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[Intervention Review]

Tramadol for neuropathic pain in adults

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ABSTRACT

Background

This review is an update of a review of tramadol for neuropathic pain, published in 2006; updating was to bring the review in line with current standards. Neuropathic pain, which is caused by a lesion or disease affecting the somatosensory system, may be central or peripheral in origin. Peripheral neuropathic pain often includes symptoms such as burning or shooting sensations, abnormal sensitivity to normally painless stimuli, or an increased sensitivity to normally painful stimuli. Neuropathic pain is a common symptom in many diseases of the peripheral nervous system.

Objectives

To assess the analgesic efficacy of tramadol compared with placebo or other active interventions for chronic neuropathic pain in adults, and the adverse events associated with its use in clinical trials.

Search methods

We searched CENTRAL, MEDLINE, and Embase for randomised controlled trials from inception to January 2017. We also searched the reference lists of retrieved studies and reviews, and online clinical trial registries.

Selection criteria

We included randomised, double-blind trials of two weeks' duration or longer, comparing tramadol (any route of administration) with placebo or another active treatment for neuropathic pain, with subjective pain assessment by the participant.

Data collection and analysis

Two review authors independently extracted data and assessed trial quality and potential bias. Primary outcomes were participants with substantial pain relief (at least 50% pain relief over baseline or very much improved on Patient Global Impression of Change scale (PGIC)), or moderate pain relief (at least 30% pain relief over baseline or much or very much improved on PGIC). Where pooled analysis was possible, we used dichotomous data to calculate risk ratio (RR) and number needed to treat for an additional beneficial outcome (NNT) or harmful outcome (NNH), using standard methods. We assessed the quality of the evidence using GRADE and created 'Summary of findings' tables.

Main results

We identified six randomised, double-blind studies involving 438 participants with suitably characterised neuropathic pain. In each, tramadol was started at a dose of about 100 mg daily and increased over one to two weeks to a maximum of 400 mg daily or the maximum tolerated dose, and then maintained for the remainder of the study. Participants had experienced moderate or severe neuropathic pain for at least three months due to cancer, cancer treatment, postherpetic neuralgia, peripheral diabetic neuropathy, spinal cord injury, or

polyneuropathy. The mean age was 50 to 67 years with approximately equal numbers of men and women. Exclusions were typically people with other significant comorbidity or pain from other causes. Study duration for treatments was four to six weeks, and two studies had a cross-over design.

Not all studies reported all the outcomes of interest, and there were limited data for pain outcomes. At least 50% pain intensity reduction was reported in three studies (265 participants, 110 events). Using a random-effects analysis, 70/132 (53%) had at least 50% pain relief with tramadol, and 40/133 (30%) with placebo; the risk ratio (RR) was 2.2 (95% confidence interval (CI) 1.02 to 4.6). The NNT calculated from these data was 4.4 (95% CI 2.9 to 8.8). We downgraded the evidence for this outcome by two levels to low quality because of the small size of studies and of the pooled data set, because there were only 110 actual events, the analysis included different types of neuropathic pain, the studies all had at least one high risk of potential bias, and because of the limited duration of the studies.

Participants experienced more adverse events with tramadol than placebo. Report of any adverse event was higher with tramadol (58%) than placebo (34%) (4 studies, 266 participants, 123 events; RR 1.6 (95% CI 1.2 to 2.1); NNH 4.2 (95% CI 2.8 to 8.3)). Adverse event withdrawal was higher with tramadol (16%) than placebo (3%) (6 studies, 485 participants, 45 events; RR 4.1 (95% CI 2.0 to 8.4); NNH 8.2 (95% CI 5.8 to 14)). Only four serious adverse events were reported, without obvious attribution to treatment, and no deaths were reported. We downgraded the evidence for this outcome by two or three levels to low or very low quality because of small study size, because there were few actual events, and because of the limited duration of the studies.

Authors' conclusions

There is only modest information about the use of tramadol in neuropathic pain, coming from small, largely inadequate studies with potential risk of bias. That bias would normally increase the apparent benefits of tramadol. The evidence of benefit from tramadol was of low or very low quality, meaning that it does not provide a reliable indication of the likely effect, and the likelihood is very high that the effect will be substantially different from the estimate in this systematic review.

PLAIN LANGUAGE SUMMARY

Tramadol for treating neuropathic pain

Bottom line

We found low-quality evidence that oral tramadol has any important beneficial effect on pain in people with moderate or severe neuropathic pain. There is very little evidence from which to take these conclusions.

Background

Neuropathic pain is pain coming spontaneously or abnormally from damaged nerves. It is different from pain messages that are carried along healthy nerves from damaged tissue (a fall or cut, or burns). Neuropathic pain is often treated by different medicines (drugs) to those used for pain from damaged tissue, which we call painkillers.

Opioid painkillers (drugs like morphine) are sometimes used to treat neuropathic pain. Morphine is derived from plants, but many opioids are made in a laboratory rather than being extracted from plants. Tramadol is a laboratory-synthesised opioid drug.

Study characteristics

In January 2017, we searched for clinical trials in which tramadol was used to treat neuropathic pain in adults. Six studies met the inclusion criteria, randomising 438 participants to treatment with tramadol or placebo. Study duration was between four and six weeks. Not all reported the outcomes of interest.

Our definition of a good result was someone who had a high level of pain relief and was able to keep taking the medicine without side effects that made them stop treatment.

Key results

Three small studies reported that pain was reduced by half or better in some people. Pain reduction by half or better was experienced by 5 in 10 with tramadol and 3 in 10 with placebo. Side effects were experienced by 6 in 10 with tramadol and 3 in 10 with placebo, and 2 in 10 with tramadol and almost no-one with placebo stopped taking the medicine because of side effects.

Quality of the evidence

The evidence was mostly of low or very low quality. This means that the research does not provide a reliable indication of the likely effect and that the likelihood is very high that the effect will be different from what is shown in the analysis of these trials. Small studies like those in this review tend to overestimate results of treatment compared to the effects found in larger, better studies. There were also other problems that might lead to over-optimistic results. The low-quality evidence and the lack of any important benefit mean that we need new, large trials before we will know if tramadol is useful for the management of neuropathic pain.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Tramadol compared with placebo for neuropathic pain

Tramadol compared with placebo for neuropathic pain

Patient or population: adults with neuropathic pain (any origin)

Settings: community

Intervention: oral tramadol (typically started at a dose of about 100 mg daily and increased over 1 to 2 weeks to a maximum of 400 mg daily)

Comparison: placebo

Outcomes (at trial end)	Probable outcome with tramadol	Probable outcome with placebo	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
At least 30% reduction in pain	Not analysed	Not analysed	Not analysed	157 participants (2 studies) 60 events	Low quality[1]	-
At least 50% reduction in pain	530 per 1000	300 per 1000	RR 2.2 (1.02, 4.6) NNT 4.4 (2.9 to 8.8)	265 participants (3 studies) 110 events	Low quality[1]	-
PGIC much or very much improved	Not analysed	Not analysed	Not analysed	35 participants (1 study) 4 events	Very low quality[2]	-
Withdrawal due to adverse event	160 per 100	30 per 1000	RR 4.1 (2.0 to 8.4) NNH 8.2 (5.8 to 14)	485 participants (6 studies) 45 events	Low quality[1]	-
Participants experiencing any adverse event	580 per 1000	340 per 1000	RR 1.6 (1.2 to 2.1) NNH 4.2 (2.8 to 8.3)	266 participants (4 studies) 123 events	Low quality[1]	-

Serious adverse events	4 serious adverse events reported in total			Not all studies reported specifically on serious adverse events	Very low quality[2]	-
Death	No data	No data	Not calculated	No data	Very low quality[3]	-

CI: confidence interval; **NNH:** number needed to treat for one additional harmful outcome; **PGIC:** Patient Global Impression of Change; **RR:** risk ratio

Descriptors for levels of evidence (EPOC 2015):
High quality: this research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.
Moderate quality: this research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.
Low quality: this research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
Very low quality: this research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

† Substantially different: a large enough difference that it might affect a decision.

[1]Downgraded 2 levels due to small number of studies and participants and relatively few events, and several sources of potential bias.
[2]Downgraded 3 levels due to small number of studies, and participants and events, and several sources of potential bias.
[3]No events.

BACKGROUND

This review is an update of a review of tramadol for neuropathic pain, published in 2006 (Hollingshead 2006). The standards for Cochrane reviews have changed substantially since 2006, and this review is based on a template for reviews of drugs used to relieve neuropathic pain. The aim is for all reviews to use the same methods, based on new criteria for what constitutes reliable evidence in chronic pain (Moore 2010a; Moore 2012; Appendix 1).

Description of the condition

The 2011 International Association for the Study of Pain definition of neuropathic pain is "pain caused by a lesion or disease of the somatosensory system" (Jensen 2011), based on a definition agreed at an earlier consensus meeting (Treede 2008). Neuropathic pain is a consequence of a pathological maladaptive response of the nervous system to 'damage' from a wide variety of potential causes. It is characterised by pain in the absence of a noxious stimulus and may be spontaneous (continuous or paroxysmal) in its temporal characteristics or be evoked by sensory stimuli (dynamic mechanical allodynia where pain is evoked by light touch of the skin). Neuropathic pain is associated with a variety of sensory loss (numbness) and sensory gain (allodynia) clinical phenomena, the exact pattern of which vary between people and disease, perhaps reflecting different pain mechanisms operating in an individual person and, therefore, potentially predictive of response to treatment (Demant 2014; Helfert 2015; von Hehn 2012). Pre-clinical research hypothesises a bewildering array of possible pain mechanisms that may operate in people with neuropathic pain, which largely reflect pathophysiological responses in both the central and peripheral nervous systems, including neuronal interactions with immune cells (Baron 2012; Calvo 2012; von Hehn 2012). Overall, the treatment gains in neuropathic pain, to even the most effective of available drugs, are modest (Finnerup 2015; Moore 2013a), and a robust classification of neuropathic pain is not yet available (Finnerup 2013).

Neuropathic pain is usually divided according to the cause of nerve injury. There may be many causes, but some common causes of neuropathic pain include diabetes (painful diabetic neuropathy (PDN)), shingles (postherpetic neuralgia (PHN)), amputation (stump and phantom limb pain), neuropathic pain after surgery or trauma, stroke or spinal cord injury, trigeminal neuralgia, and HIV infection. Sometimes the cause is unknown.

Many people with neuropathic pain conditions are significantly disabled with moderate or severe pain for many years. Chronic pain conditions comprised five of the 11 top-ranking conditions for years lived with disability in 2010 (Vos 2012), and are responsible for considerable loss of quality of life and employment, and increased healthcare costs (Moore 2014a). A US study found the healthcare costs were three-fold higher for people with neuropathic pain than matched control subjects (Berger 2004). A UK study and a German study showed a two- to three-fold higher level of use of healthcare services in people with neuropathic pain than those without (Berger 2012; Berger 2009). For postherpetic neuralgia, for example, studies demonstrate large loss of quality of life and substantial costs (Scott 2006; Van Hoek 2009).

In systematic reviews, the overall prevalence of neuropathic pain in the general population was reported to be between 7% and 10% (Van Hecke 2014), and about 7% in a systematic review of studies published since 2000 (Moore 2014a). In individual countries, prevalence rates have been reported as 3.3% in Austria (Gustorff 2008), 6.9% in France (Bouhassira 2008), and up to 8% in the UK (Torrance 2006). Some forms of neuropathic pain, such as PDN and post-surgical chronic pain (which is often neuropathic in origin), are increasing (Hall 2008). The prevalence of PHN is likely to fall if vaccination against the herpes virus becomes widespread.

Estimates of incidence vary between individual studies for particular origins of neuropathic pain, often because of small numbers of cases. In primary care in the UK, between 2002 and 2005, the incidences (per 100,000 person-years' observation) were 28 (95% confidence interval (CI) 27 to 30) for PHN, 27 (95% CI 26 to 29) for trigeminal neuralgia, 0.8 (95% CI 0.6 to 1.1) for phantom limb pain, and 21 (95% CI 20 to 22) for PDN (Hall 2008). Other studies have estimated an incidence of 4 in 100,000 per year for trigeminal neuralgia (Katusic 1991; Rappaport 1994), and 12.6 per 100,000 person-years for trigeminal neuralgia and 3.9 per 100,000 person-years for PHN in a study of facial pain in the Netherlands (Koopman 2009). One systematic review of chronic pain demonstrated that some neuropathic pain conditions, such as PDN, can be more common than other neuropathic pain conditions, with prevalence rates up to 400 per 100,000 person-years (McQuay 2007).

Neuropathic pain is difficult to treat effectively, with only a minority of people experiencing a clinically-relevant benefit from any one intervention (Kalso 2013; Moore 2013b). A multidisciplinary approach is now advocated, combining pharmacological interventions with physical or cognitive (or both) interventions. The evidence for interventional management is very weak, or non-existent (Dworkin 2013). Conventional analgesics such as paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) are not thought to be effective, but without evidence to support or refute that view (Moore 2015a). Some people may derive some benefit from a topical lidocaine patch or low-concentration topical capsaicin, although evidence about benefits is uncertain (Derry 2012; Derry 2014). High-concentration topical capsaicin may benefit some people with PHN (Derry 2013). Treatment is often by so-called 'unconventional analgesics' (pain modulators) such as antidepressants (duloxetine and amitriptyline; Lunn 2014; Moore 2014b; Moore 2015b; Sultan 2008), or antiepileptics (gabapentin or pregabalin; Moore 2009; Moore 2014c; Wiffen 2013). Evidence for efficacy of opioids is unconvincing (Gaskell 2016; Stannard 2016).

The proportion of people who achieve worthwhile pain relief (typically at least 50% pain intensity reduction; Moore 2013a) is small, generally only 10% to 25% more than with placebo, with numbers needed to treat for an additional beneficial outcome (NNT) usually between 4 and 10 (Kalso 2013; Moore 2013b). Neuropathic pain is not particularly different from other chronic pain conditions in that only a small proportion of trial participants have a good response to treatment (Moore 2013b).

The current National Institute for Health and Care Excellence (NICE) guidance for the pharmacological management of neuropathic pain suggests offering a choice of amitriptyline, duloxetine, gabapentin, or pregabalin as initial treatment for neuropathic pain (with the exception of trigeminal neuralgia), with switching if the first, second, or third drugs tried are not effective or not tolerated (NICE 2013). This concurs with other recent guidance (Finnerup 2015).

Description of the intervention

Tramadol hydrochloride is an opioid analgesic originally marketed in West Germany in 1977, and now widely available. In 2016, tramadol - alone or in combination with paracetamol (acetaminophen) - was available in products for oral use and by injection from almost 90 companies. Oral formulations include those designed for immediate release, and for modified release over a longer time period. Preparations for rectal administration are also available. The total oral daily dosage is usually up to 400 mg, although some licences state that 400 mg is the maximum dose (Martindale 2016).

Tramadol is used to treat a range of different pain conditions. It acts as a μ-opioid agonist, but also has a range of other properties that may contribute to its analgesic effect, including serotonin reuptake inhibition and norepinephrine reuptake inhibition. It is licensed for use in moderate to severe pain and is less potent than morphine or similar drugs. It is considered to fit into Step 2 of the World Health Organization (WHO) analgesic ladder (WHO 2016). In some parts of the world tramadol is classified as a controlled substance (similar to codeine in this respect), but the exact classification and controls on prescribing vary markedly.

Tramadol has reasonable efficacy in acute postoperative pain as a single agent, and in combination with paracetamol (Edwards 2002; Moore 1997), but has small benefits in osteoarthritis (Cepeda 2006), and the evidence base was inadequate to recommend it as an alternative to paracetamol plus codeine for routine use in people with cancer with mild to moderate cancer pain (Tassinari 2011). The earlier version of this review found that it probably has efficacy in neuropathic pain conditions (Hollingshead 2006).

Tramadol is associated with typical opioid adverse events of nausea, dizziness, and dry mouth, although vomiting and constipation are considered to be less of a problem than with traditional opioids. Use of tramadol with concurrent serotonergic therapy poses a risk of serotonin syndrome (Beakley 2015).

Like other opioids, tramadol is potentially subject to abuse. A study in Germany, where tramadol is not scheduled in the German Narcotic Drugs Act, calculated the incidence of abuse as 0.21 cases per million defined daily dosages (DDDs) and dependency as 0.12 cases per million DDDs, with lower incidences in recent years (Radbruch 2013). The conclusion was that tramadol had a low potential for misuse, abuse, and dependency.

How the intervention might work

Tramadol acts centrally, and both tramadol and its O-desmethyl metabolite are selective, weak OP3-receptor (μ) agonists. The mode of action is poorly understood (Reeves 2008).

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine with a central analgesic effect. Tramadol is metabolised by *N*- and *O*-demethylation via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6 and glucuronidation or sulphation in the liver. Around 40% of the analgesic action is provided by O-desmethyl tramadol (M1) created by rapid metabolism of tramadol in the liver via the cytochrome P450 enzyme CYP2D6 (Bozkurt 2005; Grond 2004; Lintz 1998). Tramadol is also metabolised by *N*-demethylation via the cytochrome P450 isoenzyme CYP3A4, and glucuronidation or sulphation in the liver (Grond 2004).

Tramadol is available as a racemic mixture of (+) and (-) enantiomers. The (+) enantiomer has only a weak affinity to μ-opioid receptors and inhibits serotonin reuptake, while the (-) enantiomer inhibits norepinephrine reuptake in the spinal cord (Bozkurt 2005; Scott 2000). These different modes action might explain the longer analgesic efficacy and the lower incidence of opioid adverse effects, but a range of other modes of action have been proposed (Bozkurt 2005; Grond 2004).

Tramadol is rapidly absorbed after oral administration and has an absolute bioavailability of 65% to 70% (Lintz 1998; Scott 2000). Generally, there are no significant differences in the pharmacokinetics (elimination half-life, distribution, serum clearance and concentration of metabolites) of tramadol between adults and children after oral dosing or intravenous injection. Genetic variances probably influence analgesic efficacy (Gan 2007). About 8% of the white population has cytochrome P450 enzyme (CYP2D6) deficiency that reduces the analgesic effects of tramadol, and this may well be greater in some other populations. Other drugs metabolised by CYP2D6 enzymes (ondansetron, for example) can potentially interfere with tramadol metabolism, changing how well it works in individuals, and possible adverse events as well.

Why it is important to do this review

The earlier version of this review indicated a benefit of tramadol over placebo for relief of neuropathic pain. This was based on pooled evidence from five studies in various different types of neuropathic pain (Hollingshead 2006); since then our understanding of methods and biases relating to opioid use in chronic pain has improved, and more studies have become available. A more recent review by the Canadian Agency for Drugs and Technologies in Health was less positive about the efficacy of tramadol (CADTH 2015). In addition, data from the US 2005 to 2011 Drug Abuse Warning Network showed that visits made to emergency departments involving misuse or abuse of tramadol increased about 250% between 2005 and 2011 (Bush 2015).

The standards used to assess evidence in chronic pain trials have changed substantially in recent years, with particular attention being paid to trial duration, withdrawals, and statistical imputation following withdrawal, all of which can substantially alter estimates of efficacy. The most important change is the move from using mean pain scores, or mean change in pain scores, to the number of people who have a large decrease in pain (by at least 50%) and who continue in treatment, ideally in trials of 8 to 12 weeks' duration or longer. Pain intensity reduction of 50% or more correlates with improvements in co-morbid symptoms, function, and quality of life generally (Moore 2013a), and in people with neuropathic pain (Hoffman 2010). These standards are set out in the *PaPaS Author and Referee Guidance* for pain studies of Cochrane Pain, Palliative and Supportive Care (PaPaS) (PaPaS 2012).

This Cochrane Review assesses evidence using improved methods that make both statistical and clinical sense, using developing criteria for what constitutes reliable evidence in chronic pain (Moore 2010a). Trials included and analysed had to meet a minimum of reporting quality (blinding, randomisation), validity (duration, dose and timing, diagnosis, outcomes, etc.), and size. Ideally at least 500 participants are needed in a comparison in which the NNT is 4 or above in order to measure the magnitude of a treatment effect adequately (Moore 1998). This approach sets high

standards for the demonstration of efficacy and marks a departure from how reviews were conducted previously.

OBJECTIVES

To assess the analgesic efficacy of tramadol compared with placebo or other active interventions for chronic neuropathic pain in adults, and the adverse events associated with its use in clinical trials.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) with double-blind assessment of participant outcomes following two weeks or more of treatment, although the emphasis of the review was on studies with a duration of eight weeks or longer. We required full journal publication, with the exception of online clinical trial results summaries of otherwise unpublished clinical trials and abstracts with sufficient data for analysis. We did not include short abstracts (usually meeting reports), and we excluded studies that were non-randomised, studies of experimental pain, case reports, and clinical observations.

Types of participants

Studies included adults aged 18 years and above with one or more chronic neuropathic pain condition including (but not limited to):

1. cancer-related neuropathy;
2. central neuropathic pain;
3. complex regional pain syndrome (CRPS) Type II;
4. HIV neuropathy;
5. painful diabetic neuropathy;
6. phantom limb pain;
7. postherpetic neuralgia;
8. postoperative or traumatic neuropathic pain;
9. spinal cord injury;
10. trigeminal neuralgia.

Types of interventions

Tramadol at any dose, by any route, administered for the relief of neuropathic pain and compared with placebo or any active comparator.

Types of outcome measures

We anticipated that studies would use a variety of outcome measures, with most studies using standard subjective scales (numerical rating scale (NRS) or visual analogue scale (VAS)) for pain intensity or pain relief, or both. We were particularly interested in Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions for moderate and substantial benefit in chronic pain studies (Dworkin 2008). These are defined as:

1. at least 30% pain relief over baseline (moderate);
2. at least 50% pain relief over baseline (substantial);
3. much or very much improved on Patient Global Impression of Change scale (PGIC; moderate);
4. very much improved on PGIC (substantial).

These outcomes are different from those used in most earlier reviews, concentrating as they do on dichotomous outcomes where pain responses do not follow a normal (Gaussian) distribution. People with chronic pain desire high levels of pain relief, ideally more than 50% pain intensity reduction, and ideally having no worse than mild pain (Moore 2013a; O'Brien 2010).

Primary outcomes

1. Participant-reported pain relief of 30% or greater
2. Participant-reported pain relief of 50% or greater
3. PGIC much or very much improved
4. PGIC very much improved

Secondary outcomes

1. Any pain-related outcome indicating some improvement
2. Withdrawals due to lack of efficacy, adverse events, and for any cause
3. Participants experiencing any adverse event
4. Participants experiencing any serious adverse event. Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardise the patient, or may require an intervention to prevent one of the above characteristics or consequences.
5. Specific adverse events, particularly somnolence and dizziness

Search methods for identification of studies

Electronic searches

For this update, we searched the following databases, without language restrictions:

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017) via Cochrane Register of Studies Online) on 9 January 2017;
2. MEDLINE (via Ovid from 1946 to 9 January 2017);
3. Embase (via Ovid from 1974 to 9 January 2017).

The search strategies for CENTRAL, MEDLINE, and Embase are in Appendix 2, Appendix 3, and Appendix 4, respectively.

For the earlier review, we searched LILACS (Appendix 5).

Searching other resources

We reviewed the bibliographies of any RCTs and review articles identified by the new searches, and searched clinical trial databases (ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTTRP) (apps.who.int/trialsearch/)) to identify additional published or unpublished data. We did not contact investigators or study sponsors.

Data collection and analysis

We planned to perform separate analyses according to particular neuropathic pain conditions. We have combined different neuropathic pain conditions in analyses for exploratory purposes only.

Selection of studies

We reassessed studies included in the earlier review to determine whether they satisfied our new, stricter inclusion criteria. For studies identified by the new searches, we determined eligibility by reading the abstract of each study identified by the search. We eliminated studies that clearly did not satisfy the inclusion criteria, and we obtained full copies of the remaining studies. Three review authors (SD, RAM, PW) made the decisions. These authors then read these studies independently and reached agreement by discussion. We did not anonymise the studies in any way before assessment. We have provided a PRISMA flow chart (Moher 2009).

Data extraction and management

Two review authors (SD, RAM) extracted data independently using a standard form and checked for agreement before entry into Review Manager 5 (RevMan 5) (RevMan 2014), or any other analysis tool. We included information about the pain condition and number of participants treated, drug and dosing regimen, study design (placebo or active control), study duration and follow-up, analgesic outcome measures and results, withdrawals, and adverse events (participants experiencing any adverse event, or serious adverse event).

We reviewed studies included in the earlier review to determine whether there was additional information relating to the updated outcomes.

Assessment of risk of bias in included studies

We used the Oxford Quality Score as the basis for inclusion (Jadad 1996), limiting inclusion to studies that were randomised and double-blind as a minimum.

Two review authors (SD, PW) independently assessed risk of bias for each study, using some of the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 8, Higgins 2011), and adapted by Cochrane PaPaS from those used by Cochrane Pregnancy and Childbirth, with any disagreements resolved by discussion. We assessed the following for each study.

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process: random number table or computer random-number generator); unclear risk of bias (when the method used to generate the sequence was not clearly stated). We excluded studies at a high risk of bias that used a non-random process (odd or even date of birth; hospital or clinic record number).
2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We assessed the methods as: low risk of bias (telephone or central randomisation; consecutively-numbered, sealed, opaque envelopes); unclear risk of bias (when the method was not clearly stated). We excluded studies that did not conceal allocation and were therefore at a high risk of bias (open list).
3. Blinding of participants and personnel (checking for possible performance bias), and blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study personnel and participants (all outcomes were self-assessed) from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, for example, identical tablets, matched in appearance and smell); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved). We excluded studies at a high risk of bias that were not double-blind.
4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk of bias (fewer than 10% of participants did not complete the study or used 'baseline observation carried forward' (BOCF) analysis, or both); unclear risk of bias (used 'last observation carried forward' (LOCF) analysis); or high risk of bias (used 'completer' analysis).
5. Size of study (checking for possible biases confounded by small size). Small studies have been shown to overestimate treatment effects, probably because the conduct of small studies is more likely to be less rigorous, allowing critical criteria to be compromised (Dechartres 2013; Nüesch 2010). We assessed studies as being at low risk of bias (200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); or high risk of bias (fewer than 50 participants per treatment arm).

Measures of treatment effect

We calculated the number needed to treat for an additional beneficial outcome (NNT) as the reciprocal of the absolute risk reduction (ARR) (McQuay 1998). For unwanted effects, the NNT becomes the number needed to treat for an additional harmful outcome (NNH) and was calculated in the same manner. We used dichotomous data to calculate a risk ratio (RR) with 95% confidence intervals (CIs) using a fixed-effect model unless significant statistical heterogeneity was found (see below). We did not use continuous data in analyses.

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

We used intention-to-treat (ITT) analysis where the ITT population consisted of participants who were randomised, took at least one dose of the assigned study medication, and provided at least one post-baseline assessment. Missing participants were assigned zero improvement wherever possible.

We paid particular attention to methods used for imputation of missing data due to withdrawals for adverse events and lack of efficacy.

Assessment of heterogeneity

We dealt with clinical heterogeneity by combining studies that examined similar conditions. We assessed statistical heterogeneity visually (L'Abbé 1987), and with the use of the I^2 statistic (Higgins 2003). When the I^2 value was greater than 50%, we considered possible reasons for this.

Assessment of reporting biases

The aim of this review was to use dichotomous outcomes of known utility and of value to patients (Hoffman 2010; Moore 2010b; Moore 2010c; Moore 2010d; Moore 2013a). The review did not depend on what the authors of the original studies chose to report or not, and studies that did not report dichotomous results for an outcome did not contribute to pooled analyses for that outcome. We extracted and used continuous data, which probably reflect efficacy and utility poorly (McQuay 1996), for illustrative purposes only.

We assessed publication bias using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean a NNT of 10 or higher in this condition; Moore 2008).

Data synthesis

We used a fixed-effect model for meta-analysis. We used a random-effects model for meta-analysis where there was significant clinical heterogeneity and it was considered appropriate to combine studies.

Quality of evidence

We used the GRADE approach to assess the quality of evidence related to each of the key outcomes, and report our judgement on the quality of the evidence in the 'Summary of findings' table (Chapter 12, Schünemann 2011a; Appendix 6).

In addition, there may be circumstances where the overall rating for a particular outcome needs to be adjusted as recommended by GRADE guidelines (Guyatt 2013a). For example, if there were so few data that the results were highly susceptible to the random play of chance, or if a studies used LOCF imputation in circumstances where there were substantial differences in adverse event withdrawals, one would have no confidence in the result, and would need to grade the quality of the evidence as very low quality.

In addition, we are aware that many Cochrane Reviews are based largely or wholly on small underpowered studies, and the danger of making conclusive assessments of evidence based on inadequate information (AlBalawi 2013; Brok 2009; Roberts 2015; Turner 2013).

'Summary of findings' table

We have included a 'Summary of findings' table as set out in the PaPaS author guide (PaPaS 2012), and recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 11, Schünemann 2011b; Guyatt 2013b). The table includes, where possible, outcomes equivalent to moderate or substantial benefit of at least 30% and at least 50% pain intensity reduction, PGIC (possibly at least substantial improvement and at least moderate improvement) (Dworkin 2008), withdrawals due to adverse events, participants experiencing any adverse event, serious adverse events, and death (a particular serious adverse event).

For the 'Summary of findings' table we used the following descriptors for levels of evidence (EPOC 2015).

High: this research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† from the estimate is low.

Moderate: this research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† from the estimate is moderate.

Low: this research provides some indication of the likely effect. However, the likelihood that it will be substantially different† from the estimate is high.

Very low: this research does not provide a reliable indication of any effect. The likelihood that the effect will be substantially different† from the estimate is very high.

† Substantially different: a large enough difference that it might affect a decision.

Subgroup analysis and investigation of heterogeneity

We planned all analyses to be according to individual painful conditions, because placebo response rates for the same outcome can vary between conditions, as can the drug-specific effects (Moore 2009).

Sensitivity analysis

We did not plan any sensitivity analysis because the evidence base is known to be too small to allow reliable analysis.

RESULTS

Description of studies

The original review included five studies that compared tramadol with placebo (Arbaiza 2007; Boureau 2003; Harati 1998; Erdine 1997; Sindrup 1999), one comparing tramadol with clomipramine (Gobel 1995), and one comparing tramadol with morphine (Leppert 2001).

For this update we included only double-blind studies, which led to the exclusion of the two active-controlled studies, which were open label (Gobel 1995; Leppert 2001). We also excluded the short conference abstract, which did not provide any usable data or methodological details (Erdine 1997).

Results of the search

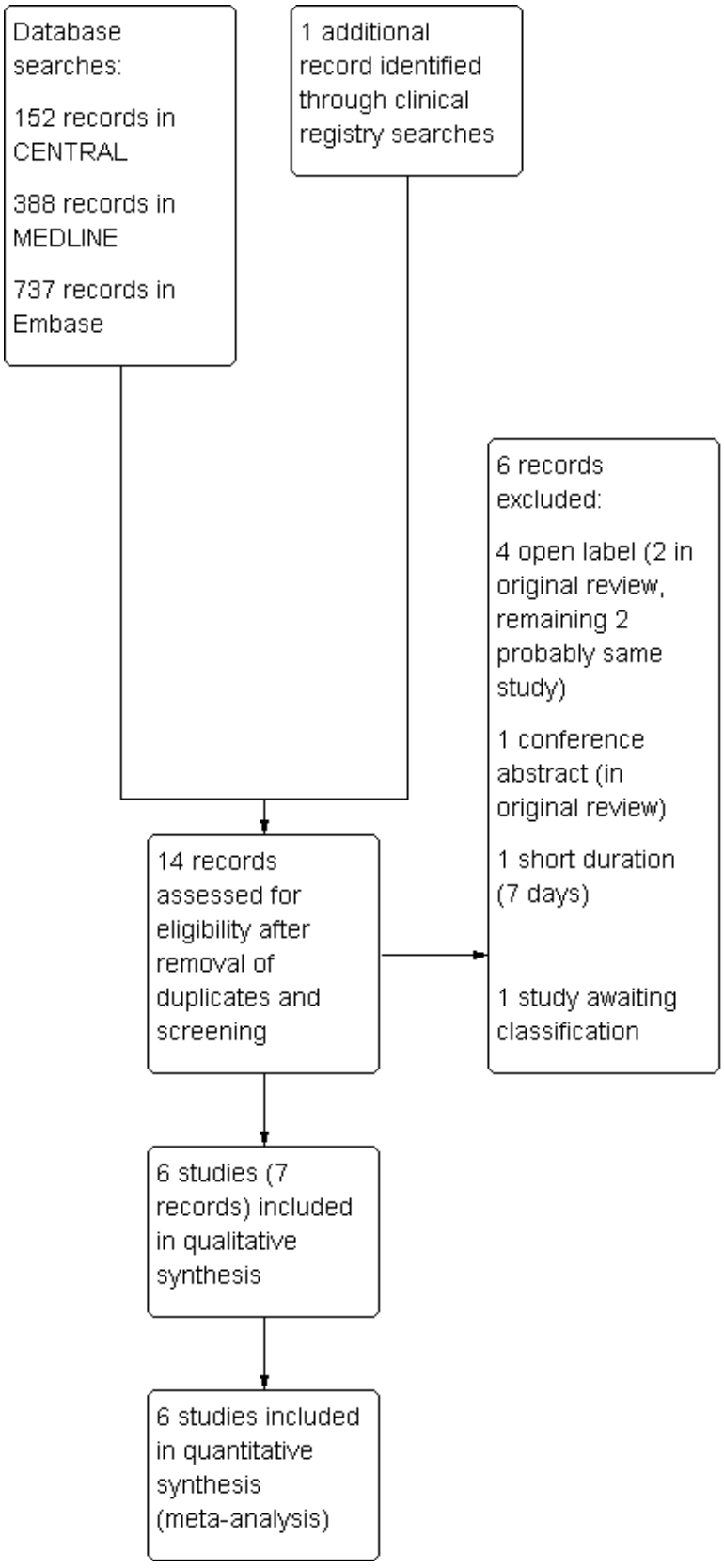
We carried out full, rather than updated, searches because the study inclusion criteria for this update had changed as above. The searches identified 152 records in CENTRAL, 388 in MEDLINE, 737 in Embase, and one additional record in clinical trials registries. They identified all the studies that had been included in the earlier review and six new reports (probably of five studies) that were potentially eligible. After reading the full texts we included four of the original included studies (Arbaiza 2007; Boureau 2003; Harati 1998; Sindrup 1999) and two new studies (Norrbrink 2009; Sindrup 2012). We excluded three of the original studies (Gobel 1995; Leppert 2001; Erdine 1997) as above, and three of the new reports (probably two studies) (NCT00610155; Saxena 2013).

We placed the remaining new study in 'Studies awaiting classification' (Ho 2009). The reason for this was the highly contrived design, with pre-testing selection of participants with two run-in periods, the very large doses of additional drug therapy that could have been taken, the very small numbers of participants, and the short one-week maintenance phase. We are unable at this time to properly classify this study. Moreover, participants had to have painful small fibre sensory neuropathy of two months' or greater

duration. This disease duration is below our threshold for inclusion, and there was no indication of what the average or typical duration of the condition actually was.

See Figure 1.

Figure 1. Study flow diagram for the updated search



Included studies

We included six studies, with 438 participants randomised to treatment with tramadol, placebo, or both (109 participants in cross-over studies) in approximately equal numbers, although efficacy data were not available for all of the randomised participants (Arbaiza 2007; Boureau 2003; Harati 1998; Norrbrink 2009; Sindrup 1999; Sindrup 2012). One cross-over study, enrolling 64 participants, included an active treatment arm using a novel analgesic (GRT9906) (Sindrup 2012). Tramadol was started at a dose of about 100 mg daily and increased over one to two weeks to a maximum of 400 mg daily (300 mg daily in people aged 75 years or more in Boureau 2003) or the maximum tolerated dose, and then maintained for the remainder of the study.

Treatment periods were from four to six weeks (45 days), with washout periods of at least one week between treatments in cross-over studies. Most studies specified paracetamol (acetaminophen) as rescue medication. Arbaiza 2007 allowed continuation of antiepileptic analgesic therapy with dose reduction if required, and Norrbrink 2009 allowed unchanged stable pain medication. The other studies required that all previous pain medication was stopped and washed out before the start of the study (Boureau 2003; Harati 1998; Sindrup 2012), or did not report on this aspect (Sindrup 1999).

Studies enrolled participants who had experienced moderate or severe neuropathic pain for at least three months due to cancer or cancer-treatment (Arbaiza 2007), postherpetic neuralgia (Boureau 2003), or peripheral diabetic neuropathy (Harati 1998); at least 12 months due to spinal cord injury (Norrbrink 2009); or at least six months due to polyneuropathy (Sindrup 1999; Sindrup 2012). The mean age ranged from 50 to 67 years (overall range 26 to 85 years), and there were approximately equal numbers of men and women overall, although the ratio varied between studies from 4:1 to 1:2.6. Three studies were multicentre (Boureau 2003; Harati 1998; Sindrup 2012). Exclusion criteria varied between studies, but generally they excluded people with other significant comorbidities or pain from other causes; contraindications to tramadol or other opioids; and a history of addiction or drug or alcohol abuse.

Further details are reported in the Characteristics of included studies table.

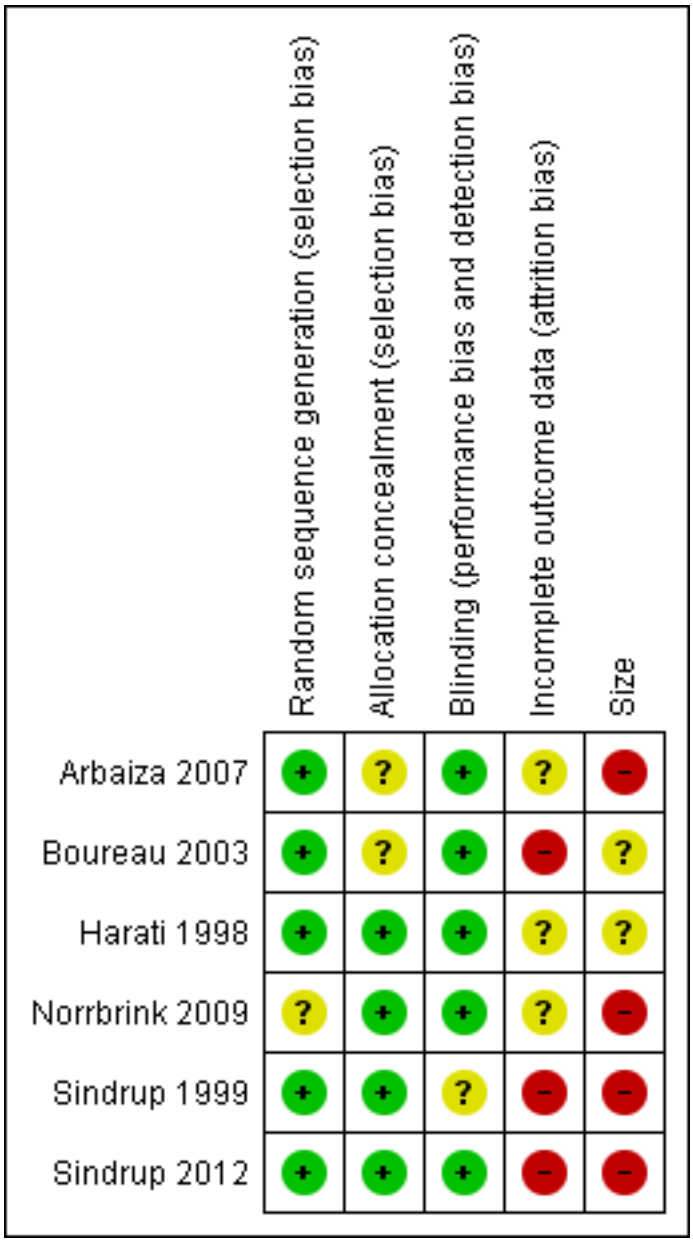
Excluded studies

We excluded three studies that were included in the original review because they did not satisfy the updated inclusion criteria (Erdine 1997; Gobel 1995; Leppert 2001), and two additional studies (three reports) because one was not a controlled trial (Saxena 2013), and the other used treatment periods of only seven days and treatment groups of fewer than 10 participants (NCT00610155). Details are reported in the Characteristics of excluded studies table.

Risk of bias in included studies

A summary of the risk of bias assessment is shown in Figure 2.

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



Allocation

All the studies were described as randomised, and all except Norrbrink 2009 adequately described the method used to generate the random sequence. Two studies (Arbaiza 2007; Boureau 2003) did not adequately describe the method used to conceal the allocation. One trial had some initial differences in participant characteristics at baseline (Norrbrink 2009).

Blinding

All the studies were described as double-blind, and all except Sindrup 1999 adequately described the method used to maintain blinding.

Incomplete outcome data

All the included studies were at unknown or high risk of attrition bias. This was because they did not report an ITT analysis using BOCF for withdrawals (or other conservative imputation method for efficacy) in a situation where there was considerable imbalance between withdrawals due to adverse events and lack of efficacy. We judged Sindrup 2012 at high risk of bias because efficacy results were based on participants who completed all three treatment periods. Both Boureau 2003 and Sindrup 1999 handled data in a way that we considered equivalent to LOCF imputation, and we considered them to be at high risk of bias. We judged the remaining studies at unclear risk of bias.

Other potential sources of bias

We judged four studies at high risk of bias due to small size (< 50 participants per treatment arm; Arbaiza 2007; Norrbrink 2009; Sindrup 1999; Sindrup 2012), and two at unknown risk of bias (63 to 66 participants per treatment arm; Boureau 2003; Harati 1998).

Effects of interventions

See: **Summary of findings for the main comparison** Tramadol compared with placebo for neuropathic pain

Results for individual studies are presented in Appendix 7 (efficacy) and Appendix 8 (adverse events and withdrawals).

Tramadol versus placebo

Participants with at least 30% pain relief

Two studies, both in polyneuropathy, provided information on this outcome. There were insufficient data for reliable analysis (157 participants).

In Sindrup 1999, 13/34 participants achieved at least 30% pain intensity reduction with tramadol, and 4/33 with placebo, using LOCF for withdrawals. In Sindrup 2012, of those participants who completed all three phases of treatment (per protocol analysis), 32/45 achieved at least 30% pain intensity reduction with tramadol, and 11/45 with placebo.

We downgraded the evidence for this outcome by two levels to low quality because of the small size of studies and pooled data set, with only 60 actual events.

Participants with at least 50% pain relief

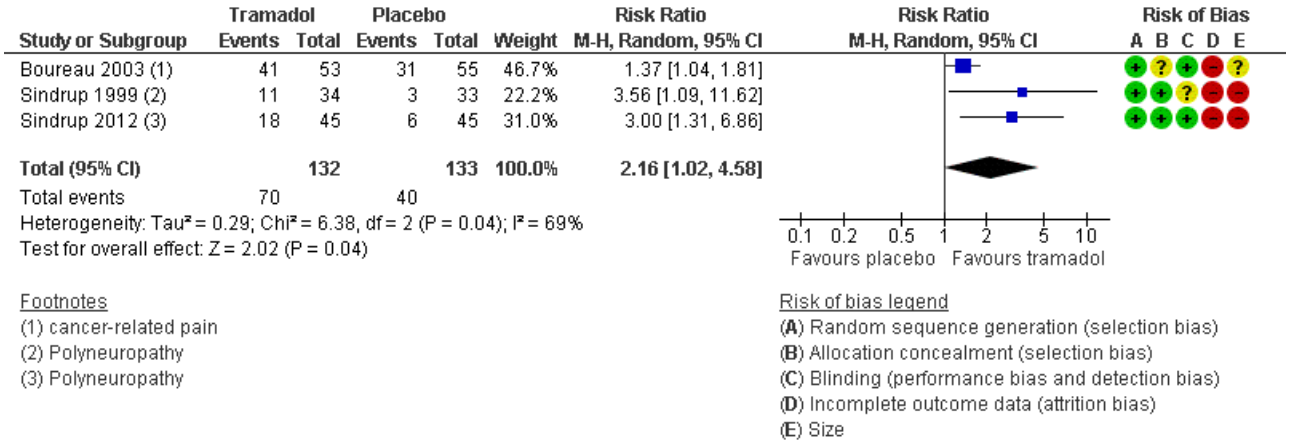
Three studies, one in cancer-related pain and two in polyneuropathy, provided information on this outcome. It was our intention to analyse different pain conditions separately, but there were insufficient data for sensible analysis (108 participants with cancer-related pain and 157 with polyneuropathy).

In Boureau 2003, 41/53 participants with postherpetic neuralgia achieved at least 50% pain intensity reduction with tramadol, and 31/55 with placebo, using a per protocol analysis and LOCF for withdrawals.

In Sindrup 1999, 11/34 participants achieved at least 50% pain intensity reduction with tramadol, and 3/33 with placebo, using LOCF for withdrawals. In Sindrup 2012, of those participants who completed all three phases of treatment (per protocol analysis, and probably LOCF imputation), 18/45 achieved at least 50% pain intensity reduction with tramadol, and 6/45 with placebo.

Pooling all three studies, and using a random-effects analysis, 70/132 (53%) had at least 50% pain relief with tramadol, and 40/133 (30%) with placebo. The RR was 2.2 (95% CI 1.02 to 4.6; Analysis 1.1; Figure 3). The NNT calculated from these data was 4.4 (95% CI 2.9 to 8.9).

Figure 3. Forest plot of comparison: 1 Tramadol versus placebo, outcome: 1.1 Participants with ≥ 50% pain intensity reduction.



We downgraded the evidence for this outcome by two levels to low quality because of the small size of studies and pooled and heterogeneous data set, which included different types of neuropathic pain with at least one high risk of potential bias, and because of the limited duration of treatment.

PGIC much or very much improved

One study reported the number of participants who considered themselves 'much or very much improved' at the end of treatment (Norrbrink 2009). The outcome was reported by 4/23 participants with tramadol and 0/12 with placebo.

None of the participants reported being 'very much improved'.

We downgraded the evidence for this outcome by three levels to very low quality because of the small size of studies and pooled data set, and because there were only five actual events.

Other pain-related measures of 'improvement'

Two studies did not report any of our primary efficacy outcomes, but did report group mean data indicating 'improvement'.

Arbaiza 2007 reported a mean pain intensity of 2.9/10 with tramadol and 4.3/10 with placebo at the end of treatment (baseline 7/10), and the use of antiepileptic drugs was reduced in the tramadol group, but not in the placebo group.

Harati 1998 reported a mean pain intensity of 1.4 with tramadol and 2.2 with placebo (scale 0 to 4) at the end of treatment (baseline 2.5).

Withdrawals

Lack of efficacy

Withdrawals due to lack of efficacy were reported in five studies, but Sindrup 1999 did not specify in which treatment arm they occurred (two withdrawals in second treatment phase). In two studies there were no lack of efficacy withdrawals (Norrbrink 2009; Sindrup 2012). In the remaining two studies there were 11 withdrawals in 79 participants with tramadol and 28 withdrawals in 84 participants with placebo (Arbaiza 2007; Harati 1998).

We downgraded the evidence for this outcome by two levels to low quality because of the small size of studies and pooled data set, with only 39 actual events.

Adverse events

All six studies reported on withdrawals due to adverse events (485 participants).

- The proportion of participants who withdrew due to adverse events with tramadol was 16% (38/249, range 7.1% to 48%).
- The proportion of participants who withdrew due to adverse events with placebo was 3% (7/236, range 0% to 17%).
- The RR for tramadol compared with placebo was 4.1 (95% CI 2.0 to 8.4); the NNH was 8.2 (95% CI 5.8 to 14) (Analysis 1.2).

We downgraded the evidence for this outcome by two levels to low quality because of the small size of studies with only 45 actual events.

All cause

Three studies clearly reported on all withdrawals by treatment group (Arbaiza 2007; Harati 1998; Norrbrink 2009) (202 participants); in Norrbrink 2009 all the withdrawals were due to adverse events. In the other three studies there was insufficient information about either the number of participants or the treatment group.

- The proportion of participants who withdrew due for any reason with tramadol was 34% (36/106, range 28% to 48%).
- The proportion of participants who withdrew due for any reason with placebo was 29% (28/96, range 17% to 33%).
- The RR for tramadol compared with placebo was 1.2 (95% CI 0.75 to 1.8); the NNH was not calculated (Analysis 1.3).

We downgraded the evidence for this outcome by three levels to very low quality because of the small size of studies and pooled data set, and with only 64 actual events.

Adverse events

Any adverse event

Four studies reported the number of participants who experienced one or more adverse events (Arbaiza 2007; Boureau 2003; Norrbrink 2009; Sindrup 1999) (266 participants).

- The proportion of participants who experienced one or more adverse events with tramadol was 58% (80/139, range 30% to 91%).
- The proportion of participants who experienced one or more adverse events with placebo was 34% (43/127, range 22% to 58%).
- The RR for tramadol compared with placebo was 1.6 (95% CI 1.2 to 2.1); the NNH was 4.2 (95% CI 2.8 to 8.3) (Analysis 1.4).

We downgraded the evidence for this outcome by two levels to low quality because of the small size of studies and with only 123 actual events.

Serious adverse events

Four studies did not report any serious adverse events (Arbaiza 2007; Harati 1998; Norrbrink 2009; Sindrup 1999). Boureau 2003 reported that three participants experienced serious adverse events; it is not clear which treatment these participants were receiving, but it is likely that they were in the tramadol group, since there were no withdrawals due to adverse events in the placebo group. The nature of the events was not reported. In Sindrup 2012, one participant each in the tramadol and active comparator (GRT9906) groups, and none in the placebo group experienced serious adverse events. The event with tramadol was vertigo. No deaths were reported.

We downgraded the evidence for this outcome by three levels to very low quality because of the small size of studies and pooled data set, and because there were only four actual events.

Specific adverse events

Specific adverse events were not consistently reported, with studies reporting events without frequencies, only the most common events, or by body system. They included nausea, somnolence, constipation, dry mouth, general malaise, dizziness, tiredness, headache, dyspepsia, diarrhoea, sweating, sleep disorders, and micturition problems. Most events were more common with tramadol than placebo; intensity was generally reported as mild to moderate with tramadol and mild with placebo.

We were able to assess the frequency of some specific adverse events (Analysis 1.5).

Event	Studies	Partici-pants	% with tra-madol	% with placebo	RR (95% CI)	NNH (95% CI)
Nausea	6	508	26	6.9	3.6 (2.2 to 5.9)	5.2 (3.9 to 7.6)
Constipation	5	381	29	6.5	4.1 (2.4 to 7.2)	4.4 (3.4 to 6.5)

Tiredness/fatigue	4	345	33	10	3.2 (1.9 to 5.4)	4.2 (3.2 to 6.5)
Dizziness	3	214	36	8.9	3.7 (1.9 to 7.1)	3.7 (2.6 to 5.9)
Dry mouth	3	214	29	11	2.4 (1.4 to 4.4)	5.5 (3.5 to 13)

CI: confidence interval; NNH: number needed to treat for one additional harmful outcome; RR: risk ratio

We graded the evidence for specific adverse events as low quality. While there was a limited number of events, there was consistency between studies.

DISCUSSION

Summary of main results

Participants in these studies typically had moderate or severe neuropathic pain, often long-lasting, and with an initial average pain score of around 6/10 at the start of the studies. The primary pain outcomes of this review were 'substantial' pain relief, ideally the reduction in pain intensity by 50% or more, and 'moderate' pain relief, a reduction by 30% or more, both sustained over the duration of the trial, which was typically three months. These outcomes are judged as desirable by people with pain (Moore 2013a).

Only some of the studies reported pain outcomes of interest to people with neuropathic pain, and we could not perform analyses according to different types of neuropathic pain. This is important because different types of neuropathic pain can respond differently to the same treatment when studies are otherwise identical (Moore 2009).

The evidence that tramadol is beneficial for neuropathic pain is very limited, despite it being commonly used and recommended for the condition (NICE 2013). The conclusion of this updated review is therefore different from that of the original (Hollingshead 2006). The evidence of any benefit from tramadol was of low or very low quality, meaning that the likelihood is very high that the effect will be substantially different from the estimate in this systematic review. This quality assessment is due predominantly to higher standards of evidence now being applied, including a growing concern about possible overestimation of treatment effect in small studies.

An important issue is that of study size and the overall amount of information available for analysis. There are issues over both random chance effects with small amounts of data, and potential bias in small studies, especially in pain (Dechartres 2013; Dechartres 2014; Moore 1998; Nüesch 2010; Thorlund 2011). Another potentially major positive bias towards experimental intervention is the use of LOCF imputation (Moore 2012). Cochrane Reviews have been criticised for perhaps over-emphasising results of underpowered studies or analyses (AlBalawi 2013; Turner 2013). On the other hand, it may be unethical to ignore potentially important information from small studies or to randomise more patients if a meta-analysis including small studies has provided conclusive evidence.

Overall completeness and applicability of evidence

Study participants were typical of people with neuropathic pain who are eligible to take part in clinical trials. As is usual, exclusion criteria included other significant comorbidities or pain from other causes, contraindications to tramadol or other opioids, and a history of addiction or drug or alcohol abuse. The problems that attend small studies, and other methodological considerations make the evidence less than complete and not easily applicable to many people with neuropathic pain. While problems of bias surrounding the studies might be expected to produce a large treatment effect, no such large treatment effect was seen.

Doses of oral tramadol in the range of 200 mg to 400 mg daily were those typically used to treat chronic pain.

One other issue of importance is that study duration was generally four to six weeks, arguably inadequate for a long-term pain condition.

Quality of the evidence

Five of the six included studies had at least one major risk of bias. Poor reporting of useful pain outcomes rendered the evidence quality low to very low. Pooled analyses were mostly on only about 200 participants, where chance effects are possible (Moore 1998). In view of the small sample sizes, as well as uncertainties for other possible risks of bias, we chose to downgrade the quality of most of the evidence by three levels to very low quality. Very low quality means that this research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different from the estimate produced here is very high.

Potential biases in the review process

We know of no potential biases in the review process. We had planned to calculate the number of participants who would need to be in trials with zero effect (risk ratio of 1.0) needed for the point estimate of the NNT to increase beyond a clinically useful level (Moore 2008), but this method is not applicable with low effect sizes and uncertain results.

Agreements and disagreements with other studies or reviews

This updated review comes to a different conclusion to the previous version of the review (Hollingshead 2006). That version concluded that tramadol is an effective treatment for neuropathic pain, but did not apply such stringent conditions to quality or bias, or benefit from recent work understanding the overestimation of effect in small studies. Another Cochrane Review examined tramadol for treating osteoarthritis (Cepeda 2006). That review concluded that

tramadol or tramadol/paracetamol decreased pain intensity, but the benefits were small (a decrease of about 12% in average pain intensity). Finnerup and colleagues calculated an NNT of 4.7 (3.6 to 6.7) based on six studies with over 700 participants (Finnerup 2015), but used different quality criteria and included one study with a tramadol/paracetamol combination.

AUTHORS' CONCLUSIONS

Implications for practice

For people with neuropathic pain

There is not enough data of adequate quality to provide convincing evidence that tramadol is effective in relieving neuropathic pain.

For clinicians

There is not enough data of adequate quality to provide convincing evidence that tramadol is effective in relieving neuropathic pain. Any biases in the small studies we have would be expected to work to increase estimates of efficacy. A few people may get a good response with tramadol.

For policy makers and funders

There is not enough data of adequate quality to provide convincing evidence to support the suggestion that tramadol has efficacy in relieving neuropathic pain. Any biases in the small studies would be expected to work to increase estimates of efficacy, and the fact that no meaningful efficacy was found strengthens the suggestion that tramadol may be ineffective in a population of patients. This does not preclude some obtaining a good response with tramadol.

Implications for research

General

The design of studies in neuropathic pain, and the outcomes, are well understood, but as the number of people experiencing good pain relief with tramadol is likely to be small, an enriched-enrolment randomised-withdrawal (EERW) design might provide the highest sensitivity to detect a signal (Moore 2015c). Since combination therapy for neuropathic pain has been reported to be more effective than monotherapy with any drug (Chaparro 2012), and combination therapy is common clinical practice, studies examining tramadol in combination with a gabapentinoid could be of interest.

Design

Reporting of clinically relevant outcomes using appropriate imputation for withdrawal would improve the relevance of the findings for clinical practice. The use of EERW designs for comparison with classic trial designs indicates that good quality EERW designs of long duration may be appropriate for neuropathic pain.

Measurement (endpoints)

Assessment of neuropathic pain and other symptoms should be based on dichotomous participant-reported outcomes of proven clinical utility.

Comparison with active treatments

Without knowing whether tramadol is effective, there seems little point in comparing it with other treatments.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Arbaiza 2007

Methods	Randomised ("matched pair"), double-blind, parallel-group, placebo-controlled Duration: 45 days Assessed at baseline, 15, 30, 45 days
Participants	Cancer-related or cancer treatment-related neuropathic pain of ≥ moderate intensity for ≥ 3 months, aged 18-60 years Exclusion: pain mainly somatic, visceral or sympathetically maintained; scheduled for surgery, radiotherapy, chemotherapy, hormone therapy; use of tricyclic antidepressants, tramadol or any opioid; respiratory failure, chronic obstructive pulmonary disease, intracranial hypertension; Hx psychiatric illness or dependency on alcohol or drugs N = 36 M 14, F 22 Mean age 50 years Mean baseline PI: 7/10
Interventions	Tramadol 1 mg/kg bodyweight every 6 h; increased to 1.5 mg/kg every 6 h if relief inadequate, n = 18 Placebo, n = 18 Participants could continue with previous antiepileptic analgesic therapy - and could reduce dose during study Rescue medication: paracetamol 500 mg/d
Outcomes	PI: 0-10 NRS Reduction in use of antiepileptics: 0 = no need for antiepileptics, 5 = 100% analgesic use at first assessment Adverse events
Notes	Peru. Sponsor: Grunenthal Laboratories, Peru
Risk of bias	

Arbaiza 2007 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants with similar pain syndromes were paired, then "randomly assigned using a computer program"
Allocation concealment (selection bias)	Unclear risk	Method not described, but effectively, the first of pair was randomised, leaving a possibility of unconcealed allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Treatments supplied in identical 10 ml bottles, "distinguished only by labels"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation not mentioned, approximately 30% withdrawals, with different reasons between groups
Size	High risk	< 50 participants per treatment arm (18)

Boureau 2003

Methods	Multicentre, randomised, double-blind, parallel-group, placebo-controlled Duration 6 weeks Assessments at 1, 8, 15, 22, 43 days
Participants	Postherpetic neuralgia ≥ 3 months and ≤ 1 year, PI ≥ 40/100, aged 18-85 years Exclusion: seizures; cerebral tumour or recent cranial trauma; severe hepatic, renal, cardiac, respiratory pathology; contraindication to tramadol or opioids; Hx depression, drug abuse N = 127 (125 in ITT population, 108 in PP) M 35, F 92 Mean age ~67 years (35-85) Mean baseline PI: 60/100
Interventions	Tramadol SR 100 mg taken in evening, n = 64 Placebo, n = 63 Dose could be increased to maximum 400 mg (≤ 75 years) or 300 mg (75+ years) taken as divided dose in morning and evening Rescue medication: paracetamol to maximum 3 g/d No MAO within 15 days, or antidepressants, anticonvulsants, opioid analgesics or local/general anaesthetics within 7 days
Outcomes	PI in last 24 h (daily): 100 mm VAS, 5-point VRS PGE: % reduction from baseline Use of rescue medication Adverse events
Notes	France. Sponsor: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Boureau 2003 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated 4-block centralised randomisation list
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"treatments were identical with regard to appearance"
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data on VAS and VRS over the 6th week were replaced by data available from the last 7 observations before the final visit (or the visit before premature discontinuation), not including more than 13 days before the end visit. Essentially an LOCF analysis
Size	Unclear risk	50-199 participants per treatment arm (63, 64)

Harati 1998

Methods	Multicenter, randomised, double-blind, placebo-controlled, parallel-group Duration: 6 weeks Assessed at 1, 14, 28, 42 days
Participants	Peripheral diabetic neuropathy (HbA1 < 14%), distal, symmetric, > 3 months, PI moderate without analgesics, aged 18 years and over Exclusion: contraindication or previous use of tramadol; cause other than diabetes; other pain > neuropathic pain; clinically significant medical conditions; use of multiple daily doses of opioids or regular mexiletine; amputations; open ulcers; Hx drug or alcohol abuse N = 131 (127 for efficacy) M 78, F 53 Mean age 57 years (32-85) Baseline pain 2.5 (scale 0-4)
Interventions	Tramadol starting at 50 mg/d, increasing to 200 mg/d on day 10, then increased again as required from day 14 to maximum 400 mg/d by day 28, then stable; minimum 100 mg/d from day 14 to end of study, n = 65 Placebo, n = 66 Divided doses, given 4 x daily Mean dose tramadol at end of study 210 ± 113 mg/day Tricyclics and antiepileptics discontinued ≥ 21 days; shorter acting analgesics discontinued ≥ 7 days before start Rescue medication: "No pain medications other than the study medications were permitted"
Outcomes	PI at end of study (5-point scale, 0-4) PR (6-point scale, -1 to 4) Adverse events
Notes	USA. Sponsor: Ortho-McNeil Pharmaceutical, Raritan, NJ (research grant)
Risk of bias	

Harati 1998 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer random-number generator
Allocation concealment (selection bias)	Low risk	Double-blind code numbers assigned sequentially
Blinding (performance bias and detection bias) All outcomes	Low risk	Identically appearing capsules, indistinguishable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation not mentioned, approximately 30% withdrawals, with different reasons between groups
Size	Unclear risk	50-199 participants per treatment arm (65, 66)

Norrbrink 2009

Methods	Randomised, double-blind, placebo-controlled, parallel-group Duration: 4 weeks Assessed at baseline and week 4 (daily pain diary)
Participants	Spinal cord injury ≥ 12 months, "at or below level of lesion neuropathic pain" ≥ 6 months, PI > 3 (Borg's Category Ratio), aged 18-70 years Exclusion: cognitive impairment; previous treatment with tramadol; intolerance to opioids in past Current use of opioids or antidepressants considered on individual basis N = 35 M 28, F 7 Mean age 51 years (SD 11) Mean 15 years post injury Some differences in baseline characteristics - level of injury, baseline PI Worst PI at baseline: 7-9/10, but general PI 4-7/10
Interventions	Tramadol 50 mg x 3 daily, n = 23 Placebo, n = 12 Dose increased every 5 days by 50 mg (1 tablet) to maximum of 400 mg/d (or 8 placebo tablets) until optimal pain relief or intolerable adverse events Stable pain medication allowed without change to dosage (20/35 took concomitant pain medication)
Outcomes	Daily PI: complete relief = 10 PGIC Adverse events
Notes	Sweden. Sponsor: not reported
Risk of bias	

Norrbrink 2009 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Low risk	"sealed coded envelopes" provided by third party
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical in appearance"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis with LOCF
Size	High risk	< 50 participants per treatment arm (12, 23)

Sindrup 1999

Methods	Randomised, double-blind, placebo-controlled, cross-over Duration: 2 x 4 weeks with washout of ≥ 1 week between periods Assessed at end of treatment periods
Participants	Polyneuropathy > 6 months, PI without treatment ≥ 4/10, aged 20-80 years Exclusion: pain from other causes; previous allergy to tramadol; intolerance to tramadol or other opioids; use of MAO inhibitors; epilepsy; severe terminal illness N = 45 (34 provided data for both periods) M 27, F 18 Median age 58 years (range 26-77) Median baseline PI: 6/10
Interventions	Tramadol SR, titrated to 100-200 mg twice daily over at least 1 week Placebo (22 participants took tramadol first, 23 placebo first) Rescue medication: up to 6 x paracetamol 500 mg/d Existing pain medication slowly discontinued over a maximum of 1 week
Outcomes	Daily PI: NRS 0-10 (also paraesthesia and touch-evoked pain) used to calculate median for each week Use of rescue medication Adverse events Preference at end of study
Notes	Denmark. Sponsor: Grunenthal GmbH

Risk of bias

Bias	Authors' judgement	Support for judgement

Sindrup 1999 *(Continued)*

Random sequence generation (selection bias)	Low risk	"computer generated randomisation code with a block size of six"
Allocation concealment (selection bias)	Low risk	"sealed envelopes", participants numbered consecutively and treated with drugs with corresponding randomisation number
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	High risk	LOCF imputation, efficacy data only for participants providing data for both phases; reasons for withdrawals per treatment arm not fully reported
Size	High risk	< 50 participants per treatment arm (≤ 43, 40)

Sindrup 2012

Methods	Multicentre, randomised, double-blind, active- and placebo-controlled, cross-over Duration: 3 x 4 weeks with washout of 1-2 weeks between periods Assessed weekly and at end of each treatment period
Participants	Polyneuropathy (distal, symmetric) > 6 months, PI ≥ 4/10, aged 18-74 years Exclusion: pain from other causes; psychiatric disease; raised creatinine or liver enzymes; chronic disease affecting drug absorption; HbA1c > 12%; QT interval > 500 ms; contraindication to opioids, tramadol, paracetamol; Hx drug or alcohol abuse; use of other analgesics or MAO inhibitors or non-pharmacological pain therapy N = 64 (48 completed) M 44, F 20 Mean age 58 years (38-75) Baseline PI: 6/10
Interventions	Tramadol SR 100 mg/d, increasing to 200-400 mg/d GRT9906 (experimental drug) 60 mg/d, increasing to 120-240 mg/d Placebo Dose increased over 1 week, then kept constant for remaining 3 weeks Most participants took maximum dose Rescue medication: paracetamol up to 6 x 500 mg/d
Outcomes	Daily PI: (NRS 0-10), then averaged over last 3 days of each period, and for each week ≥ 50% and ≥ 30% reduction in pain at end of each period PGIC (7-point scale; 1 = very much better) Use of rescue medication Adverse events
Notes	Denmark, Germany. Sponsor: Grunenthal GmbH
Risk of bias	

Sindrup 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"the randomization list was generated via computer"
Allocation concealment (selection bias)	Low risk	Each site given "a unique series of numbers which were assigned to each trial patient in ascending order and marked at the corresponding drug packages"
Blinding (performance bias and detection bias) All outcomes	Low risk	The three treatments "had identical appearance and weight and were dosed similarly"
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis used for PP analysis of dichotomous efficacy data.
Size	High risk	< 50 participants per treatment arm for efficacy data (maximum 56 for safety data)

F: female; HbA1c: glycosylated haemoglobin; Hx: history of; LOCF: last observation carried forward; M: male; MAO: monoamine oxidase; N: number of participants in study; n: number of participants in treatment arm; NRS: numerical rating scale; PGIC: Patient Global Impression of Change; PI: pain intensity; PP: per protocol; PR: pain relief; SD: standard deviation; SR: sustained-release; VAS: visual analogue scale; VRS: verbal rating scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ashry 2001	Commentary on Harati 1998
Attal 2001	Review article
Benedetti 1998	Investigates buprenorphine, not tramadol
Erdine 1997	Short conference abstract with inadequate method description and no usable data
Gobel 1995	Open-label study
Harati 1999	Correspondence with no new trial data
Harati 2000	Follow up to Harati 1998. Not randomised or controlled
Herrera Silva 2001	Review article
Leppert 2001	Open-label study
Moulin 1999	Correspondence with no new trial data
NCT00610155	7-day treatment periods, < 10 participants per treatment arm
Saxena 2013	Open-label cohort study
Xiao 2004	Observational study. Not a randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Ho 2009

Methods	Enriched enrolment, randomised withdrawal design. Single-blind run-in phases in which participants were treated with gabapentin then active placebo. Responders were randomised to a double-blind, 3-period cross-over of gabapentin, tramadol, and active placebo Participants with PI ≤ 7.5/10 at end of Period A could proceed to Period B Participants whose average pain scores at end of Period B were ≥ 3 and increased by ≥ 30% from Period A could proceed to randomisation and a double-blind cross-over phase Duration: Period A: 1 week; Period B: 2 weeks; double-blind: 3 x 2-week periods (1-week titration, 1-week stable), each followed by 1-week washout
Participants	Idiopathic small fibre neuropathy ≥ 2 months, self-reported gabapentin responders (on stable dose 900 - 4800 mg/d), PI > 3 to ≤ 7.5 on medication, aged ≥ 18 years Exclusion: allergies to any study drug; Hx fibromyalgia, epilepsy; cancer within 5 years; pernicious anaemia; HIV infection; multi-organ autoimmune disease; peripheral vascular disease; renal or hepatic disease; use of insulin or antiglycaemic drugs N = 59 entered run-in A, 48 entered run-in B M 21, F 20 Mean age 60 years N = 18 randomised M 10, F 8 Mean age 59 years Baseline PI: 4.9/10 Baseline PGIC 5.5 (after B)
Interventions	Period A: gabapentin at pre-study dose + matching active placebo (diphenhydramine). Pain scores ≤ 7.5/10 entered period B Period B: gabapentin at pre-study dose + matching active placebo (diphenhydramine) with tapering off gabapentin. Pain scores ≥ 3/10 and increasing by ≥ 30% entered treatment period Treatment period (2-week test and 1-week washout in multiple cross-overs): Tramadol 50 mg x 4 daily Gabapentin pre-study dose Placebo (diphenhydramine 50 mg at bedtime) Rescue medication: 325 mg tablets (probably paracetamol) - limit not specified If still inadequate, additional 400 mg gabapentin every 8 h, up to 1200 every 24 h
Outcomes	Daily PI: (NRS 0-10), averaged over 24 h. If rescue medication or additional gabapentin taken, used score before first rescue dose of the day PGIC (7-point scale; 1 = very much better) Adverse events
Notes	USA. Sponsor: Merck Research Laboratories

F: female; Hx: history of; M: male; N: number of participants in study; NRS: numerical rating scale; PGIC: Patient Global Impression of Change; PI: pain intensity.

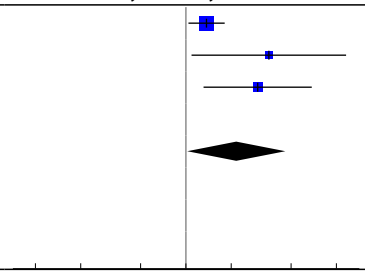
DATA AND ANALYSES

Comparison 1. Tramadol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with ≥ 50% pain intensity reduction	3	265	Risk Ratio (M-H, Random, 95% CI)	2.16 [1.02, 4.58]
2 Withdrawal due to adverse events	6	485	Risk Ratio (M-H, Fixed, 95% CI)	4.08 [1.99, 8.37]
3 All cause withdrawal	3	202	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.75, 1.76]
4 Participants with any adverse event	4	266	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.22, 2.13]
5 Participants with specific adverse events	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Nausea	6	508	Risk Ratio (M-H, Fixed, 95% CI)	3.62 [2.23, 5.88]
5.2 Constipation	5	381	Risk Ratio (M-H, Fixed, 95% CI)	4.11 [2.36, 7.16]
5.3 Tiredness/fatigue/somnolence	4	345	Risk Ratio (M-H, Fixed, 95% CI)	3.22 [1.93, 5.36]
5.4 Dizziness	3	214	Risk Ratio (M-H, Fixed, 95% CI)	3.72 [1.94, 7.12]
5.5 Dry mouth	3	214	Risk Ratio (M-H, Fixed, 95% CI)	2.44 [1.35, 4.42]

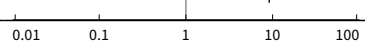
Analysis 1.1. Comparison 1 Tramadol versus placebo, Outcome 1 Participants with ≥ 50% pain intensity reduction.

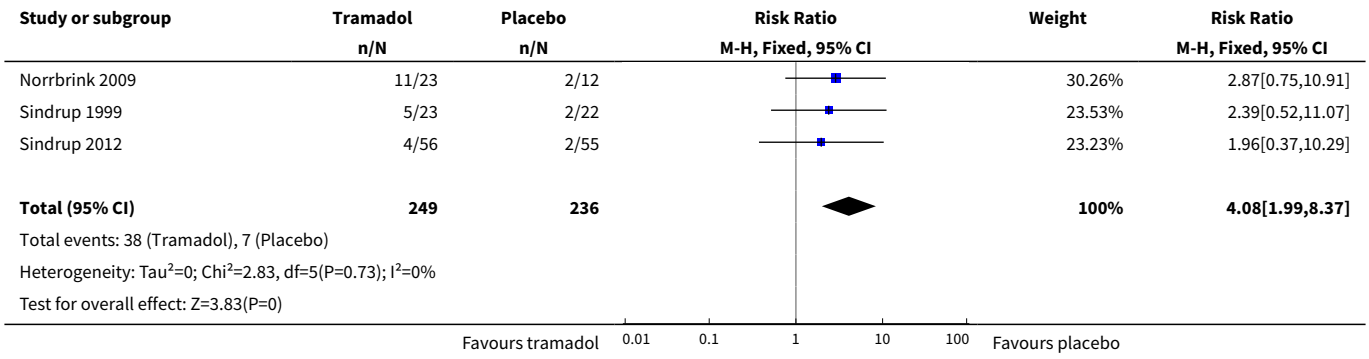
Study or subgroup	Tramadol n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Boureau 2003	41/53	31/55		46.71%	1.37[1.04,1.81]
Sindrup 1999	11/34	3/33		22.24%	3.56[1.09,11.62]
Sindrup 2012	18/45	6/45		31.05%	3[1.31,6.86]
Total (95% CI)	**132**	**133**		**100%**	**2.16[1.02,4.58]**
Total events: 70 (Tramadol), 40 (Placebo)					
Heterogeneity: Tau^2=0.29; Chi^2=6.38, df=2(P=0.04); I^2=68.65%					
Test for overall effect: Z=2.02(P=0.04)					



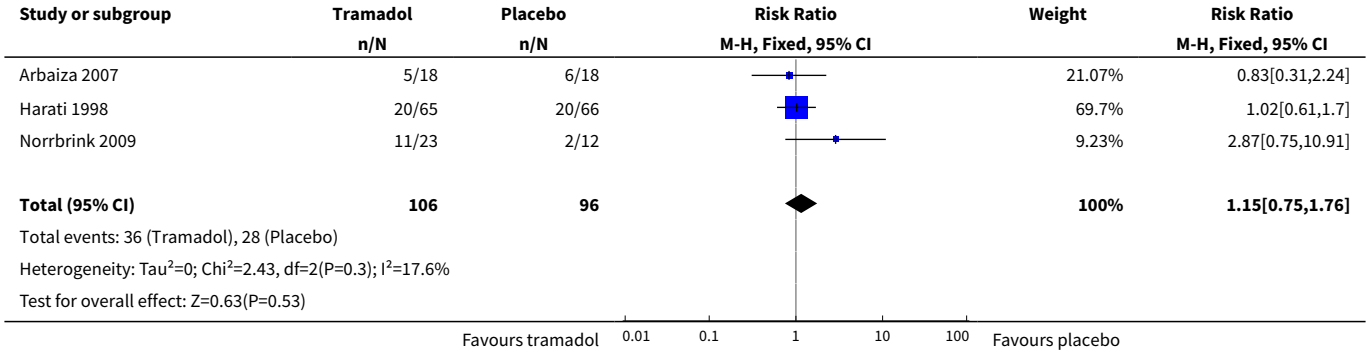
Analysis 1.2. Comparison 1 Tramadol versus placebo, Outcome 2 Withdrawal due to adverse events.

Study or subgroup	Tramadol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Arbaiza 2007	3/18	0/18		5.76%	7[0.39,126.48]
Boureau 2003	6/64	0/63		5.8%	12.8[0.74,222.54]
Harati 1998	9/65	1/66		11.42%	9.14[1.19,70.1]

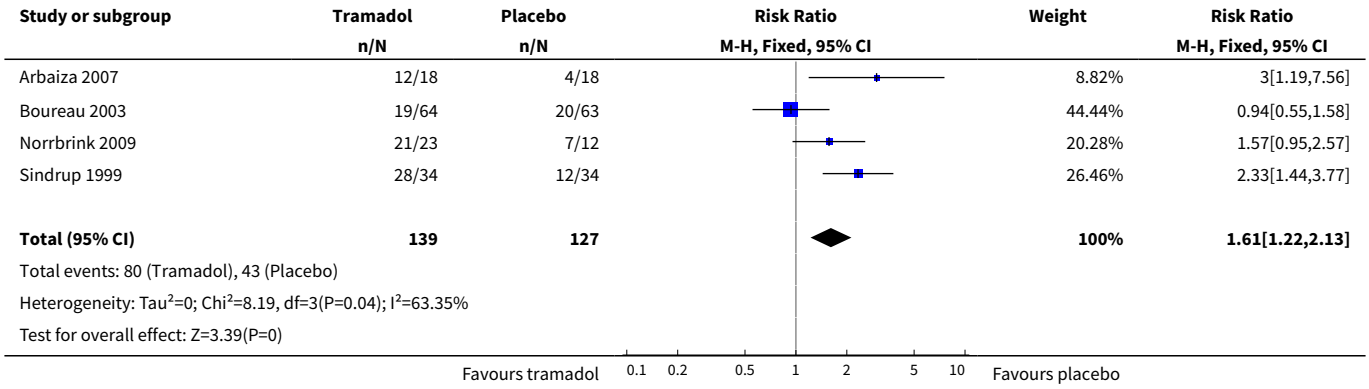




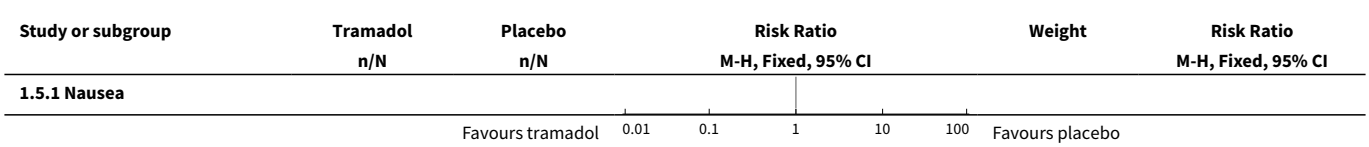
Analysis 1.3. Comparison 1 Tramadol versus placebo, Outcome 3 All cause withdrawal.

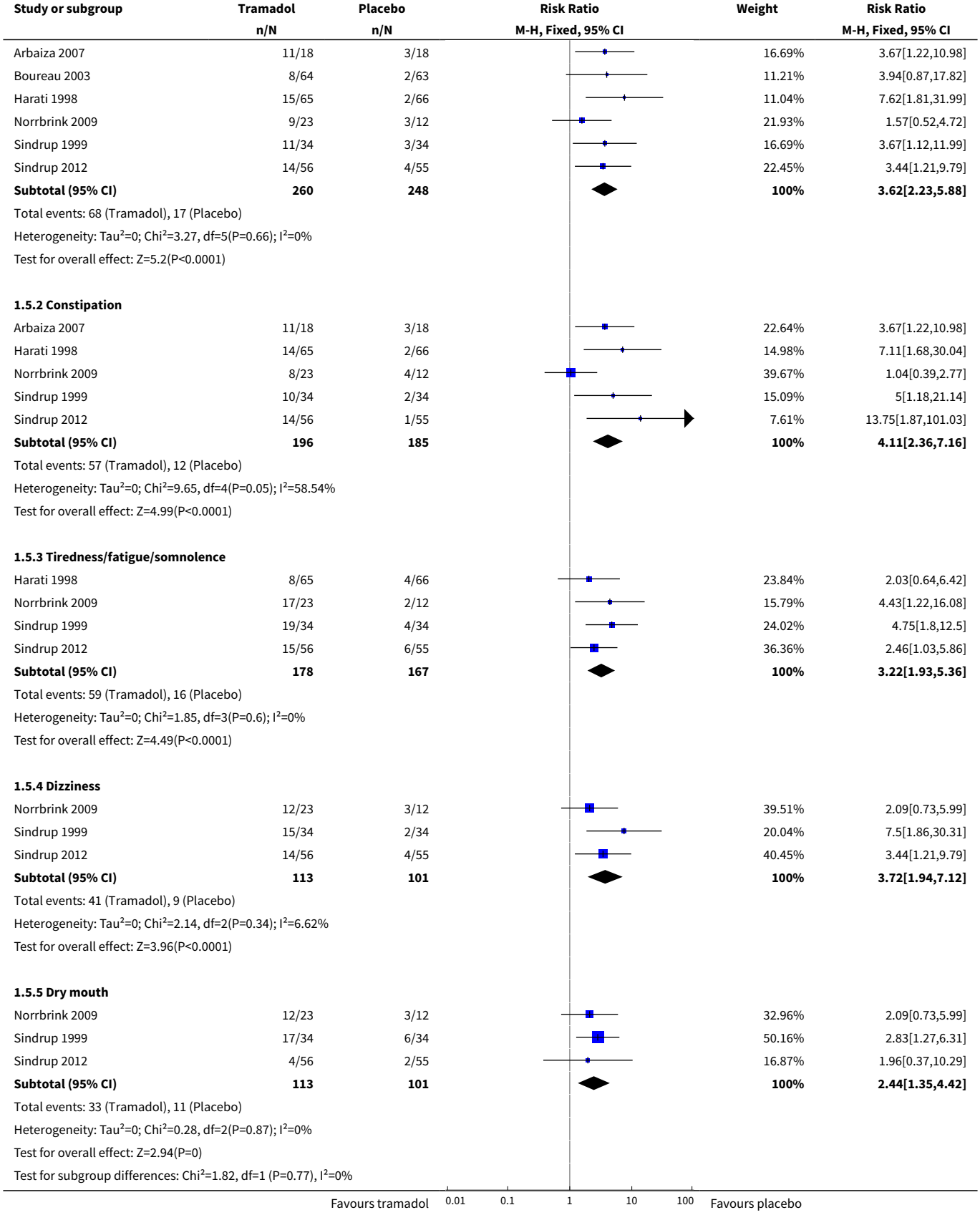


Analysis 1.4. Comparison 1 Tramadol versus placebo, Outcome 4 Participants with any adverse event.



Analysis 1.5. Comparison 1 Tramadol versus placebo, Outcome 5 Participants with specific adverse events.





Study or subgroup	Tramadol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Arbaiza 2007	11/18	3/18		16.69%	3.67[1.22,10.98]
Boureau 2003	8/64	2/63		11.21%	3.94[0.87,17.82]
Harati 1998	15/65	2/66		11.04%	7.62[1.81,31.99]
Norrbrink 2009	9/23	3/12		21.93%	1.57[0.52,4.72]
Sindrup 1999	11/34	3/34		16.69%	3.67[1.12,11.99]
Sindrup 2012	14/56	4/55		22.45%	3.44[1.21,9.79]
Subtotal (95% CI)	**260**	**248**		**100%**	**3.62[2.23,5.88]**
Total events: 68 (Tramadol), 17 (Placebo)					
Heterogeneity: Tau²=0; Chi²=3.27, df=5(P=0.66); I²=0%					
Test for overall effect: Z=5.2(P<0.0001)					
1.5.2 Constipation					
Arbaiza 2007	11/18	3/18		22.64%	3.67[1.22,10.98]
Harati 1998	14/65	2/66		14.98%	7.11[1.68,30.04]
Norrbrink 2009	8/23	4/12		39.67%	1.04[0.39,2.77]
Sindrup 1999	10/34	2/34		15.09%	5[1.18,21.14]
Sindrup 2012	14/56	1/55		7.61%	13.75[1.87,101.03]
Subtotal (95% CI)	**196**	**185**		**100%**	**4.11[2.36,7.16]**
Total events: 57 (Tramadol), 12 (Placebo)					
Heterogeneity: Tau²=0; Chi²=9.65, df=4(P=0.05); I²=58.54%					
Test for overall effect: Z=4.99(P<0.0001)					
1.5.3 Tiredness/fatigue/somnolence					
Harati 1998	8/65	4/66		23.84%	2.03[0.64,6.42]
Norrbrink 2009	17/23	2/12		15.79%	4.43[1.22,16.08]
Sindrup 1999	19/34	4/34		24.02%	4.75[1.8,12.5]
Sindrup 2012	15/56	6/55		36.36%	2.46[1.03,5.86]
Subtotal (95% CI)	**178**	**167**		**100%**	**3.22[1.93,5.36]**
Total events: 59 (Tramadol), 16 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.85, df=3(P=0.6); I²=0%					
Test for overall effect: Z=4.49(P<0.0001)					
1.5.4 Dizziness					
Norrbrink 2009	12/23	3/12		39.51%	2.09[0.73,5.99]
Sindrup 1999	15/34	2/34		20.04%	7.5[1.86,30.31]
Sindrup 2012	14/56	4/55		40.45%	3.44[1.21,9.79]
Subtotal (95% CI)	**113**	**101**		**100%**	**3.72[1.94,7.12]**
Total events: 41 (Tramadol), 9 (Placebo)					
Heterogeneity: Tau²=0; Chi²=2.14, df=2(P=0.34); I²=6.62%					
Test for overall effect: Z=3.96(P<0.0001)					
1.5.5 Dry mouth					
Norrbrink 2009	12/23	3/12		32.96%	2.09[0.73,5.99]
Sindrup 1999	17/34	6/34		50.16%	2.83[1.27,6.31]
Sindrup 2012	4/56	2/55		16.87%	1.96[0.37,10.29]
Subtotal (95% CI)	**113**	**101**		**100%**	**2.44[1.35,4.42]**
Total events: 33 (Tramadol), 11 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.28, df=2(P=0.87); I²=0%					
Test for overall effect: Z=2.94(P=0)					
Test for subgroup differences: Chi²=1.82, df=1 (P=0.77), I²=0%					

APPENDICES

Appendix 1. Methodological considerations for chronic pain

There have been several recent changes in how the efficacy of conventional and unconventional treatments is assessed in chronic painful conditions. The outcomes are now better defined, particularly with new criteria for what constitutes moderate or substantial benefit (Dworkin 2008); older trials may only report participants with 'any improvement'. Newer trials tend to be larger, avoiding problems from the random play of chance. Newer trials also tend to be of longer duration, up to 12 weeks, and longer trials provide a more rigorous and valid assessment of efficacy in chronic conditions. New standards have evolved for assessing efficacy in neuropathic pain, and we are now applying stricter criteria for the inclusion of trials and assessment of outcomes, and are more aware of problems that may affect our overall assessment. To summarise some of the recent insights that must be considered in this new review:

1. Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution. This is true in acute pain (Moore 2011a; Moore 2011b), back pain (Moore 2010c), and arthritis (Moore 2010d), as well as in fibromyalgia (Straube 2010); in all cases average results usually describe the experience of almost no-one in the trial. Data expressed as averages are potentially misleading, unless they can be proven to be suitable.
2. As a consequence, we have to depend on dichotomous results (the individual either has or does not have the outcome) usually from pain changes or patient global assessments. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has helped with their definitions of minimal, moderate, and substantial improvement (Dworkin 2008). In arthritis, trials of less than 12 weeks' duration, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010c); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.
3. The proportion of patients with at least moderate benefit can be small, even with an effective medicine, falling from 60% with an effective medicine in arthritis to 30% in fibromyalgia (Moore 2009; Moore 2010c; Moore 2010d; Moore 2013b; Moore 2014b; Straube 2008; Sultan 2008). A Cochrane Review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so.
4. Individual patient analyses indicate that patients who get good pain relief (moderate or better) have major benefits in many other outcomes, affecting quality of life in a significant way (Moore 2010b; Moore 2014a).
5. Imputation methods such as last observation carried forward (LOCF), used when participants withdraw from clinical trials, can overstate drug efficacy especially when adverse event withdrawals with drug are greater than those with placebo (Moore 2012).

Appendix 2. CENTRAL search strategy (via CRSO)

1. MESH DESCRIPTOR Tramadol (757)
2. (tramadol* or tramal* or ultram or zamadol or zydol):TI,AB,KY (2227)
3. 1 OR 2 (2227)
4. MESH DESCRIPTOR Neuralgia EXPLODE ALL TREES (718)
5. MESH DESCRIPTOR Peripheral Nervous System Diseases EXPLODE ALL TREES (2963)
6. MESH DESCRIPTOR Somatosensory Disorders EXPLODE ALL TREES (796)
7. ((pain* or discomfort*) adj10 (central or complex or nerv* or neuralg* or neuropath*)):TI,AB,KY (3875)
8. ((neur* or nerv*) adj6 (compress* or damag*)):TI,AB,KY (721)
9. 4 OR 5 OR 6 OR 7 OR 8 (7310)
10. 3 AND 9 (151)

Appendix 3. MEDLINE search strategy (via Ovid)

1. Tramadol/ (2637)
2. (tramadol* or tramal* or ultram or zamadol or zydol).mp. (3719)
3. 1 or 2 (3719)
4. exp NEURALGIA/ (17673)
5. exp PERIPHERAL NERVOUS SYSTEM DISEASES/ (137699)
6. exp SOMATOSENSORY DISORDERS/ (20383)
7. ((pain* or discomfort*) adj10 (central or complex or nerv* or neuralg* or neuropath*)).mp. (49191)
8. ((neur* or nerv*) adj6 (compress* or damag*)).mp. (57636)
9. 4 or 5 or 6 or 7 or 8 (222483)
10. randomized controlled trial.pt. (469510)

11.randomized.ab. (359272)
12.placebo.ab. (177279)
13.drug therapy.fs. (2035842)
14.randomly.ab. (250055)
15.trial.ab. (379955)
16.groups.ab. (1554754)
17.10 or 11 or 12 or 13 or 14 or 15 or 16 (3875115)
18.3 and 9 and 17 (388)

Appendix 4. Embase search strategy (via Ovid)

1. Tramadol/ (16416)
2. (tramadol* or tramal* or ultram or zamadol or zydol).mp. (16918)
3. 1 or 2 (16918)
4. exp neuropathy/ (465954)
5. exp peripheral neuropathy/ (61799)
6. postherpetic neuralgia/ or neuralgia/ or trigeminus neuralgia/ (20978)
7. exp somatosensory disorder/ (82589)
8. ((pain* or discomfort*) adj10 (central or complex or nerv* or neuralg* or neuropath*)).mp. (93462)
9. ((neur* or nerv*) adj6 (compress* or damag*)).mp. (80148)
10.4 or 5 or 6 or 7 or 8 or 9 (327771)
11.random*.ti,ab. (1153236)
12.factorial*.ti,ab. (29202)
13.(crossover* or cross over* or cross-over*).ti,ab. (85870)
14.placebo*.ti,ab. (249172)
15.(doubl* adj blind*).ti,ab. (175156)
16.assign*.ti,ab. (302886)
17.allocat*.ti,ab. (111144)
18.Randomized Controlled Trial/ (463655)
19.Double-blind procedure/ (138148)
20.Crossover Procedure/ (53925)
21.11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (1623468)
22.3 and 10 and 21 (737)

Appendix 5. Clinical trials registers search strategy

Conditions: neuropathic pain OR neuralgia OR neuropathy OR phantom OR stump

Intervention: tramadol

Limits: Adult and Senior

ClinicalTrials.gov identified 8 studies.

apps.who.int/trialsearch/ identified 3 studies.

Appendix 6. GRADE: criteria for assigning grade of evidence

The GRADE system uses the following criteria for assigning a quality level to a body of evidence (Chapter 12, Schünemann 2011a).

- **High**: randomised trials; or double-upgraded observational studies
- **Moderate**: downgraded randomised trials; or upgraded observational studies
- **Low**: double-downgraded randomised trials; or observational studies
- **Very low**: triple-downgraded randomised trials; or downgraded observational studies; or case series/case reports

Factors that may decrease the quality level of a body of evidence are:

- limitations in the design and implementation of available studies suggesting high likelihood of bias;
- indirectness of evidence (indirect population, intervention, control, outcomes);

- unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses);
- imprecision of results (wide confidence intervals).
- high probability of publication bias.

Factors that may increase the quality level of a body of evidence are:

- large magnitude of effect;
- all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results show no effect;
- dose-response gradient.

Appendix 7. Summary of outcomes in individual studies: efficacy

Study	Treatment	Pain outcome	Other efficacy outcome
Arbaiza 2007 Peru	Tramadol 1 mg/kg bodyweight every 6 h; increased to 1.5 mg/kg every 6 h if relief inadequate, n = 18 Placebo, n = 18	Mean PI at 45 days: Tramadol 2.9 Placebo 4.3 % reduction: Tramadol 57% Placebo 39%	Use of antiepileptic drugs reduced in tramadol group, but not in placebo group Significant improvements with tramadol versus placebo for Karnofsky score, ADL, sleep, but not appetite, anxiety, depression
Boureau 2003 France	Tramadol SR 100 mg taken in evening, n = 64 Placebo, n = 63 Dose could be increased to max 400 mg (≤ 75 years) or 300 mg (75+ years) taken as divided dose in morning and evening	≥ 50% PIR (PP population, LOCF) Tramadol 77.3% = 41/53 Placebo 56.3% = 31/55	Mean PI on day 43 (ITT population, similar for PP population): Tramadol 25/100 Placebo 34/100 QoL improved for both groups, but no significant difference
Harati 1998 USA	Tramadol 100 mg to 200 mg daily, titrated from 50 mg daily over maximum 28 days, n = 65 Placebo, n = 66	Mean (SD) PR at end of study (scale -1 to 4): Tramadol 2.1 (± 0.2) Placebo 0.9 (± 0.2) Mean PI at end of study (scale 0 to 4): Tramadol 1.4 (± 0.1) Placebo 2.2 (± 0.1)	Subset of participants with severe/extreme pain after washout: "Improved" (not defined) at final visit Tramadol 25/28 Placebo 12/33
Norrbrink 2009 Sweden	Tramadol 150 mg to 400 mg daily, n = 23 Placebo, n = 12	PGIC "much improved or very much improved" Tramadol 4/23 Placebo 0/12 (No participants had very much improved; 3 tramadol and 1 placebo had minimally improved)	Proportion of participants reporting decreased pain intensity larger with tramadol than placebo
Sindrup 1999 Denmark	Tramadol SR 200 mg to 400 mg daily, titrated over at least one week Placebo N = 45 (34 in both periods of cross-over)	≥ 50% PIR (participants in both periods) Tramadol 11/34 Placebo 3/33 ≥ 30% PIR (participants in both periods) Tramadol 13/34	PI reduced from ≥ 3/10 to < 3/10 by 4th week: Tramadol 6/34 Placebo 2/34 (both these participants had same response with tramadol)

(Continued)

		Placebo 4/33	
Sindrup 2012 Denmark, Germany	Tramadol SR 200 mg to 400 mg daily, titrated over one week GRT9906 120 mg to 240 mg daily, titrated over one week Placebo N = 64 (48 completed cross-over)	PP (completer) population ≥ 50% PIR: Tramadol 18/45 GRT9906 18/45 Placebo 6/45 ≥ 30% PIR: Tramadol 32/45 GRT9906 25/45 Placebo 11/45 PGIC - mean score at end of study: Tramadol 2.4 (SD 1.1) GRT9906 2.4 (SD 1.1) Placebo 3.8 (SD 1.6)	Full analysis set Mean change from baseline: Tramadol -2.4 (SD 2.1) GRT9906 -2.3 (SD 2.0) Placebo -0.7 (SD 1.8)

ADL: activities of daily living; h: hour; ITT: intention to treat; LOCF: last observation carried forward; N: number of participants in study; n: number of participants in treatment arm; PGIC: Patient Global Impression of Change; PI: pain intensity; PIR: pain intensity reduction; PP: per protocol; SD: standard deviation; SR: sustained release.

Appendix 8. Summary of outcomes in individual studies: adverse events, withdrawals

Study	Treatment	Adverse events	Specific adverse events	Withdrawals
Arbaiza 2007 Peru	Tramadol 1 mg/kg bodyweight every 6 h. Increased to 1.5 mg/kg every 6 h if relief inadequate, n = 18 Placebo, n = 18	Any AE: Tramadol 12/18 Placebo 4/18 No SAE reported	Events with tramadol: nausea, somnolence, constipation, dry mouth, general malaise, dizziness, tiredness, sweaty hands Most common: Nausea and constipation Tramadol 11/18 Placebo 3/18 Vomiting Tramadol 7/18 Placebo 1/18	All cause: Tramadol 5/18 Placebo 6/18 LoE: Tramadol 2/18 Placebo 6/18 AE: Tramadol 3/18 Placebo 0/18
Boureau 2003 France	Tramadol SR 100 mg taken in evening, n = 64 Placebo, n = 63 Dose could be increased to max 400 mg (≤ 75 years) or 300 mg (75+ years) taken as divided dose in morning and evening	Any AE: Tramadol 19/64 Placebo 20/63 Mostly mild in placebo group, moderate in tramadol group SAE: 3 participants had SAE - unclear which group, but probably tramadol (1 participant on tramadol had two SAE, both	Tramadol: mostly digestive system (11), body as a whole (6), nervous system (6) Placebo: mostly digestive system (5), body as a whole (6), nervous system (5), respiratory system (5) Nausea: Tramadol 12.5% = 8/64 Placebo 3.2% = 2/63	AE: Tramadol 6/64 (5 nausea) Placebo 0/63 All cause: Tramadol 11/64 Placebo 5/63 (Note: denominators uncertain)

(Continued)

		judged unrelated to treatment)		
Harati 1998 USA	Tramadol 100 mg to 200 mg daily, titrated from 50 mg daily over maximum 28 days, n = 65 Placebo, n = 66	Participants with any AE not reported No SAE reported	AEs occurring in ≥ 5% reported Nausea: Tramadol 15/65 Placebo 2/66 Constipation: Tramadol 14/65 Placebo 2/66 Headache: Tramadol 11/65 Placebo 3/66 Somnolence: Tramadol 8/65 Placebo 4/66 Dyspepsia: Tramadol 6/65 Placebo 2/66 'Flu symptoms: Tramadol 4/65 Placebo 6/66 Rhinitis: Tramadol 3/65 Placebo 5/66 Diarrhoea: Tramadol 2/65 Placebo 5/66 Pruritus, rash, fatigue, dizziness, vomiting each reported by 3 or 4 participants in tramadol group	All cause: Tramadol 20/65 Placebo 25/66 LoE: Tramadol 9/65 Placebo 22/66 AE: Tramadol 9/65 (mostly nausea and dyspepsia) Placebo 1/66
Norrbrink 2009 Sweden	Tramadol 150 mg to 400 mg daily, n = 23 Placebo, n = 12	Any AE: Tramadol 21/23 Placebo 7/12 More moderate or severe with tramadol No SAE reported	Tiredness: Tramadol 17/23 Placebo 2/12 Dry mouth: Tramadol 12/23 Placebo 3/12 Dizziness: Tramadol 12/23 Placebo 3/12 Sweating: Tramadol 9/23 Placebo 3/12 Constipation: Tramadol 8/23 Placebo 4/12 Nausea: Tramadol 9/23 Placebo 3/12 Voiding dysfunction: Tramadol 1/23 Placebo 0/12	All cause: Tramadol 11/23 Placebo 2/12 All AE, 1 judged unrelated to drug
Sindrup 1999 Denmark	Tramadol SR 200 mg to 400 mg daily, titrated	Any AE: Tramadol 28/34 Placebo 12/34	Tiredness: Tramadol 19/34 Placebo 4/34 Dizziness:	All cause (both periods): Tramadol 8/43 Placebo 3/40

(Continued)

	over at least one week Placebo N = 45 (34 in both periods of cross-over)	No SAE reported	Tramadol 15/34 Placebo 2/34 Dry mouth: Tramadol 17/34 Placebo 6/34 Sweating: Tramadol 14/34 Placebo 6/34 Constipation: Tramadol 10/34 Placebo 2/34 Micturation problems: Tramadol 6/34 Placebo 1/34 Nausea: Tramadol 11/34 Placebo 3/34 Tramadol AEs mild or moderate Placebo AEs mainly mild	(Does not appear to include 4 participants who provided data for analyses but did not complete - 2 for LoE, 2 logistic problems) LoE: 2 participants in second period - group unclear AE: Tramadol 5/23 (first period), 2/20 (second period) Placebo 2/22 (first period)
Sindrup 2012 Denmark, Germany	Tramadol SR 200 mg to 400 mg daily, titrated over one week GRT9906 120 mg to 240 mg daily, titrated over one week Placebo N = 64 (48 completed cross-over)	Any AE not reported SAE: Tramadol 1/56 (vertigo) GRT9906 1/58 Placebo 0/55	Nausea: Tramadol 14/56 Placebo 4/55 Constipation: Tramadol 14/56 Placebo 1/55 Dry mouth: Tramadol 4/56 Placebo 2/55 Vomiting: Tramadol 6/56 Placebo 0/55 Diarrhoea: Tramadol 3/56 Placebo 4/55 Fatigue: Tramadol 15/56 Placebo 6/55 Drug withdrawal syndrome: Tramadol 5/56 Placebo 0/55 Dizziness: Tramadol 14/56 Placebo 4/55 Headache: Tramadol 7/56 Placebo 3/55 Sleep disorder: Tramadol 14/56 Placebo 3/55	All cause: 16 - not reported per treatment group AE: Tramadol 4/56 GRT9906 4/58 Placebo 2/55 LoE: Tramadol 0/56 GRT9906 1/58 Placebo 0/55 Participant withdrew consent: Tramadol 5/56 GRT9906 3/58 Placebo 0/55 Protocol violation: Tramadol 0/56 GRT9906 2/58 Placebo 1/55 Note participants could terminate for more than one reason, so unclear how many withdrew in each phase

AE: adverse event; hour: h; LoE: lack of efficacy; N: number of participants in study; n: number of participants in treatment arm; SAE: serious adverse event; SR: sustained release.

WHAT'S NEW

Date	Event	Description
10 January 2017	New citation required and conclusions have changed	Using stricter criteria for inclusion of studies and patient-centred outcomes we are more uncertain about the size of any effect of tramadol for neuropathic pain
9 January 2017	New search has been performed	New searches and revised selection criteria, limiting the review to randomised, double-blind studies only. Four studies from original review and two new studies included in update. Additional risk of bias assessments and evaluation of evidence using GRADE.

HISTORY

Protocol first published: Issue 3, 2002
Review first published: Issue 2, 2004

Date	Event	Description
17 November 2008	New search has been performed	Searches were run in 2008. One new randomised controlled trial was identified.
9 September 2008	Amended	Converted to new review format.
14 March 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

For this update, the background and methods were revised by SD, PW, and RAM, based on a template for reviews of drugs for neuropathic pain.

SD, PW, and RAM ran searches and selected studies for inclusion. SD and RAM carried out data extraction, and SD and PW assessed the risk of bias. SD and RAM carried out analyses. All authors were involved in writing the full review.

In the original review, the background was written by RMD and reviewed by J Hollingshead. The description of studies and results were written by J Hollingshead and RMD and reviewed by D Cornblath. The objectives, study criteria, search strategy, and discussion were written jointly by J Hollinghsead and RMD. The entire review was reviewed by D Cornblath.

DECLARATIONS OF INTEREST

RMD: none known

SD: none known

PW: none known

RFB: none known. RFB is a retired specialist pain physician who has managed patients with neuropathic pain.

DA: is a specialist pain physician and manages patients with neuropathic pain. He has received lecture fees from Grünenthal (2014, 2015) and Pfizer (2016).

RAM: RAM has received grant support from Grünenthal relating to individual patient-level analyses of trial data regarding tapentadol in osteoarthritis and back pain (2015). He has received honoraria for attending boards with Menarini concerning methods of analgesic trial design (2014), with Novartis (2014) about the design of network meta-analyses, and RB on understanding pharmacokinetics of drug uptake

(2015). He has received honoraria from Omega Pharma (2016) and Futura Pharma (2016) for providing advice on trial and data analysis methods.

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Internal sources

- Oxford Pain Relief Trust, UK.

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  NIHR Cochrane Programme Grant: 13/89/29 - Addressing the unmet need of chronic pain: providing the evidence for treatments of pain

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The background and methods sections have been updated in line with the current template. The title is changed to emphasise that the review concerns adults only, in line with other, similar, reviews.

We are no longer including quasi-randomised studies, or studies that were not double-blind, or comparisons with no treatment (because studies cannot be blinded). We limited the review to adults only. The primary outcome is now substantial or moderate pain relief (50% or more, or 30% or more, or equivalent measures using Patient Global Impression of Change scale).

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics, Opioid [adverse effects] [*therapeutic use]; Neuralgia [*drug therapy] [etiology]; Randomized Controlled Trials as Topic; Tramadol [adverse effects] [*therapeutic use]

MeSH check words

Adult; Aged; Humans; Middle Aged