.244
K-ODI score	11.216 ± 11.856	7.178 ± 13.879	0.053
[a]Data reported as mean ± SD			

Adverse events with tramadol 75 mg + acetaminophen 650 mg (ER-TA) versus placebo in patients with chronic low back pain

Adverse events (AEs) category[a]	Tramadol + acetaminophen N = 125	Placebo N = 120
All AE	83.2	54.2
Common AE (occurring in ≥5% of patients)		
Nausea	36.8	10.0
Dizziness	28.0	8.3
Constipation	18.4	NR
Vomiting	16.8	NR
Pruritus	15.2	NR
Somnolence	14.4	NR
Dyspepsia	10.4	10.0
Headache	8.8	5.0
[a]Data presented as % of patients		

Withdrawals: Percentage of patients who discontinued treatment because of an adverse event was 19.2% in the ER-Ta group and 5.0% in the placebo group.

Serious adverse events: There were four serious adverse events during the study but were considered unrelated to the study agents.

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>
Details of the assessment tools
<table>
<tr><th>Assessment tool</th><th>Description</th></tr>
<tr><td>Visual analog scale (VAS)</td><td>10 cm visual analog scale, where 0 = no pain and 10 = worst pain imaginable</td></tr>
<tr><td>Pain relief, 6-point scale</td><td>-1 = pain worsening, 0 = no change, 1 = slight pain relief, 2 = moderate pain relief, 3 = fair pain relief, 4 = complete pain relief,</td></tr>
<tr><td>Korean short form-36 (K-SF-36)</td><td>Scale: 0 to 100, with higher scores indicating better quality of life (QoL). Higher scores in reported health transition domain indicate deteriorating QoL</td></tr>
</table>
Details of the population in the analyses
<table>
<tr><th>Assessment population</th><th>Description</th></tr>
<tr><td>Intent-to-treat (ITT)</td><td>All patients who received at least one dose of the study agent. Population used for adverse event analysis.</td></tr>
<tr><td>Full analysis set (FAS)</td><td>All patients who received the study agent and had at least one measurement of change in average pain intensity.</td></tr>
</table>
Authors' Conclusion:
"TA-ER was significantly more effective than placebo in providing pain relief, functional improvements, and improved quality of life. It exhibited a predictable safety profile in patients with chronic low back pain." P. 1830

(TA-ER = extended release tramadol hydrochloride 75 mg + acetoaminophen 650 mg fixed dose combination)
</td></tr>
<tr><td>Lasko,[16] 2012, Canada</td><td>
Main Findings:
Pain relief with tramadol + paracetamol (DDS-06C) versus placebo in patients with acute low back pain
<table>
<tr><th>Outcome[a]</th><th>Tramadol + paracetamol (DDS-06C)
N = 141</th><th>Placebo
N = 136</th><th>P value</th></tr>
<tr><td>SPID50[b]</td><td>-6.0 (-22 to 3)</td><td>-4.0 (-23 to 10)</td><td>0.038[c]</td></tr>
<tr><td>TOTPAR50</td><td>13.0 (0 to 32)</td><td>11.0 (0 to 40)</td><td>0.026[c]</td></tr>
<tr><td>SPID4</td><td>-2.0 (15 to 5)</td><td>-1.0 (-10 to 5)</td><td>0.024[c]</td></tr>
<tr><td>SPIDW50</td><td>-20.0 (-67 to 18)</td><td>-15.3 (-69 to 26)</td><td>0.162[c]</td></tr>
<tr><td>TOTPARW50</td><td>43 (0 to 97)</td><td>30.5 (0 to 104)</td><td>0.066[c]</td></tr>
<tr><td>PGI[d] (%)</td><td>very effective: 19.4
effective: 26.6
somewhat effective: 40.3
ineffective: 13.7</td><td>very effective: 13.3
effective: 22.2
somewhat effective: 34.1
ineffective: 30.4</td><td>0.005[e]</td></tr>
</table>
[a]Outcomes expressed as median (minimum to maximum) unless otherwise stated.
[b]Primary outcome
[c]Wilcoxon rank-sum test
[d]PGI of study drug expressed as % of patients with non-missing data; N= 139 for DDS-06C group and N = 135 for placebo group
[e]Cochran-Mantel-Haenszel mean score statistic
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>
Percentage of patients with clinically significant SPID50 or TOTPAR50 score
<table>
<tr><th>Outcome</th><th>Tramadol + paracetamol (DDS-06C)
N = 141</th><th>Placebo
N = 136</th></tr>
<tr><td>SPID5 ≤ -10, n (%)</td><td>39 (27.7)</td><td>27 (19.9)</td></tr>
<tr><td>TOTPAR50 ≥ 13 , n (%)</td><td>78 (55.3)</td><td>60 (44.1)</td></tr>
</table>
Adverse events reported by > 5% of patients
<table>
<tr><th>Outcome</th><th>Tramadol + paracetamol (DDS-06C)
N = 141</th><th>Placebo
N = 136</th></tr>
<tr><td>Nausea, n (%)</td><td>34 (24.1)</td><td>3 (2.2)</td></tr>
<tr><td>Dizziness, n (%)</td><td>21 (14.9)</td><td>2 (1.5)</td></tr>
<tr><td>Vomiting, n (%)</td><td>21 (14.9)</td><td>NR</td></tr>
<tr><td>Somnolence, n (%)</td><td>13 (9.2)</td><td>5 (3.7)</td></tr>
</table>
One patient in the DDS-06C experienced a serious adverse event (exacerbation of back pain requiring hospitalization) which was not considered to be related to the study medication. The patient recovered completely.
</td></tr>
<tr><td></td><td>
Authors' Conclusion:
"Using acute low back pain, a model with a high degree of heterogeneity and intrinsic variability, DDS-06C was superior to placebo on measures of pain intensity and relief, and was well-tolerated." P. 847

(DDS-06C = 75 mg tramadol+ 650 mg paracetamol)
</td></tr>
<tr><td colspan="2">Tramadol versus active treatment</td></tr>
<tr><td>Leng,[18] 2014, China</td><td>
Main Findings:
Outcomes with tramadol (TA-SR) versus buprenorphine (BTDS) in patients with musculoskeletal pain; FAS
<table>
<tr><th>Outcome[a]</th><th>TA-SR
N = 133</th><th>BTDS
N = 136</th><th>P value</th></tr>
<tr><td>Change in VAS score from baseline</td><td>-3.75 ± 2.15</td><td>-3.30 ± 2.29</td><td>0.095</td></tr>
<tr><td>Pain relief any degree, n (%)</td><td>123 (93.9)</td><td>115 (89.2)</td><td>NR</td></tr>
<tr><td>Pain relief none or aggravation, n (%)</td><td>8 (6.1)</td><td>14 (10.8)</td><td>NR</td></tr>
<tr><td>Paracetamol tablets used during maintenance period</td><td>0.09 ± 0.30</td><td>0.07 ± 0.28</td><td>NR</td></tr>
<tr><td>Improvement in waking nights</td><td>-1.06 ± 1.98</td><td>-0.79 ± 1.47</td><td>NR</td></tr>
<tr><td colspan="4">[a]Outcomes expressed as (mean ± SD) unless otherwise stated.</td></tr>
</table>
</td></tr>
</table>

First Author, Publication Year, Country	Main Findings and Authors' Conclusion

Adverse events with tramadol (TA-SR) versus buprenorphine (BTDS) in patients with musculoskeletal pain; SS

Outcome[a]	TA-SR N = 139	BTDS N =141
Nausea	30 (21.7)	30 (21.0)
Dizziness	24 (17.4)	34 (24.0)
Vomiting	15 (10.6)	14 (9.6)
Constipation	10 (7.5)	9 (6.0)
Somnolence	9 (6.2)	9 (6.0)
Cutaneous reaction	9 (6.2)	8 (5.4)
Serious adverse events	3 (2.2)	0
[a]Outcome expressed as n (%)		

Withdrawals with tramadol (TA-SR) versus buprenorphine (BTDS) in patients with musculoskeletal pain

Outcome	TA-SR N = 139	BTDS N =141
Withdrawals		
due to adverse events	25	29
due to lost to follow up	1	3
due to withdrawal of consent	4	2
due to lack of effectiveness	2	1
due to other reasons	1	5

Details of the population in the analyses

Assessment population	Description
Intent-to-treat (ITT)	All patients who received at least one dose of the study agent
Full analysis set (FAS)	All patients who received at least one dose of the study agent and who provided at least one post-dose effectiveness observation
Safety set (SS)	Patients who received at least one dose of the study agent and who provided at least one post-dose safety observation

Authors' Conclusion:

"In conclusion, our data confirmed that BTDs was effective in pain relieving, and that it is was well tolerated in Chinese patients with moderate to severe MSP insufficiently controlled under NSAIDs treatment. Furthermore, BTDS treatment was non-inferior to sustained release tramadol tablets." From manuscript accepted for publication

(BTDS = buprenorphine; MSP = musculoskeletal pain; NSAID = non-stedroidal anti-inflammatory drugs)

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td>Banerjee,[12] 2012, India</td><td>

Main Findings:

Outcomes with tramadol versus flupirtine in patients with mechanical low back pain

Outcome	Time point	Tramadol	Flupirtine
VAS	Visit 0/ Baseline	8.6 ± 0.58	8.57 ± 0.53
	Visit 1	5.6 ± 0.49	5.51 ± 0.5
	Visit 2	3.71 ± 0.62	3.62 ± 0.65
	Visit 3	1.45 ± 0.54	1.26 ±0.48
NRS	Visit 0/ Baseline	8.52 ± 0.50	8.67 ± 0.63
	Visit 1	5.67 ± 0.69	5.82 ± 0.66
	Visit 2	2.46 ± 0.50	2.39 ± 0.49
	Visit 3	1.62 ± 0.60	1.43 ± 0.67
Indian HAQ	Visit 0/ Baseline	2.31 ± 1.77	2.14 ± 0.18
	Visit 1	1.72 ± 0.23	1.65 ± 0.26
	Visit 2	1.36 ± 0.25	1.25 ± 0.25
	Visit 3	0.97 ± 0.19	0.82 ± 0.2

Pain relief: Percentage of patients experiencing significant to completed pain relief after 4 weeks (i.e. in Visit 3) was less in the tramadol group compared to the flupirtine group 39.81% versus 55.14%, *P* < 0.05

Adverse events tramadol versus flupirtine in patients with mechanical low back pain

Outcome[a]	Tramadol	Flupirtine
Nausea	25.24	7.48
Dizziness	24.27	11.21
Vomiting	11.65	3.74
Constipation	9.71	2.8
[a]Outcomes expressed as %		

Authors' Conclusion:

"Our study suggests that flupirtine may have superior sustained effect compared to tramadol in subacute low back pain, along with better tolerability. But the unicenter, single-blinded nature of this study involving relatively small number of subjects necessitates further studies to confirm this observation." P. 139

</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td>Park,[17] 2012, Korea</td><td>

Main Findings:

Outcomes with tramadol + acetaminophen (TA) versus NSAID in patients with osteoarthritis pain; ITT

Outcome[a]	Time point	TA N = 44	NSAID N = 47	*P* value
NRS score	Day 29	4.58 ± 1.94	4.26 ± 1.54	NS
	Day 57	4.55 ± 2.31	3.89 ± 1.81	NS
WOMAC OA total score	Day 29	37.74 ± 17.17	32.29 ± 16.43	NS
	Day 57	33.64 ± 18.06	29.89 ± 15.56	NS
[a]Outcomes expressed as (mean ± SD)				

Adverse events with tramadol + acetaminophen (TA) versus NSAID in patients with osteoarthritis pain

Outcome[a]	TA	NSAID
Nausea	8.5	12.0
Dizziness	8.5	8.0
Heartburrn	6.4	NR
Constipation	4.3	2.0
[a]Outcomes expressed as %		

Discontinuations with tramadol + acetaminophen (TA) versus NSAID in patients with osteoarthritis pain

Outcome[a]	TA	NSAID
Discontinued	11	7
due to withdrawal of consent	4	1
due to protocol violation	3	3
due to adverse effect	1	
due to lost to follow up	1	3
due to other reasons	2	

Details of the population in the analyses

Assessment population	Description
Intent-to-treat (ITT)	All patients who received at least one dose of the study agent and had available efficacy measurements

Authors' Conclusion:
"In conclusion, when added to NSAID, tramadol/APAP was generally well tolerated and significantly improved knee OA pain which was previously refractory to NSAID therapy. In those subjects who showed favorable response to tramadol/APAP and NSAID combination therapy, both tramadol/APAP and NSAIDs were effective at maintaining the pain-reduced state and there was no significant difference in efficacy between tramadol/APAP and NSAIDs." P. 322

(APAP = acetaminophen; OA = osteoarthritis; NSAID = non-steroidal anti-inflammatory drug)

</td></tr>
</table>

First Author, Publication Year, Country	Main Findings and Authors' Conclusion
AE = adverse event; ASAS20 = assessment in ankylosing spondylitis criteria; ASQoL; = ankylosing spondylitis quality of life ; BASDAI = Bath ankylosing spondylitis disease activity index ; BASFI = Bath ankylosing spondylitis functional index; BASG = Bath ankylosing spondylitis global index; bid = twice daily; BTDS = buprenorphine; CI = confidence interval; ER-TA extended release tramadol; FAS = full analysis set; FU = follow up; HAQ = health assessment questionnaire; IQR = inter quartile range; NR = not reported; NRS = numerical rating scale; NS = not significant; OA = osteoarthritis; PGA = physician global assessment; PGI-I = patients' global impression of improvement – index; qd = once daily; RMDQ = Rolland Morris disability questionnaire; RR = relative risk; SD = standard deviation; SF-36 = short-form 36 questionnaire for quality of life; SPID = sum of pain intensity difference; SPID4 = SPID over first 4 hours; SPID50 = SPID over 50 hours; SS = safety set; TA = tramadol combination; TA-SR = tramadol sustained release; TOTPAR = total pain relief score; TOTPAR50 = total pain relief score score over 50 hours; TOTPARW50 = weighted TOTPAR50; Tx = treatment; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities	