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Tapentadol for chronic musculoskeletal pain in adults (Review)

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[Intervention Review]

Tapentadol for chronic musculoskeletal pain in adults

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ABSTRACT

Background

Chronic musculoskeletal pain is a prevalent condition and a major cause of disability and absence from the workplace worldwide. Opioids are frequently used to treat chronic pain, although adverse effects often restrict their long-term benefits. Tapentadol is an opioid and noradrenaline re-uptake inhibitor, which may cause a lower incidence (and severity) of adverse effects compared to other strong opioids.

Objectives

To determine the efficacy, safety, and tolerability of tapentadol extended-release for moderate-to-severe pain for at least three months for any musculoskeletal cause.

Search methods

We searched electronic databases (the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and Web of Science) to March 2014, unrestricted by language, as well as trials registers and reference lists from retrieved studies. We contacted drug manufacturers for further information.

Selection criteria

Randomised controlled trials (RCTs) of tapentadol in people with chronic musculoskeletal pain compared to placebo or active control.

Data collection and analysis

Two review authors independently selected trials for inclusion, assessed risk of bias of included studies, and extracted data. We performed two meta-analyses for the comparisons tapentadol extended release versus placebo and tapentadol extended release versus active control (oxycodone). We used random-effects models when there was heterogeneity and fixed-effect models when there was no heterogeneity. In addition, we performed subgroup analyses. The primary efficacy outcome was pain control assessed by change in pain intensity scores and responder's rate (at least 50% pain relief). The primary safety outcome was withdrawal rate due to adverse effects.

Main results

Four parallel-design RCTs of moderate quality including 4094 participants with osteoarthritis or back pain, or both, met the inclusion criteria. Three trials were phase III studies with 12 weeks' follow-up and the fourth trial was an open-label safety study of 52 weeks' follow-up. All trials were oxycodone-controlled and three were also placebo-controlled. Two trials included people with knee osteoarthritis, one evaluated people with low back pain, and one enrolled both. All studies reported last-observation-carried-forward (LOCF) as the imputation method. We requested baseline-observation-carried-forward (BOCF) imputed analyses and any unpublished data from the manufacturers but the manufacturers denied the request. Two of the four oxycodone-controlled studies and one of the three placebo-controlled studies did not provide data on responder rate. We considered two studies to be of high risk of bias.

In comparison to placebo, tapentadol was associated with a mean reduction of 0.56 points (95% confidence interval (CI) -0.92 to -0.20) in the 11-point numerical rating scale (NRS) at 12 weeks and with a 1.36 increase (95% CI 1.13 to 1.64) in the risk of responding to treatment (number needed to treat for an additional beneficial outcome (NNTB) 16; 95% CI 9 to 57, for 12 weeks). There was moderate-to-high heterogeneity for the efficacy outcome estimates. Tapentadol was associated with a 2.7-fold increase (95% CI 2.05 to 3.52) in the risk of discontinuing treatment due to adverse effects (number needed to treat for an additional harmful outcome (NNTH) 10; 95% CI 7 to 12, for 12 weeks).

In comparison to oxycodone, pooled data showed a 0.24 point reduction (95% CI -0.43 to -0.05) in pain intensity from baseline in the 11-point NRS. The two studies that evaluated responder's rate showed a non-significant 1.46 increase (95% CI 0.92 to 2.32) in the risk of responding to treatment among tapentadol-treated participants. Tapentadol was associated with a 50% risk reduction (95% CI 42% to 60%) of discontinuing treatment due to adverse effects (NNTH 6; 95% CI 5 to 7, for 12 weeks). Tapentadol was also associated with a 9% reduction (95% CI 4% to 15%) in the overall risk of adverse effects (NNTH 18; 95% CI 12 to 35, for 12 weeks) and with a non-significant 43% reduction (95% CI 33% to 76%) in the risk of serious adverse effects. There was moderate-to-high heterogeneity for most efficacy (except for the primary outcome) and safety outcome estimates. Subgroup analysis showed a higher improvement with tapentadol among people with knee osteoarthritis and among pooled results from studies of higher quality and shorter follow-up period, although there were no statistical significant differences in the effect size between these subgroups.

Authors' conclusions

Tapentadol extended release was associated with a reduction in pain intensity in comparison to placebo and oxycodone. However, the clinical significance of the results is uncertain due to the following reasons: modest difference between interventions in efficacy outcomes, high heterogeneity in some comparisons and outcomes, high withdrawals rates, lack of data for the primary outcome in some studies, and the impossibility of using BOCF as the imputation method. Tapentadol is associated with a more favourable safety profile and tolerability than oxycodone.

PLAIN LANGUAGE SUMMARY

Tapentadol for chronic musculoskeletal pain in adults

Pain in bones, joints, and muscles is very common and can often be persistent. It is expected that 50% of the general population will suffer from this type of pain for at least three months or longer during their lifetime. This condition is called chronic musculoskeletal pain.

Opioids are a type of strong pain-killer drug that are used to treat people that have moderate-to-severe chronic pain. People taking these drugs frequently have side effects, including severe side effects.

This Cochrane review aimed to assess the effectiveness (reduction in pain intensity) and safety of tapentadol (a new opioid) in moderate-to-severe chronic musculoskeletal pain, in comparison to placebo (a pretend medicine) and other drugs that work for such pain.

We performed a literature search in March 2014 for studies that compared tapentadol with placebo or other drugs in adults with musculoskeletal pain.

We found four studies comparing tapentadol with placebo or oxycodone (another opioid) in 4094 adults.

There was moderate-quality evidence that 3 out of 10 people treated with tapentadol had at least 50% pain reduction (responded to the treatment) while only 2 out of 10 people treated with oxycodone and placebo responded to the treatment.

There was also moderate-quality evidence that tapentadol-treated people were at a higher risk of withdrawal from the trial due to side effects in comparison to placebo (2 out of 10 tapentadol-treated people and 1 out of 10 placebo-treated people). For oxycodone-treated people, 4 out of 10 withdrew due to side effects. Constipation, nausea and vomiting, and itching (pruritus) were less with tapentadol than with oxycodone but there was no difference in fatigue, insomnia, sleepiness (somnolence), and headache.

The overall clinical benefit of tapentadol in moderate-to-severe chronic musculoskeletal pain found in clinical trials was relatively small (a common conclusion found in all opioids trials for chronic pain). Further studies are needed to find out which people with chronic musculoskeletal pain would benefit the most from this new opioid.

BACKGROUND

Description of the condition

The International Association for the Study of Pain (IASP) defines chronic pain as pain without apparent biological value that has persisted beyond the normal tissue healing time (usually taken to be three months) (IASP 1986). This definition is widely accepted, although other definitions have also been proposed. The exact time point that differentiates between acute and chronic pain (three to six months) is controversial (Marcus 2000), and it can be argued that every pain that is not chronic is acute. Chronic pain is usually categorised as cancer-related or non-cancer-related in origin, and most treatment guidelines are specifically directed to one or the other. In the case of chronic musculoskeletal pain, it includes various painful local or regional musculoskeletal disorders (such as low back pain and osteoarthritis), but also people with chronic widespread pain.

Musculoskeletal pain is extremely prevalent, with virtually every adult having at least one episode in the last year and about 50% of adults in the last month (Crombie 1999). Most of these episodes are brief but recurrent or chronic pain is also common (Papageogiou 1995; Urwin 1998). The exact prevalence of chronic musculoskeletal pain is difficult to estimate. The prevalence rates reported in individual studies vary widely, from 10% (Buskila 2000) to over 50% (Andersson 1993). This variation is due to different case definitions, methods used to collect data, time periods, and populations studied. The most important risk factors for chronic musculoskeletal pain are age (the most common causes of chronic musculoskeletal pain have a higher incidence and prevalence in older people, sex (some causes are more common in one gender), and the presence of degenerative disease processes (eg osteoarthritis) (Crombie 1999; LeResche 2000).

Moderate-to-severe chronic musculoskeletal pain is an important cause of physical disability and work absence, carrying a huge economic and social cost (Breivik 2006; McAlindon 1992; Reisine 2001). Therefore, it represents a relevant problem (although at different levels) to patients, health professionals, the healthcare system, and society.

Description of the intervention

Opioids started to be used for pain relief thousands of years ago when opium analgesic properties were discovered. Nowadays, opioids are well established as pharmacological treatment options for both oncological and non-oncological chronic moderate-to-severe pain (Jadad 1995; Trescot 2008a), and the use of chronic opioid therapy for chronic non-cancer pain has increased substantially (Chou 2009). Commercially available strong opioids for clinical use include morphine, hydromorphone, levorphanol, oxycodone, and fentanyl. The primary activity of these drugs is at the μ -opioid receptors (μ -agonists), which are found primarily in the central nervous system (brainstem and medial thalamus) (Trescot 2008b).

Although the strength of the actual evidence-based recommendations differ according to the person's condition (e.g. malignant versus non-malignant pain) and for specific drugs, they all agree that strong opioids should only be considered when other pharmacological options have failed to control pain adequately (Chou 2009; Trescot 2008a). However, up to 50% of people still

receive inadequate pain relief. In these situations, pain relief is very challenging due to the variety of pain mechanisms involved and adverse effects of the available analgesics (Freynhagen 2006).

Tapentadol is a novel opioid analgesic that is currently being evaluated in clinical trials for chronic moderate-to-severe pain.

How the intervention might work

Tapentadol is a centrally acting opioid analgesic with two complementary mechanisms of action, namely μ -opioid receptor agonism and noradrenaline re-uptake inhibition. In comparison with other strong opioids, tapentadol is a weak opioid agonist due to the lower binding affinity to opioid receptors. The synergistic analgesic effect of the noradrenaline re-uptake inhibition contributes to an opioid-sparing effect. These properties may reduce the incidence (and severity) of adverse effects associated with μ -opioid agonism, such as constipation, nausea, and vomiting.

The analgesic effects of tapentadol are independent of metabolic activation and have no known active metabolites. Therefore, there are claims that tapentadol may be associated with a low inter-individual efficacy variations and drug-drug interactions, while providing broad pain inhibition due to its complementary modes of action.

Tapentadol should be considered in clinical practice as an option to other strong opioids in the third step of the World Health Organization (WHO) Pain Relief Ladder (WHO 2010).

Why it is important to do this review

The Food and Drug Administration (FDA) approved tapentadol extended-release (ER) formulation in chronic pain in September 2011 for the US market, following the European Medicines Agency's (EMA) decentralised decision in 2010. Several clinical trials have been conducted and others are in progress, with the aim of assessing the efficacy and safety of tapentadol for non-oncological chronic pain. Therefore, it is relevant to evaluate in a systematic review the benefits and risks of this new analgesic agent in people with moderate-to-severe musculoskeletal chronic pain, which is the most frequent cause of non-oncological chronic pain.

OBJECTIVES

To determine the efficacy, safety, and tolerability of tapentadol extended-release for moderate-to-severe pain for at least three months for any musculoskeletal cause.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs), published and unpublished, where randomisation was explicit and appropriate. We included both parallel and cross-over studies.

Types of participants

Participants included adults, both male and female, aged 18 years or older. We considered all participants with moderate-to-severe chronic musculoskeletal pain of any cause.

We considered any person with pain for at least three months to have chronic pain. We classified people as having moderate pain if they scored "moderate" in the 4-point verbal categorical rating scale (VRS), 4 to 6 (inclusive) in the 11-point numerical rating scale (NRS), or 40 to 60 mm (inclusive) in the visual analogue scale (VAS). People were classified as having severe pain if they score "severe" in the 4-point VRS, 7 or greater in the 11-point NRS, or more than 60 mm in the VAS (Breivik 2000; Farrar 2001).

Types of interventions

We included all studies comparing tapentadol with placebo, other strong analgesic agents, both, or other active controls.

Two oral tapentadol formulations are available: immediate release and ER. Since the scope of this Cochrane review was chronic musculoskeletal pain, we considered the ER formulation in doses of 100 to 500 mg a day, which corresponds to the dosage range approved by the FDA and EMA.

Types of outcome measures

Primary outcomes

- Primary efficacy outcome: pain control assessed by change in pain intensity scores and responder's rate (at least 50% pain relief).
- Primary safety outcome: withdrawal rate due to adverse effects.

For primary efficacy outcome assessment, we considered the VAS, categorical scales, or other validated assessment tools measuring pain intensity.

We evaluated primary outcomes by direct participant report. We considered and extracted data for the intention-to-treat (ITT) population for quantitative analysis.

We planned to use baseline-observation-carried-forward (BOCF) imputation method for primary efficacy outcome analysis because this method gives a more accurate reflection of results with zero pain relief in situations of trial withdrawal. However, none of the published studies provided this information and the drug manufacturer denied our requests to access unpublished data (e-mail correspondence).

Therefore, we considered last-observation-carried-forward (LOCF) imputation method for primary efficacy outcome estimate.

Secondary outcomes

- Patient Global Impression of Change (PGIC).
- Quality of life scores using validated scales.
- Requirements for breakthrough analgesia.
- Other relevant outcome measure, for example functional health status and well-being (assessed by the 36-item Short Form (SF-36) health survey, the EQ-5D health survey or the Western Ontario and McMaster Universities Index of Osteoarthritis scale), and sleep evaluation.
- Withdrawals rate (global).
- Adverse effects (global, serious, and most frequently reported).

Search methods for identification of studies

Electronic searches

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library*; Issue 2 of 12, 2014); MEDLINE and MEDLINE in Process (Ovid) 1950 to 17 March 2014; EMBASE (Ovid) (1974 to 17 March 2014); Web of Science (SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH) searched to March 2014. We listed the search strategies we used in [Appendix 1](#). We attempted to identify all relevant studies irrespective of language.

Searching other resources

On the 18 March 2014, we screened the bibliographies of studies and review articles in this field for other potentially relevant studies. We also searched trials registries for details of unpublished and ongoing trials: the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), clinicaltrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/).

Data collection and analysis

Selection of studies

Following the search for relevant studies, we read the titles and abstracts of the identified potential eligible trials. If it was clear from the abstract that the trial did not meet the selection criteria we excluded the study. If it was unclear from the abstract whether the trial met the selection criteria, we read the full report. We obtained the full reports of all studies that appeared to meet the selection criteria.

Two review authors independently assessed the studies and, using the above inclusion criteria, decided which articles to include. We resolved any differences in opinion with respect to inclusion of the studies by consensus, and if necessary by consultation with a third review author. We documented the justification for excluding studies (see [Characteristics of excluded studies](#) table).

Data extraction and management

We designed a systematic data extraction form to record the following information from the studies.

- Publication details.
- Participant population details (including nature of pain).
- Interventions.
- Outcome measures.
- Analgesic results.
- Adverse effect results.
- Quality of life scores.
- Participant preference.
- Withdrawals.
- Quality assessment criteria.

Two review authors extracted data and cross-checked for accuracy. A third review author helped to resolve disagreements by consensus.

Assessment of risk of bias in included studies

Two review authors independently assessed the quality of studies and risk of bias in accordance with the domain-based evaluation proposed by Cochrane, using Cochrane's 'Risk of bias' assessment tool (Higgins 2011), and the definitions suggested in the Authoring or assessing a Cochrane Protocol, Review, or Review Update for the Cochrane Pain, Palliative and Supportive Care (PaPaS) Review Group (AUREF 2012) as well as the "ACTINPAIN Writing Group of the IASP Special Interest Group on Systematic Reviews in Pain Relief; Cochrane Pain, Palliative and Supportive Care Systematic Review Group Editors. "Evidence" in chronic pain-establishing best practice in the reporting of systematic reviews (Moore 2010).

Measures of treatment effect

Continuous data

We used the summary statistic of mean difference (MD) and 95% confidence interval (CI) between treatment groups.

Dichotomous data

The summary statistic was the risk ratio (RR) and 95% CI between groups. We also calculated the number needed to treat (or to harm) for an additional beneficial (or harmful) outcome (NNTB/NNTB) (and 95% CI) from meta-analysis estimates (adjusted odds ratios (OR)) taking into account the baseline risk, defined as the percentage of participants with events in the control arm.

Unit of analysis issues

All included trials used the same dose range for tapentadol and active-control during treatment maintenance period (tapentadol ER 200 to 500 mg/day and oxycodone controlled release (CR) 40 to 100 mg/day).

We did not identify any cross-over trials for inclusion.

Dealing with missing data

We contacted the pharmaceutical companies responsible for the development of tapentadol (Johnson & Johnson Pharmaceutical Research and Development L.L.C., and Grünenthal GmbH) for further relevant information.

Assessment of heterogeneity

We used the I^2 statistic to detect the presence of heterogeneity. When we found statistical heterogeneity (I^2 statistic > 50%), we investigated this by conducting non-planned subgroup analyses (see [Subgroup analysis and investigation of heterogeneity](#)). We performed fixed-effect or random-effects meta-analyses according to the presence (I^2 statistic > 50%) or absence (I^2 statistic < 50%) of statistical significant heterogeneity.

Assessment of reporting biases

We prepared a matrix containing the major outcomes that were routinely measured in studies assessing opioids for pain relief and compared these with the outcomes that were reported in tapentadol studies. If we identified mismatches, we contacted the trial authors and the drug manufacturers for further information. In these cases, we also searched the clinical trials registers to find trial protocols and look for differences between protocol and trial publications.

We planned to assess the risk of publication bias by comparing the pooled NNTB from present meta-analysis estimates with the NNTB value of 8 (considered to be the limit of clinical utility) (Moore 2002), and calculate the number of participants enrolled in unavailable trials that was needed to achieve the point clinical non-utility (NNTB 8 or greater).

Data synthesis

We used Review Manager 5 to pool studies and calculate an estimate of overall treatment effects (RevMan 2014). We performed fixed-effect or random-effects meta-analysis according to statistical heterogeneity. For continuous data, we used the inverse variance method; for dichotomous data, we used the Mantel-Haenszel method. Data synthesis included the systematical description of the studies' findings and the quantitative data pooling.

Subgroup analysis and investigation of heterogeneity

We performed two meta-analyses, one for placebo-controlled and one for active-controlled trials.

For each meta-analysis, we planned to conduct the following subgroup analyses independently of whether or not statistical significant heterogeneity was present.

- Pain intensity (moderate versus severe).
- Chronic musculoskeletal pain conditions (eg low back pain or osteoarthritis) versus chronic musculoskeletal pain syndromes (eg fibromyalgia).
- Aetiology of chronic pain conditions.
- Study quality (poorer quality versus higher quality). We considered a trial to be of higher quality if it had an adequate allocation concealment and rated 'low' or 'unclear' in the risk assessment of all other type of bias according to the Cochrane 'Risk of bias' assessment tool. We considered a trial to be of poorer quality if it had an inadequate or unclear allocation concealment, or if it rated 'high' in the 'Risk of bias' assessment of any other type of bias (Higgins 2011).

For the comparison tapentadol versus placebo, the data available only allowed us to perform one of the pre-planned subgroup analysis (aetiology of chronic pain conditions). For the comparison tapentadol versus active control intervention, the data available only allowed us to perform two of the pre-planned subgroup analysis (aetiology of chronic pain conditions and study quality). For the tapentadol versus active control comparison, we decided to perform a post-hoc subgroup analysis based on the trial follow-up period because we included studies with different lengths of follow-up.

Sensitivity analysis

We pre-planned no further sensitivity analyses besides those described in [Subgroup analysis and investigation of heterogeneity](#): study quality, characteristics of the participants and outcomes (e.g. pain intensity and aetiology), characteristics of interventions (e.g. dosage of control and intervention groups), data analysis (e.g. LOCF and BOCF, data from cross-over trials), and methods of analysis (e.g. fixed-effect or random-effects methods). We did not identify any further issues when conducting the review that should have been subjected to further sensitivity analysis.

RESULTS

Description of studies

Results of the search

[Figure 1](#) shows the flow diagram of study selection ([Moher 2009](#)).

Figure 1. Study flow diagram.

The search strategy yielded 291 potentially relevant reports. After applying inclusion/exclusion criteria, we included four RCTs (cited in 32 reports) that enrolled 4094 participants (1876 treated with tapentadol, 992 treated with placebo, and 1226 treated with oxycodone).

We did not identify any trials on-going or awaiting publication that matched our selection criteria. We were able to include data from all relevant phase III studies. However, the drug manufacturer did not grant access to the final clinical reports of those studies, and, therefore, some potentially useful information was unavailable for meta-analysis.

Included studies

See: [Characteristics of included studies](#) table.

All included studies were RCTs, of which three were double-blind, active and placebo controlled ([Afilalo 2010](#); [Afilalo 2013](#); [Buynak 2010](#)), and one was an open-label trial comparing tapentadol ER to oxycodone CR ([Wild 2010](#)).

Two studies evaluated people with knee osteoarthritis ([Afilalo 2010](#); [Afilalo 2013](#)), one trial evaluated people with low back pain ([Buynak 2010](#)), and one trial evaluated people with both chronic pain conditions ([Wild 2010](#)).

All studies used tapentadol ER in a dose range of 200 to 500 mg/day and oxycodone CR as active comparator in doses ranging from 40 to 100 mg/day. Three studies used a placebo-controlled arm ([Afilalo 2010](#); [Afilalo 2013](#); [Buynak 2010](#)), and one study was an open-label, long-term safety trial ([Wild 2010](#)).

Three studies aimed to evaluate efficacy as primary outcome (change from baseline in pain intensity score) and had a follow-up period of 12 weeks ([Afilalo 2010](#); [Afilalo 2013](#); [Buynak 2010](#)).

The open-label trial aimed to evaluate safety (primary outcome was the number of participants with treatment emergent adverse effects) and had a longer follow-up period (52 weeks) ([Wild 2010](#)). Despite these differences, the outcome measurements reported in all studies were similar.

[Afilalo 2013](#) was not fully published. We collected data for this trial from [ClinicalTrials.gov](#) and review articles reporting results from this trial.

Excluded studies

See: [Characteristics of excluded studies](#) table.

We excluded 217 reports after initial screening due to at least one of the following reasons: tapentadol formulation (immediate release), pain condition (acute pain, post-operative pain, neuropathic pain, etc), trial design (uncontrolled studies, non-randomised studies, cost-effectiveness studies, pooled analysis, review articles), and duplicates (see [Figure 1](#)).

We excluded five reports, corresponding to three studies ([Ashworth 2010](#); [Gálvez 2013](#); [Lange 2010](#)), after full-text review because of trial design. Two studies were not controlled trials ([Ashworth 2010](#); [Gálvez 2013](#)), and one study used pooled analysis ([Lange 2010](#)).

Risk of bias in included studies

See: [Characteristics of included studies](#) table.

We considered two trials to be at low risk of bias ([Afilalo 2010](#); [Buynak 2010](#)). [Wild 2010](#) was at high risk of bias due to its open-label design. We also judged [Afilalo 2013](#) to be at high risk of bias due to concerns regarding the outcomes selected and because we could not find an allocation concealment description ([Figure 2](#)).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Duration	Outcomes	Size	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)
Afilalo 2010	+	+	+	+	+	+	+	?	+
Afilalo 2013	+	?	+	+	+	-	+	?	+
Buynak 2010	+	+	+	+	+	+	+	?	+
Wild 2010	+	+	-	-	+	-	+	?	+

The drug manufacturer funded all included studies.

Allocation

All studies, except [Afilalo 2013](#), reported that allocation sequences were computer generated, and interactive voice response systems

were used to hide allocation ([Afilalo 2010](#); [Buynak 2010](#); [Wild 2010](#)). We did not find any allocation concealment description regarding [Afilalo 2013](#).

Blinding

[Wild 2010](#) was an open-label trial, hence neither the personnel or participants were blinded. In all other studies, participants, investigators, and outcome assessment were blinded until the end of the trial ([Afilalo 2010](#); [Afilalo 2013](#); [Buynak 2010](#)).

Incomplete outcome data

All included studies had overall withdrawal rates that were considerably high (ranging from 48% to 56%). These withdrawal rates are not unusual in this clinical condition (chronic musculoskeletal pain) and in studies evaluating opioids. Taking into account the overall withdrawal rate and the fact that only LOCF data were available, we could not exclude the possibility of bias.

There was no evidence of differential overall withdrawal rates.

Selective reporting

We have no reasons to suspect incompleteness of data reporting in the fully published trials ([Afilalo 2010](#); [Buynak 2010](#); [Wild 2010](#)). [Afilalo 2013](#) was not published. However, the trial protocol was available and all of the study's pre-specified primary and secondary outcomes were reported.

Other potential sources of bias

[Afilalo 2013](#) was not published. We obtained its data from [ClinicalTrials.gov](#). The trial efficacy results were generally less favourable than those in the remaining studies, which may be due to some publication bias.

It would be highly desirable to have responder rates published in all studies. Unfortunately, neither [Afilalo 2013](#) nor [Wild 2010](#) reported this outcome.

We did not identify any other potential sources of bias.

Effects of interventions

Tapentadol extended release versus placebo

Pain control

For the primary efficacy outcomes, we were able to retrieve data from three studies (1973 participants) for the outcome 'change in pain intensity from baseline at week 12' ([Afilalo 2010](#); [Afilalo 2013](#); [Buynak 2010](#)), and from two studies (1313 participants) for the outcome 'responders rate' (at least 50% pain relief) ([Afilalo 2010](#); [Buynak 2010](#)). In comparison with placebo, tapentadol was associated with a higher reduction in pain intensity from baseline at week 12 (MD on the 11-point NRS of -0.56, 95% CI -0.92 to -0.2; $I^2 = 65\%$; [Analysis 1.1](#)) and with a higher responder rate (RR 1.36, 95% CI 1.13 to 1.64; $I^2 = 0\%$; NNTB tapentadol versus placebo for 12 weeks: 16, 95% CI 9 to 57; [Analysis 1.2](#)).

Patient Global Impression of Change

Concerning PGIC (much or very much improved), we included data from three studies (1554 participants) ([Afilalo 2010](#); [Afilalo 2013](#); [Buynak 2010](#)). Tapentadol-treated participants were more likely to consider themselves much or very much improved (RR 1.53, 95% CI 1.28 to 1.82; $I^2 = 60\%$).

Quality of life

With respect to functional health status and well-being scores (EQ-5D, SF-36, WOMAC), three studies provided data for EQ-5D ([Afilalo 2010](#); [Afilalo 2013](#); [Buynak 2010](#)), two studies for SF-36 ([Afilalo 2010](#); [Buynak 2010](#)), and two studies for WOMAC ([Afilalo 2010](#); [Afilalo 2013](#)). Tapentadol was associated with a higher increase in SF-36 physical component summary score (MD 2.57, 95% CI 1.69 to 3.44; $I^2 = 0\%$). There were no significant differences with respect to placebo for the other functional health status and well-being scores.

Withdrawals due to adverse effects

The primary safety outcome was trial discontinuation due to treatment-emergent adverse effects. We were able to retrieve data from all three studies (1975 participants) ([Afilalo 2010](#); [Afilalo 2013](#); [Buynak 2010](#)). Tapentadol was associated with a higher risk of withdrawal due to adverse effects (RR 2.68, 95% CI 2.05 to 3.52; $I^2 = 0\%$; [Analysis 1.3](#)), in comparison with placebo (NNTH 10; 95% CI 7 to 12, for 12 weeks). The overall withdrawal risk was also higher among tapentadol-treated participants (RR 1.09, 95% CI 0.90 to 1.32; $I^2 = 73\%$). The causes for trial discontinuation in placebo-controlled trials were: withdrawal by participant (30%), adverse effects (27%), lack of efficacy (18%), lost to follow-up (5%), and trial drug non-compliance (5%). Tapentadol-treated participants were at a lower risk of withdrawal due to lack of efficacy (RR 0.36, 95% CI 0.25 to 0.50; $I^2 = 0\%$). There were no differences for the remaining withdrawal causes.

Adverse effects

Regarding overall incidence of adverse effects and based on data from two studies ([Afilalo 2010](#); [Buynak 2010](#)), tapentadol was also associated with a higher risk (RR 1.25, 95% CI 1.16 to 1.35; $I^2 = 0\%$, 1318 participants; [Analysis 1.4](#)). Considering the incidence of serious adverse effects, based on data from three studies ([Afilalo 2010](#); [Afilalo 2013](#); [Buynak 2010](#)), there were no differences between tapentadol and placebo (RR 1.01, 95% CI 0.47 to 2.16; $I^2 = 21\%$, 1974 participants; [Analysis 1.5](#)).

Three studies (1974 participants) reported data on specific adverse effects (gastrointestinal disorders, nervous system disorders, fatigue, and pruritus) ([Afilalo 2010](#); [Afilalo 2013](#); [Buynak 2010](#)). Tapentadol was associated with a higher risk of constipation (RR 2.43, 95% CI 1.86 to 3.17; $I^2 = 4\%$), nausea (RR 2.81, 95% CI 2.18 to 3.62; $I^2 = 0\%$), vomiting (RR 2.77, 95% CI 1.83 to 4.21; $I^2 = 56\%$), dry mouth (RR 3.08, 95% CI 1.92 to 4.94; $I^2 = 0\%$), somnolence (RR 3.27, 95% CI 2.26 to 4.73; $I^2 = 19\%$), dizziness (RR 2.73, 95% CI 2.08 to 3.60; $I^2 = 13\%$), and fatigue (RR 2.15, 95% CI 1.48 to 3.11; $I^2 = 0\%$). There were no differences for diarrhoea (RR 0.85, 95% CI 0.59 to 1.23; $I^2 = 0\%$), headache (RR 1.13, 95% CI 0.91 to 1.40; $I^2 = 44\%$), and pruritus (RR 2.67, 95% CI 0.85 to 8.37; $I^2 = 72\%$).

Subgroup analyses

We performed subgroup analysis based on pain aetiology and study quality.

Pain aetiology

Regarding pain aetiology, there were no significant differences between estimates from both groups (low back pain and osteoarthritis) for all outcomes. However, the difference between

tapentadol and placebo for the primary outcome (change in pain intensity from baseline at week 12) among the subgroup of people with osteoarthritis did not reach statistical significance (MD -0.45, 95% CI -0.94 to 0.04; $I^2 = 74\%$, two trials). This analysis fails to explain, at least partially, the statistical heterogeneity found in the efficacy outcomes.

Trial quality

In subgroup analysis based on trial quality, the 'change in pain intensity from baseline at week 12' (MD -0.74, 95% CI -1.00 to -0.48; $I^2 = 0\%$, two trials), the PGIC (RR 1.67, 95% CI 1.45 to 1.92; $I^2 = 60\%$, two trials, 1012 participants), and the change in WOMAC score (MD -0.27, 95% CI -0.42 to -0.12; one trial) outcomes were higher in pooled analysis of high-quality studies, without significant heterogeneity.

Tapentadol extended release versus oxycodone

Wild 2010, a long-term safety trial of 52 weeks' follow-up, was also included in this comparison. In general, the size effect estimate in this trial was smaller in comparison with the 12-week studies (Afilalo 2010; Afilalo 2013; Buynak 2010) for both efficacy and safety outcomes. Therefore, the inclusion of this trial represented a conservative approach. Further issues regarding this decision are dealt with when presenting the results of a subgroup analysis and in the Discussion.

Pain control

For the primary efficacy outcomes, we retrieved data from four studies (2427 participants) for the outcome 'change in pain intensity from baseline' (Afilalo 2010; Afilalo 2013; Buynak 2010; Wild 2010), and from two studies (1327 participants) for the outcome 'responders rate' (at least 50% pain relief) (Afilalo 2010; Buynak 2010).

In comparison with oxycodone, tapentadol was associated with a higher reduction in pain intensity from baseline at week 12 (MD on the 11-point NRS -0.24, 95% CI -0.43 to -0.05; $I^2 = 14\%$; Analysis 2.1), without significant difference in the responders rate (RR 1.46, 95% CI 0.92 to 2.32; $I^2 = 82\%$; NNTB tapentadol versus oxycodone for 12 weeks 11, 95% CI 7 to 21; Analysis 2.2).

Patient Global Impression of Change

Regarding PGIC (much or very much improved), we included all four studies (2360 participants) for analysis (Afilalo 2010; Afilalo 2013; Buynak 2010; Wild 2010). There was no significant difference between tapentadol and oxycodone (RR 1.15, 95% CI 0.98 to 1.35; $I^2 = 70\%$).

Quality of life

Considering functional health status and well-being scores (EQ-5D, WOMAC), we were able to use data from two studies (Afilalo 2010; Afilalo 2013). Tapentadol was associated with a higher increase in EQ-5D health status index (MD 0.1, 95% CI 0.07 to 0.13; $I^2 = 0\%$). The mean change in WOMAC pain subscale was similar between tapentadol and oxycodone (MD -0.03, 95% CI -0.23 to 0.17; $I^2 = 76\%$, two trials).

We retrieved data for trial discontinuation due to treatment-emergent adverse effects from all four studies (3102 participants) (Afilalo 2010; Afilalo 2013; Buynak 2010; Wild 2010).

Withdrawals due to adverse effects

Tapentadol had a lower risk of withdrawal due to adverse effects compared to oxycodone (RR 0.5, 95% CI 0.42 to 0.60; $I^2 = 44\%$; NNTB tapentadol versus oxycodone for 12 weeks: 6, 95% CI 5 to 7; Analysis 2.3). The overall withdrawal risk was also higher among oxycodone-treated participants (RR 0.76, 95% CI 0.70 to 0.83; $I^2 = 41\%$, four trials, 3102 participants). Tapentadol-treated participants were at a higher risk of withdrawal due to loss to follow-up (RR 1.73, 95% CI 1.04, 2.89; $I^2 = 0\%$, four trials, 3102 participants) and to lack of efficacy (RR 2.23, 95% CI 1.45 to 3.42; $I^2 = 0\%$, four trials, 3102 participants). There were no differences for the remaining withdrawal causes. The causes for trial discontinuation in oxycodone-controlled trials were: adverse effects (49%), withdrawal by participant (24%), lack of efficacy (8%), trial drug non-compliance (6%), and loss to follow-up (5%).

Adverse effects

We included three studies for incidence of overall adverse effects of any type (Afilalo 2010; Buynak 2010; Wild 2010). Tapentadol was associated with a lower risk (RR 0.91, 95% CI 0.85 to 0.96; $I^2 = 57\%$; 2449 participants; Analysis 2.4).

Considering the incidence of serious adverse effects and based on data from all included studies, there was no significant difference between tapentadol and oxycodone (RR 0.57, 95% CI 0.24 to 1.33; $I^2 = 64\%$; 3099 participants; Analysis 2.5) (Afilalo 2010; Afilalo 2013; Buynak 2010; Wild 2010).

For specific adverse effects, four studies (3099 participants) reported data on gastrointestinal disorders, nervous system disorders, fatigue, insomnia, and pruritus (Afilalo 2010; Afilalo 2013; Buynak 2010; Wild 2010), and two studies supplied data on incidence of insomnia (Buynak 2010; Wild 2010). Tapentadol was associated with a lower risk of constipation (RR 0.53, 95% CI 0.47 to 0.61; $I^2 = 0\%$), nausea (RR 0.57, 95% CI 0.50 to 0.64; $I^2 = 0\%$), vomiting (RR 0.41, 95% CI 0.33 to 0.51; $I^2 = 18\%$), dizziness (RR 0.81, 95% CI 0.69 to 0.95; $I^2 = 0\%$), and pruritus (RR 0.41, 95% CI 0.26 to 0.65; $I^2 = 64\%$). There was no difference regarding diarrhoea (RR 1.13, 95% CI 0.82 to 1.56; $I^2 = 69\%$), fatigue (RR 0.93, 95% CI 0.73 to 1.17; $I^2 = 0\%$), insomnia (RR 0.94, 95% CI 0.31 to 2.85; $I^2 = 82\%$), somnolence (RR 0.81, 95% CI 0.57 to 1.16; $I^2 = 71\%$), and headache (RR 1.22, 95% CI 0.99 to 1.50; $I^2 = 6\%$). Tapentadol was associated with a higher risk of dry mouth (RR 1.80, 95% CI 1.29 to 2.50; $I^2 = 0\%$).

Subgroup analyses

The data available allowed us to perform two of the pre-planned subgroup analysis (aetiology of chronic pain conditions and trial quality) and a post-hoc subgroup analysis (trial follow-up period: 12 versus 52 weeks' follow-up).

Aetiology of chronic pain conditions

Concerning the subgroup analysis based on pain aetiology (low back pain (Buynak 2010) and osteoarthritis (Afilalo 2010; Afilalo 2013)), tapentadol was associated with a higher improvement in the 11-point NRS in people with osteoarthritis pain (MD -0.40, 95% CI -0.66 to -0.14; $I^2 = 0\%$), but not in people with low back pain. Nevertheless, there were no statistical significant differences in the effect size between these subgroups. Tapentadol was also associated with a higher responder rate (RR 1.85, 95% CI 1.40

to 2.45; $I^2 = 82.5\%$, one trial, 686 participants) and improvement in PGIC (RR 1.28, 95% CI 1.12 to 1.46; $I^2 = 0\%$, two trials, 918 participants) in people with osteoarthritis than those with low back pain. There were no data available to explore subgroup differences in the other efficacy outcomes. There were no statistical significant differences between these subgroups in safety outcomes.

Trial quality

In subgroup analysis based on trial quality, the risk reduction of adverse effects among tapentadol-treated participants was significantly higher in better-quality studies (RR 0.88, 0.83 to 0.93; $I^2 = 0\%$, two trials, 1332 participants) than in low-quality studies (RR 0.95, 95% CI 0.90 to 0.99, one trial, 1117 participants).

In the post-hoc subgroup analysis based on trial follow-up period (12 and 52 weeks) tapentadol was associated with a higher improvement in the 11-point NRS in studies of shorter follow-up period (MD -0.28, 95% CI -0.50 to -0.07; $I^2 = 26\%$, three trials) than in the trial of longer follow-up period. Nevertheless there were no statistically significant differences in the effect size between these subgroups. Safety outcomes results for this subgroup analysis were similar to those found in the global analysis, that is, tapentadol was associated with a lower risk of withdrawals due to adverse effects and with a lower incidence of adverse effects. These differences with respect to oxycodone were higher in studies of shorter follow-up period. In this subgroup of studies, tapentadol was also associated with a lower risk of serious adverse effects (RR 0.41, 95% CI 0.19 to 0.87; $I^2 = 23\%$, three trials, 1982 participants) and somnolence (RR 0.69, 95% CI 0.54 to 0.87; $I^2 = 14\%$, three trials, 1982 participants).

There was no significant heterogeneity among study results for the primary efficacy outcome 'change in pain intensity from baseline'. Subgroup analysis explained, at least partially, the heterogeneity we found for the other main efficacy and safety outcomes.

We have no evidence of publication bias based on the comparison between pre-specified outcomes in study protocols and published reported outcomes. Studies reported data for the major outcomes that are routinely measured in studies assessing opioids for pain relief. We did not perform a funnel plot analysis because of the low number of included studies.

DISCUSSION

Opioids are commonly used in the treatment of chronic musculoskeletal pain. We have reviewed the efficacy and safety of tapentadol in people with osteoarthritis of the knee and low back pain. Other non-Cochrane reviews with the same scope have been published since we started this review (Afilalo 2013; Lange 2010; Manchikanti 2011; Riemsma 2011). We performed a meta-analysis for the most relevant efficacy and safety outcomes.

Summary of main results

We included four parallel-design RCTs enrolling 4094 participants. Three were phase III efficacy studies with a follow-up of 12 weeks and one was a safety study with a follow-up of 52 weeks. All studies had a control-active group (oxycodone) and three studies were also placebo-controlled. We judged Wild 2010 and Afilalo 2013 to be at high risk of bias: Wild 2010 due to its open-label design and Afilalo 2013 due to missing information.

Of the three placebo-controlled trials, two were in favour of tapentadol regarding primary efficacy outcomes (Afilalo 2010; Buynak 2010), and one trial did not find significant differences between treatment groups (Afilalo 2013). Pooled results from these studies showed a 0.56 point reduction in pain intensity from baseline at 12 weeks in the 11-point NRS and a 1.36 increase in the risk of respond to the treatment (ie at least 50% pain relief). Tapentadol was associated with a 2.68-fold increase in the risk of discontinuing treatment due to adverse effects.

The overall withdrawal risk was not significantly higher among tapentadol-treated participants as the withdrawals due to lack of efficacy favoured tapentadol in comparison to placebo and account for the no significant difference between groups.

We found moderate-to-high statistical heterogeneity for the efficacy outcome estimates, although heterogeneity tests can be misleading due to the number and clinical heterogeneity of the studies included in the meta-analysis.

Subgroup analysis based on pain aetiology did not show differences between the subgroups of people with osteoarthritis of the knee and low back pain.

For the outcomes 'change in pain intensity from baseline at week 12', 'PGIC', and 'WOMAC change', pooled effect size was higher in high-quality studies, favouring tapentadol, without significant heterogeneity.

Of the four oxycodone-controlled studies, two were in favour of tapentadol regarding the primary efficacy outcome 'change in pain intensity from baseline' (Afilalo 2010; Afilalo 2013), and two studies found no significant differences between treatment groups (Buynak 2010; Wild 2010). The results of the two studies that evaluated responder's rate were in favour of tapentadol (Afilalo 2010; Buynak 2010). Pooled results from these studies showed a 0.24 points reduction in pain intensity from baseline in the 11-point NRS and a non-significant 1.46 increase in the risk of respond to the treatment.

Tapentadol was associated with a 50% reduction in the risk of discontinuing treatment due to adverse effects (primary safety outcome). Tapentadol was also associated with a 9% reduction in the risk of adverse effects and with a non-significant 43% reduction in the risk of serious adverse effects. Specific adverse effects less frequently reported among tapentadol-treated participants were constipation, nausea, vomiting, dizziness, and pruritus. Tapentadol was associated with a higher risk of dry mouth.

The overall withdrawal risk was also higher among oxycodone-treated participants as adverse effects accounted for half of all withdrawals in this group. Tapentadol had a higher withdrawal rate due to lack of efficacy.

Moderate-to-high statistical heterogeneity was found for most efficacy (except for change in pain intensity from baseline) and safety outcome estimates. As for the comparison against placebo, the small number of trials included in the meta-analysis precludes strong conclusions about the significance of statistical heterogeneity, particularly in the case of clinical heterogeneity.

Subgroup analysis showed a higher improvement in reduction in pain intensity from baseline with tapentadol among people with osteoarthritis of the knee, studies of higher quality and shorter

follow-up periods, although there were no statistical significant differences in the effect size between these subgroups. Overall, the main safety outcomes results for all subgroup analysis were similar to those found in the global analysis, that is tapentadol was associated with a lower risk of withdrawals due to adverse effects and with a lower incidence of adverse effects.

Subgroup analyses explained, at least partially, the heterogeneity found in most efficacy and safety outcomes. In summary, low heterogeneity was found among people with osteoarthritis of the knee and between results of studies of higher quality and shorter follow-up periods.

Overall completeness and applicability of evidence

Although we included a large number of participants (more than 4000) in this Cochrane review, tapentadol is a recent drug and only a relatively small number of studies met the inclusion criteria (four RCTs). Nevertheless, these studies can be considered very large in relation to other studies in chronic pain. The number of studies may have contributed to the high statistical heterogeneity found for some results. In fact, subgroup and sensitivity analysis explained most, but not all, the heterogeneity found. All included studies were well designed, but two studies were rated as having high risk of bias due to an open-label design and unclear allocation concealment. The drug manufacturer funded all included studies.

The [Afilalo 2013](#) study was never published and its data were collected from the clinical trials site, clinicaltrials.gov. This trial's efficacy results were generally worse than those in the remaining studies, which may point to publication bias. Given the effect size and number of studies, our review findings are considerably susceptible to further publications of opposite direction. Nevertheless, it is likely that we found all of the available information of the completed studies as we searched the clinical trials registers and agencies to find further trials. We searched the publications for differences between them and the original protocols and found all outcomes to be consistently reported.

We were only able to include people with low back pain and knee osteoarthritis. We did not identify any evidence for tapentadol in chronic musculoskeletal pain of other causes.

All included studies had high withdrawal rates, with withdrawal due to adverse effects comprising 27% of the total in the placebo-controlled arm and 49% of the total in the oxycodone-controlled arm. For every six people treated with tapentadol, one more presented an adverse effects than if they were treated with placebo, reflecting the high incidence of adverse effects in chronic opioid consumption. This is in line with other studies of opioids in chronic pain. This high withdrawal rate makes the imputation method considerably important. We planned to use BOCF, but had to use LOCF due to data access limitations, as such our results can be slightly overestimated.

Three trials had a follow-up period of 12 weeks and one trial had a follow-up of 52 weeks. When considering long-term use, the review results can be somewhat overestimated as all opioid results are worse with long-term follow-up ([Nüesch 2009](#); [Trescot 2008c](#)), and, judging by [Wild 2010](#), this is also the case with tapentadol.

As such, opioid treatment in chronic pain conditions remains controversial due to concerns about adverse effects, long-term efficacy, functional outcomes, and the potential for drug abuse and addiction. These concerns may contribute to the hesitancy to prescribe tapentadol, as may the regulatory and legal barriers in the prescription of controlled substances.

Nevertheless, we believe there is sufficient evidence to justify this meta-analysis and moderate strength in our recommendations regarding the use of tapentadol as an option in chronic musculoskeletal pain treatment.

Quality of the evidence

See [Characteristics of included studies](#), 'Risk of bias' tables, and 'Risk of bias' summary tables ([Figure 2](#); [Figure 3](#)).

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Of the included four studies, we only judged two studies to be of high quality ([Afilalo 2010](#); [Buynak 2010](#)). We considered [Wild 2010](#) to be at high risk of performance and detection bias due to its open-label design. We were unable to obtain any information regarding

[Afilalo 2013](#) allocation concealment and so we considered it to be at high risk of bias.

Although enrolling more than 4000 participants, the number of included studies was still limited and we found significant heterogeneity for most efficacy and safety outcomes. Moreover, as is usual in these conditions, the withdrawal rates were high. Therefore, we considered that there is only moderate evidence that tapentadol is more efficacious than placebo and oxycodone in the treatment of people with chronic musculoskeletal pain. There is also moderate evidence that tapentadol has a better tolerability and safety profile than oxycodone.

Potential biases in the review process

The main potential source of bias in this review comes from the changes to the original protocol (see [Differences between protocol and review](#)) as we had to use LOCF for primary efficacy outcome analysis. The LOCF method may overestimate treatment effect mostly in studies with shorter follow-up and high withdrawal rates, as are the studies included in this Cochrane review. We analysed data for pain intensity change from baseline at week 12 and not during the overall treatment maintenance period. This may also overestimate effect size. We were unable to conduct subgroup analyses for pain intensity, and the possibility exists that effect size may be different for moderate versus severe cases of chronic musculoskeletal pain. An additional bias was that we could not obtain data from all studies for all outcomes.

A further limitation of this review was the relatively small number of included studies, although enrolling a large number of participants. In this context, the results of the pooled analysis should be viewed with caution especially in the presence of statistically heterogeneity, as further studies may have an important impact in effect size estimations.

Agreements and disagreements with other studies or reviews

[Lange 2010](#) published a pooled analysis of three studies included in this review ([Afilalo 2010](#); [Afilalo 2013](#); [Buynak 2010](#)). The authors of this paper worked at that time for the companies responsible for the development of tapentadol, and had access to the individual participant data from these studies. The imputation issue was central in this paper. This pooled analysis reported that, when compared to placebo, tapentadol effectively reduced pain. When using BOCF instead of LOCF, the results were slightly less positive for tapentadol but still significant in comparison to placebo (change in pain intensity from baseline at week 12 in the 11-point NRS of -0.60 (95% CI -0.80 to 0.39) using LOCF and -0.30 (95% CI -0.47 to -0.90) using BOCF). The trial authors did not report results for the comparison tapentadol versus oxycodone. The only possible inference is based on indirect descriptive analysis. [Lange 2010](#)'s pooled analysis found a significant reduction of -0.30 (95% CI -0.53 to -0.12) in pain intensity at week 12 for oxycodone versus placebo when using LOCF, but not when using BOCF. In fact, when using the BOCF imputation method, oxycodone was not associated with a decrease in pain intensity at week 12 in comparison to placebo (0.30, 95% CI 0.11 to 0.50), as such we would expect tapentadol to perform better compared to oxycodone when using BOCF. This seems to be associated with the fact that tapentadol has fewer withdrawals and withdrawals due to adverse effects when compared to oxycodone. In those participants when using BOCF, there would be no pain reduction from the baseline, as when using LOCF the pain reduction is still considered despite the drop-out. These results are in accordance with ours and considerations

regarding the risk of slight overestimation of results were already made.

[Manchikanti 2011](#) published a systematic review on opioid treatment for chronic non-cancer pain but did not conduct a meta-analysis. With respect to tapentadol, the review authors included three studies (also included in this Cochrane review: [Afilalo 2010](#); [Buynak 2010](#); [Wild 2010](#)), and concluded that tapentadol has "similar effects as other opioids, and with fewer side effects".

Another systematic review funded by Grünenthal GmbH, [Riemsma 2011](#), compared different opioids in severe and moderate-to-severe chronic pain, including neuropathic and malignant aetiology. Based on a network meta-analysis, the review authors concluded that tapentadol was superior for the primary outcome (mean change in pain intensity) to oxycodone, hydromorphone, and morphine. Tapentadol had fewer gastrointestinal adverse effects in comparison with the other opioids.

Another Cochrane review on oral tapentadol for cancer pain is under way ([Wiffen 2015](#)).

Overall, our findings and conclusion are in accordance with these previous studies.

AUTHORS' CONCLUSIONS

Implications for practice

Four included trials provided data (of moderate quality) and evidence for the use of tapentadol extended release. There was insufficient evidence to support (or not support) its use and its efficacy in achieving relief from moderate-to-severe chronic musculoskeletal pain, in doses of 200 to 500 mg/day.

In this Cochrane review, we found tapentadol to improve pain control slightly in comparison to placebo and oxycodone and to have a better safety and tolerability profile than oxycodone. However, this difference in terms of pain reduction was small. The available evidence showed more consistent results for people with osteoarthritis of the knee than for people with low back pain.

Although a relatively large number of participants were enrolled in the included studies, the number of studies was relatively low, heterogeneity was high for some efficacy and safety outcomes, and withdrawal rates were high in all studies. This may be responsible for some overestimation of tapentadol efficacy. Furthermore, the available evidence did not allow a clear assessment of function and quality of life improvement. Most included studies were of 12-week duration and further long-term studies are needed in order to determine tapentadol safety and tolerability in longer periods. Therefore, caution is warranted in making definitive conclusions.

For clinicians treating moderate-to-severe chronic musculoskeletal pain, the safety profile of tapentadol may prove advantageous, while the overall clinical benefit of tapentadol in terms of pain reduction will probably be small.

Implications for research

We did not have access to the full research data produced so far for tapentadol in chronic musculoskeletal pain. Therefore, it is difficult to determine which and how many resources should be invested in future research.

Nevertheless, we suggest that future research evaluates other musculoskeletal conditions associated with chronic pain (eg fibromyalgia or generalised musculoskeletal pain). Currently, we only have data for chronic low back pain and knee osteoarthritis. We need to understand which people benefit most from this treatment or if there is any particular subgroup where the treatment is detrimental. In that sense, further trials of people with osteoarthritis or low back pain may be of use.

Researchers should be demanding with the outcomes, and include, by default, responder's rate (at least 50% pain relief) or pain no worse than mild. These data were not available for all tapentadol trials and should be presented in future trials. It is also important that future trials report their main results using the baseline-observation-carried-forward imputation method for missing data. This is particularly relevant in conditions where withdrawal rate is high, such as chronic pain.

Well-designed pragmatic studies are also required to characterise long-term efficacy and safety better, as well as to confirm the clinical benefit in terms of function, quality of life, and other participant-related outcomes.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Afilalo 2010

Study characteristics	
Methods	Randomised double-blind active- and placebo-controlled, parallel-arm, multicentre, phase III study
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> Men and women ≥ 40 years of age Diagnosis of osteoarthritis of the knee according to ACR criteria Functional capacity class I-III Pain at the reference joint requiring the use of analgesics (non-opioids or opioids at doses equivalent to morphine 160 mg/day oral) ≥ 3 months prior to screening <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Clinically significant or unstable medical or psychiatric disease Requirement for painful procedures (eg surgery) during the study that could influence efficacy or safety assessments History of substance abuse Epilepsy/seizure disorder Stroke/transient ischaemic attack Malignancy (preceding 2 years) HIV infection Chronic hepatitis B or C Uncontrolled hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 95 mmHg, or both) Severe renal impairment (creatinine clearance < 60 mL/minute) Moderate or severe hepatic impairment Alanine transaminase or aspartate transaminase concentrations > 3 times the upper limit of normal Hypersensitivity to study medications or their excipients

Afilalo 2010 (Continued)

- Conditions potentially influencing the assessment of osteoarthritis pain (anatomical deformities, fibromyalgia, gout, or infectious or autoimmune diseases affecting the knee)

Interventions	<p>Tapentadol ER 100-250 mg twice daily, n = 346</p> <p>Oxycodone CR 20-50 mg twice daily, n = 345</p> <p>Placebo n = 339</p> <p>Follow-up 15 weeks</p>
Outcomes	<p>Primary outcome:</p> <ul style="list-style-type: none"> • Change from baseline of the mean pain intensity based on an 11-point NRS over the last week of the maintenance period at week 12 <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Change from baseline in WOMAC assessing pain, disability, and joint stiffness of the knee over the last week of the maintenance period at week 12 • Change from baseline in sleep latency time in hours over the last week of the maintenance period at week 12 • Percentage of participants who reported very much improved or much improved from baseline in PGIC over the last week of the maintenance period at week 12 • Distribution of time to treatment discontinuation due to lack of efficacy • Change from baseline in EQ-5D health status index to week 12 • Change from baseline in responder analysis 50% improvement to week 12
Notes	<p>The main outcome of interest was measured in the study and published</p> <p>The study was funded by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.</p> <p>The study started in January 2007 and ended in December 2008</p> <p>M Afilalo received funding for study support from Johnson & Johnson Pharmaceutical Research & Development, L.L.C.</p> <p>M Etropolski, B Kuperwasser, K Kelly, A Okamoto, I Van Hove, C Rauschkolb, and J Haeussler were Johnson & Johnson employees and shareholders</p> <p>A Steup and B Lange were employees of Grünenthal GmbH</p> <p>Editorial support for the writing of this manuscript was provided by Cherie Koch, PhD, of MedErgy, and was funded by Johnson & Johnson Pharmaceutical Services, L.L.C., and Grünenthal GmbH</p> <p>M Afilalo, who was not employed by Johnson & Johnson Pharmaceutical Services, L.L.C., or Grünenthal GmbH, was not compensated for his contribution to the writing of this manuscript and had no conflicts of interest that were directly relevant to the content of this study</p> <p>Although writing assistance was provided, the authors retained full editorial control over the content of the manuscript</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation was based on a computer-generated randomisation list, balanced using permuted blocks, and stratified by study site"
Allocation concealment (selection bias)	Low risk	Quote: "randomisation was implemented through an interactive voice response system (IVRS) to dispense blinded study medication"

Tapentadol for chronic musculoskeletal pain in adults (Review)

Afilalo 2010 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "placebo tablets and capsules (one for each active treatment) were used to maintain blinded treatments. Investigators were not provided with the randomisation codes, and the schedule was maintained with the IVRS"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "blinding was not broken until all patients had completed the trial, except in the case of a suspected unexpected serious adverse reaction or if emergency treatment required knowledge of a patient's treatment status"
Duration	Low risk	Follow-up 15 weeks
Outcomes	Low risk	See 'Characteristics of included studies' table
Size	Low risk	Tapentadol ER 100-250 mg twice daily, n = 346 Oxycodone CR 20-50 mg twice daily, n = 345 Placebo n = 339
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "last observation carried forward was applied to impute missing pain measurements in the event of early discontinuation"
Selective reporting (reporting bias)	Low risk	The study protocol was available and all of the study's pre-specified primary and secondary outcomes were reported

Afilalo 2013

Study characteristics

Methods	Randomised double-blind, placebo- and active-control, parallel-arm, phase III trial
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • People diagnosed with osteoarthritis of the knee based on the ACR criteria and functional capacity class of I-III; people taking analgesic medications for at least 3 months prior to screening and dissatisfied with their current therapy • People requiring opioid treatment must be taking daily doses of opioid-based analgesic, equivalent to morphine < 160 mg orally • Baseline score of ≥ 5 on an 11-point NRS, calculated as the mean pain intensity during the last 3 days prior to randomisation <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • History of alcohol or drug abuse, or both in investigator's judgement • Chronic hepatitis B or C, or HIV, presence of active hepatitis B or C within the past 3 months • Life-long history of seizure disorder or epilepsy; history of malignancy within past 2 years, with exception of basal cell carcinoma that was successfully treated • Uncontrolled hypertension • People with severely impaired renal function • People with moderately to severely impaired hepatic function or with laboratory values reflecting inadequate hepatic function • Treatment with neuroleptics, monoamine oxidase inhibitors, serotonin noradrenaline (norepinephrine) reuptake inhibitors, tricyclic antidepressants, anticonvulsants, or anti-parkinsonian drugs, treatment with any other analgesic therapy than investigational medication or rescue medication during the trial

Afilalo 2013 (Continued)

Interventions	<p>Tapentadol ER 100-250 mg twice daily, n = 320</p> <p>Oxycodone CR 20-50 mg twice daily, n = 333</p> <p>Placebo, n = 337</p> <p>Follow-up 12 weeks</p>
Outcomes	<p>Primary outcome:</p> <ul style="list-style-type: none"> Change from baseline of the mean pain intensity overall in the 12-week maintenance period of the daily pain intensity on an 11-point NRS <p>Secondary outcomes:</p> <ul style="list-style-type: none"> Change from baseline of the mean pain intensity based on an 11-point NRS over the last week of the maintenance period at week 12 PGIC Change from baseline in the WOMAC global score assessing pain, disability, and joint stiffness of the knee over the last week of the maintenance period at week 12 Time to treatment discontinuation due to lack of efficacy Change in the health survey scores form (SF-36) EQ-5D health status index outcome over time Sleep questionnaire: <ul style="list-style-type: none"> change from baseline in sleep latency time in hours to the last week of the maintenance period amount of time slept in hours number of awakenings during sleep number of participants reporting a category from the quality of sleep Patient Assessment of Constipation Symptoms (PAC-SYM) over time
Notes	<p>This study was not fully published (data were only available at ClinicalTrials.gov)</p> <p>The main outcomes of interest were measured in this study</p> <p>The study was sponsored by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.</p> <p>The study started in November 2006 and ended in July 2008</p> <p>Authors declarations of interests were not available</p> <p>The principal investigator Alain Serrie, Dr C.E.T.D Hôpital Lariboisière, Paris, France</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation was based on a computer-generated randomisation list, balanced using permuted blocks, and stratified by study site"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "placebo tablets and capsules (one for each active treatment) were used to maintain blinded treatments. Investigators were not provided with the randomisation codes, and the schedule was maintained with the IVRS"

Afilalo 2013 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "blinding was not broken until all patients had completed the trial, except in the case of a suspected unexpected serious adverse reaction or if emergency treatment required knowledge of a patient's treatment status"
Duration	Low risk	Follow-up 12 weeks
Outcomes	High risk	See 'Characteristics of included studies' table
Size	Low risk	Tapentadol ER 100-250 mg twice daily, n = 320 Oxycodone CR 20-50 mg twice daily, n = 333 Placebo, n = 337
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "last observation carried forward was applied to impute missing pain measurements in the event of early discontinuation"
Selective reporting (reporting bias)	Low risk	The study protocol was available and all of the study's pre-specified primary and secondary outcomes were reported

Buynak 2010

Study characteristics

Methods	Randomised double-blind, active- and placebo-controlled trial, parallel-arm, multicentre, phase III study
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> Men and non-pregnant, non-lactating women having a diagnosis of LBP of non-malignant origin present for at least 3 months People taking analgesic medications for ≥ 3 months prior to screening or dissatisfied with their current therapy, or both People requiring opioid treatment taking daily doses of opioid-based analgesic, equivalent to morphine < 160 mg orally Baseline score of 5 on an 11-point NRS, calculated as the mean pain intensity during the last 3 days prior to randomisation <p>Exclusion criteria:</p> <ul style="list-style-type: none"> History of alcohol or drug abuse, or both, in the investigator's judgement History of significant liver insufficiency Chronic hepatitis B or C, or HIV, presence of active hepatitis B or C within the past 3 months Life-long history of seizure disorder or epilepsy History of malignancy within past 2 years, with exception of basal cell carcinoma that was successfully treated Uncontrolled hypertension People with severely impaired renal function People with moderately to severely impaired hepatic function or with laboratory values reflecting inadequate hepatic function
Interventions	<p>Tapentadol ER 100-250 mg twice daily, n = 321</p> <p>Oxycodone HCl 20-50 mg twice daily, n = 334</p>

Buynak 2010 (Continued)

Placebo, n = 326

Follow-up 12 weeks

Outcomes	<p>Primary outcome:</p> <ul style="list-style-type: none"> Change from baseline of the mean pain intensity based on an 11-point NRS over the last week of the maintenance period at week 12. <p>Secondary outcomes:</p> <ul style="list-style-type: none"> Change from baseline in Brief Pain Inventory total pain score over the last week of the maintenance period at week 12 Change from baseline in sleep latency time in hours over the last week of the maintenance period at week 12 Percentage of participants who reported very much improved or much improved from baseline in PGIC over the last week of the maintenance period at week 12 Number of participants with treatment discontinuation due to lack of efficacy Change from baseline in EQ-5D health status index to week 12 Responder analysis 50% improvement
Notes	<p>The main outcome of interest was measured in the study and published</p> <p>The study was sponsored by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.</p> <p>The study started in February 2007 and ended in May 2008</p> <p>Editorial support for the writing of this manuscript was provided by Megan Knagge, PhD, of MedErgy, and was funded by Johnson & Johnson Pharmaceutical Research & Development L.L.C., and Global Development, Grünenthal GmbH, Aachen, Germany</p> <p>R Buynak, who is not employed by Johnson & Johnson Pharmaceutical Services, L.L.C., or Grünenthal GmbH, was not compensated for this manuscript</p> <p>Although writing assistance was provided, the authors retained full editorial control over the content of the manuscript</p> <p>R Buynak received funding for study support from Johnson & Johnson Pharmaceutical Research & Development, L.L.C. DY Shapiro, A Okamoto, I Van Hove, C Rauschkolb, and M Etropolski were Johnson & Johnson employees and shareholders</p> <p>A Steup and B Lange were employees of Grünenthal GmbH. C Lange was a former employee of Grünenthal GmbH</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization of patients to treatment was based on a computer-generated randomization list, balanced by randomly permuted blocks, and stratified by study site"
Allocation concealment (selection bias)	Low risk	Quote: "Investigators were not provided with the randomisation code and the schedule was maintained with IVRS [interactive voice response system]"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "placebo tablets and capsules (one for each active treatment) were used to maintain the blind in this double-blind, double-dummy design. Investigators were not provided with the randomisation codes and the schedule was maintained with the IVRS [interactive voice response system]"

Buynak 2010 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "blind was not broken until all patients completed the trial and the database was locked"
Duration	Low risk	Follow-up 12 weeks
Outcomes	Low risk	See 'Characteristics of included studies' table
Size	Low risk	Tapentadol ER 100-250 mg twice daily, n = 321 Oxycodone HCl 20-50 mg twice daily, n = 334 Placebo, n = 326
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "the primary efficacy analysis used linear interpolation to impute intermittent missing pain scores and the last observation carried forward (LOCF) method to impute missing pain scores after early discontinuation"
Selective reporting (reporting bias)	Low risk	The study protocol was available and all of the study's pre-specified primary and secondary outcomes were reported

Wild 2010

Study characteristics

Methods	Randomised, open-label, parallel-arm, phase III long-term safety trial
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> Clinical diagnosis of knee or hip osteoarthritis with history of pain at the reference joint for ≥ 3 months or clinical diagnosis of LBP of benign origin for ≥ 3 months Dissatisfied with their current analgesic therapy (e.g. nonsteroidal anti-inflammatory drugs, cyclo-oxygenase-2 inhibitors, opioids, paracetamol (acetaminophen)) Pain intensity > 4 on NRS <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Life-long history of seizure disorder or epilepsy Any of the following within 1 year: mild/moderate traumatic brain injury, stroke, transient ischaemic attack, and brain neoplasm Severe traumatic brain injury within 15 years (consisting of > 1 of the following: brain contusion (injuries resulting in haemorrhage), intracranial haematoma, unconsciousness, or post-traumatic amnesia lasting > 24 hours) or residual sequelae suggesting transient changes in consciousness History of malignancy within past 2 years, with exception of a successfully treated basal cell carcinoma Presence of significant pain associated with conditions other than osteoarthritis or LBP that could confound the assessment or self evaluation of pain
Interventions	<p>Tapentadol ER 50 mg oral tablet twice daily administered for first 3 days, 100 mg oral tablet twice daily administered for next 4 days, 100-250 mg oral tablet twice daily administered for the next 51 weeks, n = 894</p> <p>Oxycodone CR 10 mg oral tablet twice daily administered for first 3 days, 20 mg oral tablet twice daily administered for next 4 days, 20-50 mg oral tablet twice daily administered for the next 51 weeks, n = 223</p>
Outcomes	Primary outcome:

Wild 2010 (Continued)

- Number of participants with treatment-emergent adverse effects

Secondary outcome:

- Change from baseline in mean pain intensity scores at week 52 using the NRS

Notes	<p>The main outcomes of interest measured in this study were published</p> <p>The study was sponsored by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.</p> <p>The study started in November 2006 and ended in July 2008</p> <p>Editorial support for the writing of this manuscript was provided by Megan Knagge, PhD, of MedErgy, and was funded by Johnson & Johnson Pharmaceutical Services, L.L.C. and Global Development, Grünenthal GmbH, Aachen, Germany</p> <p>The authors retained full editorial control over the content of the manuscript</p> <p>All authors made significant scientific contributions to this work, were familiar with the content of this manuscript, and were willing to take responsibility for the completeness and accuracy of the content</p> <p>The authors declared the following financial relationships: B Kuperwasser, J Gilbert, B McCann, M Etropolski, and C Rauschkolb were employees and stockholders of Johnson & Johnson Pharmaceutical Services, L.L.C.; B Lange, A Steup, and R Lange were employees of Grünenthal GmbH; J. Wild was an employee of Upstate Clinical Research Associates (Williamsville, New York), and S Grond was an employee of the Hospital Lippe-Detmold (Detmold, Germany), both of whom received funding to perform these clinical trials</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were assigned to treatment based on a computer-generated randomisation schedule; randomisation was balanced using randomly permuted blocks and stratified by location (Europe or North America)"
Allocation concealment (selection bias)	Low risk	Quote: "Medication kits matching each patient's randomly assigned code were assigned using an interactive voice response system"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "because this was an open-label study, the investigators were provided with the treatment assignment for each patient"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "because this was an open-label study, the investigators were provided with the treatment assignment for each patient"
Duration	Low risk	Follow-up 52 weeks
Outcomes	High risk	See 'Characteristics of included studies' table
Size	Low risk	Tapentadol ER, n = 894 Oxycodone CR, n = 223
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "analyses included all randomised patients and last observation carried forward was used for imputation of missing pain intensity values imputation method is unclear"

Wild 2010 (Continued)

Selective reporting (reporting bias)	Low risk	The study protocol was available and all of the study's pre-specified primary and secondary outcomes were reported
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ACR: American College of Rheumatology; CR: controlled release; EQ-5D: EuroQol-5; ER: extended release; HCl: hydrochloride; HIV: human immunodeficiency virus; LBP: low back pain; n: number; NRS: numerical rating scale; PGIC: Patient Global Impression of Change; SF-36: 36-item Short Form; WOMAC: Western Ontario McMaster Questionnaire.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ashworth 2010	Not a controlled trial
Gálvez 2013	Not a controlled trial
Lange 2010	Pooled analysis

DATA AND ANALYSES
Comparison 1. Tapentadol Extended Release (100 to 250 mg/day) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Change in pain intensity from baseline at week 12 (11-point numerical rating scale)	3	1973	Mean Difference (IV, Random, 95% CI)	-0.56 [-0.92, -0.20]
1.2 Responder rate (at least 50% pain reduction)	2	1313	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.13, 1.64]
1.3 Study discontinuation due to treatment-emergent adverse effects	3	1975	Risk Ratio (M-H, Fixed, 95% CI)	2.68 [2.05, 3.52]
1.4 Adverse effects	2	1318	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.16, 1.35]
1.5 Serious adverse effects	3	1974	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.47, 2.16]

Analysis 1.1. Comparison 1: Tapentadol Extended Release (100 to 250 mg/day) versus placebo, Outcome 1: Change in pain intensity from baseline at week 12 (11-point numerical rating scale)

Analysis 1.2. Comparison 1: Tapentadol Extended Release (100 to 250 mg/day) versus placebo, Outcome 2: Responder rate (at least 50% pain reduction)

Analysis 1.3. Comparison 1: Tapentadol Extended Release (100 to 250 mg/day) versus placebo, Outcome 3: Study discontinuation due to treatment-emergent adverse effects

Analysis 1.4. Comparison 1: Tapentadol Extended Release (100 to 250 mg/day) versus placebo, Outcome 4: Adverse effects

Analysis 1.5. Comparison 1: Tapentadol Extended Release (100 to 250 mg/day) versus placebo, Outcome 5: Serious adverse effects

Comparison 2. Tapentadol expended release (100 to 250 mg/day) versus oxycodone controlled release (20 to 50 mg/day)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Change in pain intensity from baseline (11-point numerical rating scale)	4		Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.43, -0.05]
2.2 Responder rate (at least 50% pain reduction)	2	1327	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.92, 2.32]
2.3 Study discontinuation due to treatment-emergent adverse effects	4	3102	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.42, 0.60]
2.4 Adverse effects	3	2449	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.85, 0.96]
2.5 Serious adverse effects	4	3099	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.24, 1.33]

Analysis 2.1. Comparison 2: Tapentadol expended release (100 to 250 mg/day) versus oxycodone controlled release (20 to 50 mg/day), Outcome 1: Change in pain intensity from baseline (11-point numerical rating scale)

Analysis 2.2. Comparison 2: Tapentadol expended release (100 to 250 mg/day) versus oxycodone controlled release (20 to 50 mg/day), Outcome 2: Responder rate (at least 50% pain reduction)

Analysis 2.3. Comparison 2: Tapentadol expended release (100 to 250 mg/day) versus oxycodone controlled release (20 to 50 mg/day), Outcome 3: Study discontinuation due to treatment-emergent adverse effects

Analysis 2.4. Comparison 2: Tapentadol expended release (100 to 250 mg/day) versus oxycodone controlled release (20 to 50 mg/day), Outcome 4: Adverse effects

Analysis 2.5. Comparison 2: Tapentadol expended release (100 to 250 mg/day) versus oxycodone controlled release (20 to 50 mg/day), Outcome 5: Serious adverse effects

APPENDICES

Appendix 1. Search strategies

CENTRAL

1 tapentad*:ti,ab,kw (Word variations have been searched)

#2 3-dimethylamino-1-ethyl-2-methylpropyl:ti,ab,kw (Word variations have been searched)

#3 palexia:ti,ab,kw (Word variations have been searched)

#4 nucynta:ti,ab,kw (Word variations have been searched)

#5 #1 or #2 or #3 or #4

MEDLINE (Ovid)

1 tapentad*.tw.

2 3-dimethylamino-1-ethyl-2-methylpropyl.tw.

3 palexia.tw.

4 nucynta.tw.

5 or/1-4

6 randomized controlled trial.pt.

7 controlled clinical trial.pt.

8 randomized.ab.

9 placebo.ab.

10 drug therapy.fs.

11 randomly.ab.

12 trial.ab.

13 groups.ab.

14 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15 exp animals/ not humans.sh.

16 14 not 15

17 5 and 16

EMBASE (Ovid)

1 tapentad*.tw.

2 3-dimethylamino-1-ethyl-2-methylpropyl.tw.

3 palexia.tw.

4 nucynta.tw.

5 tapentadol/

6 or/1-5

7 random\$.tw.

8 factorial\$.tw.

9 crossover\$.tw.

10 cross over\$.tw.

11 cross-over\$.tw.

12 placebo\$.tw.

13 (doubl\$ adj blind\$).tw.

14 (singl\$ adj blind\$).tw.

15 assign\$.tw.

16 allocat\$.tw.

17 volunteer\$.tw.

18 Crossover Procedure/

19 double-blind procedure.tw.

20 Randomized Controlled Trial/

21 Single Blind Procedure/

22 or/7-21

23 (animal/ or nonhuman/) not human/)

24 22 not 23

25 6 and 24

Web of Science (ISI)

5 #4 OR #3 OR #2 OR #1

Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All Years

4 Topic=(nucynta)

Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All Years

3 Topic=(palexia)

Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All Years

2 Topic=(3-dimethylamino-1-ethyl-2-methylpropyl)

Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All Years

1 Topic=(tapentad*)

Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All Years

WHAT'S NEW

Date	Event	Description
7 May 2020	Review declared as stable	Seeking a new author team to complete the update. See Published notes .

HISTORY

Protocol first published: Issue 6, 2012

Review first published: Issue 5, 2015

Date	Event	Description
31 July 2015	Amended	Minor spelling errors corrected.

CONTRIBUTIONS OF AUTHORS

Task	Who has agreed to undertake task
Drafted the protocol	Santos J; Costa J
Developed a search strategy	Santos J; Costa J
Searched for studies (usually 2 review authors)	Santos J; Costa J; Alarcão J

Obtained copies of studies	Santos J; Costa J; Fareleira F; Alarcão J
Selected which studies to include (2 + 1 arbiter)	Santos J; Costa J; Alarcão J
Extracted data from studies (2 review authors)	Santos J; Costa J; Alarcão J
Entered data into RevMan 2014	Santos J; Costa J; Alarcão J
Carried out the analysis	Santos J; Costa J; Alarcão J; Fareleira F
Interpreted the analysis	Santos J; Costa J; Alarcão J; Vaz-Carneiro A
Drafted the final write-up of the review	Santos J; Costa J; Vaz-Carneiro A; Alarcão J
Update the review	Santos J; Costa J; Fareleira F; Vaz-Carneiro A
Content expert name	Santos J; Costa J
Methodologist name	Costa J; Vaz-Carneiro A
Statistician name	Gouveia M. Associated Professor at Portuguese Economics Catholic University, Lisbon, Portugal

DECLARATIONS OF INTEREST

Vaz-Carneiro A and Costa J are the Director and Associated Director of the Evidence Based Medicine (EBM) Center at Lisbon School of Medicine, Portugal. This research centre is devoted to pre- and postgraduate medical education. Since 2002, the Lisbon EBM Center has undertaken several clinical and epidemiological research projects, which had unrestricted funding from over 20 different pharmaceutical companies. One of those was the Grünenthal Group, which developed tapentadol.

The centre has not received any direct or indirect payment or other type of benefit for conducting this Cochrane review. The initiative for this project is also entirely due to the Lisbon EBM Center.

Santos J, Fareleira F, and Alarcão J are Lisbon EBM Center collaborators.

We have no other known conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- Cochrane Coordinating Center, Portugal
- Technical and scientific support.

External sources

- None, Other

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We planned to use baseline-observation-carried-forward (BOCF) imputation method for primary efficacy outcome analysis because this method gives a more accurate reflection of results with zero pain relief in situations of trial withdrawal ([Santos 2012](#)). However, none of the published studies provided this data and we were not granted access to unpublished data by the drug manufacturer. Therefore, we considered last-observation-carried-forward (LOCF) imputation method for the primary efficacy outcome estimate.

For the comparison tapentadol versus placebo, the available data only allowed us to perform subgroup analysis based on aetiology of chronic pain conditions and study quality. For the comparison tapentadol versus active control intervention, the available data allowed us to perform subgroup analysis of the aetiology of chronic pain conditions, study quality, and follow-up duration. For this last comparison, we decided to perform a post-hoc subgroup analysis based on trial follow-up period because we included studies of different follow-up durations.

NOTES

An update for this review was initiated in 2017, however there were no new studies to affect the conclusions. At April 2020, we are seeking a new author team to update the review to meet current standards and expectations.

We recognise the contribution of Dr Gonalo S Duarte, Faculdade de Medicina de Lisboa, who joined the author team to work on the update.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics, Opioid [*therapeutic use]; Chronic Pain [*drug therapy]; Clinical Trials, Phase III as Topic; Low Back Pain [*drug therapy]; Musculoskeletal Pain [*drug therapy]; Osteoarthritis, Knee [*drug therapy]; Oxycodone [therapeutic use]; Phenols [*therapeutic use]; Randomized Controlled Trials as Topic; Tapentadol

MeSH check words

Adult; Humans