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Combination pharmacotherapy for the treatment of neuropathic pain in adults (Review)

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[Intervention Review]

Combination pharmacotherapy for the treatment of neuropathic pain in adults

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A B S T R A C T

Background

Pharmacotherapy remains an important modality for the treatment of neuropathic pain. However, as monotherapy current drugs are associated with limited efficacy and dose-related side effects. Combining two or more different drugs may improve analgesic efficacy and, in some situations, reduce overall side effects (e.g. if synergistic interactions allow for dose reductions of combined drugs).

Objectives

This review evaluated the efficacy, tolerability and safety of various drug combinations for the treatment of neuropathic pain.

Search methods

We identified randomised controlled trials (RCTs) of various drug combinations for neuropathic pain from CENTRAL, MEDLINE, EMBASE and handsearches of other reviews and trial registries. The most recent search was performed on 9 April 2012.

Selection criteria

Double-blind, randomised studies comparing combinations of two or more drugs (systemic or topical) to placebo and/or at least one other comparator for the treatment of neuropathic pain.

Data collection and analysis

Data extracted from each study included: proportion of participants a) reporting ≥ 30% pain reduction from baseline OR ≥ moderate pain relief OR ≥ moderate global improvement; b) dropping out of the trial due to treatment-emergent adverse effects; c) reporting each specific adverse effect (e.g. sedation, dizziness) of ≥ moderate severity. The primary comparison of interest was between study drug(s) and one or both single-agent comparators. We combined studies if they evaluated the same drug class combination at roughly similar doses and durations of treatment. We used RevMan 5 to analyse data for binary outcomes.

Main results

We identified 21 eligible studies: four (578 participants) evaluated the combination of an opioid with gabapentin or pregabalin; two (77 participants) evaluated an opioid with a tricyclic antidepressant; one (56 participants) of gabapentin and nortriptyline; one (120 participants) of gabapentin and alpha-lipoic acid, three (90 participants) of fluphenazine with a tricyclic antidepressant; three (90 participants) of an N-methyl-D-aspartate (NMDA) blocker with an agent from a different drug class; five (604 participants) of various topical medications; one (313 participants) of tramadol with acetaminophen; and another one (44 participants) of a cholecystokinin blocker (L-365,260) with morphine. The majority of combinations evaluated to date involve drugs, each of which share some element of central nervous system (CNS) depression (e.g. sedation, cognitive dysfunction). This aspect of side effect overlap between the combined

agents was often reflected in similar or higher dropout rates for the combination and may thus substantially limit the utility of such drug combinations. Meta-analysis was possible for only one comparison of only one combination, i.e. gabapentin + opioid versus gabapentin alone. This meta-analysis involving 386 participants from two studies demonstrated modest, yet statistically significant, superiority of a gabapentin + opioid combination over gabapentin alone. However, this combination also produced significantly more frequent side effect-related trial dropouts compared to gabapentin alone.

Authors' conclusions

Multiple, good-quality studies demonstrate superior efficacy of two-drug combinations. However, the number of available studies for any one specific combination, as well as other study factors (e.g. limited trial size and duration), preclude the recommendation of any one specific drug combination for neuropathic pain. Demonstration of combination benefits by several studies together with reports of widespread clinical polypharmacy for neuropathic pain surely provide a rationale for additional future rigorous evaluations. In order to properly identify specific drug combinations which provide superior efficacy and/or safety, we recommend that future neuropathic pain studies of two-drug combinations include comparisons with placebo and both single-agent components. Given the apparent adverse impact of combining agents with similar adverse effect profiles (e.g. CNS depression), the anticipated development and availability of non-sedating neuropathic pain agents could lead to the identification of more favourable analgesic drug combinations in which side effects are not compounded.

P L A I N   L A N G U A G E   S U M M A R Y

Drug combinations for chronic neuropathic pain in adults

Neuropathic pain – due to nerve disease or damage – is often treated by pain medications which have limited effect and/or dose-related side effects when given alone. Combinations of more than one drug are often used with the goal of achieving better pain relief or fewer side effects (if the pain relieving effects of the combined drugs are more additive than the side effects), or both. Despite evidence that over 45% of individuals suffering from neuropathic pain take two or more drugs for their pain, we could find only 21 high-quality studies of various different systemic and topical drug combinations. Given the wide possible variety of different drug combinations and the small number of studies, results for neuropathic pain from this review are insufficient to suggest the value of any one specific drug combination. However, the publication of multiple high-quality studies suggesting the superiority of some drug combinations, together with evidence that drug combinations are widely used in clinical practice, underline the importance of conducting more combination studies with improved methodology.

B A C K G R O U N D

Description of the condition

Neuropathic pain has recently been redefined by the International Association for the Study of Pain (IASP) as "pain caused by a lesion or disease of the somatosensory system" (Jensen 2011) and comprises a wide variety of different central (e.g. post-stroke thalamic pain, spinal cord injury pain) and peripheral (e.g. diabetic neuropathy, postherpetic neuralgia) disorders. Depending on estimation methods, recent reports on the prevalence of neuropathic pain have varied from 5% (Bouhassira 2008) to 8% (Torrance 2006).

Description of the intervention

In addition to a wide variety of non-pharmacological approaches and interventional techniques for the treatment of neuropathic pain, pharmacological therapy remains an important component of neuropathic pain management (Gilron 2006). To address limitations in the efficacy and tolerability of neuropathic pain drugs as monotherapies clinicians often resort to concurrent administration of more than one pharmacological agent, i.e. 'polypharmacy' or 'combination pharmacotherapy'. In acute pain and migraine, combinations of analgesics used simultaneously provide additive pain relief (Moore 2012a), and combination analgesics are among the most effective drugs in acute pain (Moore 2011).

How the intervention might work

Evidence suggests that, even among individuals with seemingly singular neuropathic conditions (e.g. postherpetic neuralgia), substantial diversity exists with respect to various clinical manifestations, sensory examination features and presumably underlying pain mechanisms (e.g. see Baron 2009a; Maier 2010). This mechanistic diversity may be one reason for limited analgesic efficacy of pharmacologic agents as monotherapy, i.e. incomplete suppression of multiple nociceptive mechanisms. Also, dose-related drug side effects (e.g. somnolence, dizziness) may limit the tolerability of higher, more efficacious doses of analgesic drugs. Thus, combining drugs with different pharmacological mechanisms may result in greater efficacy by simultaneously suppressing multiple pain mechanisms (Gilron 2005a). Furthermore, the potential for favourable additive or synergistic interactions between different analgesics may allow for lower doses of individual drugs which may provide a better safety/tolerability profile (as long as there is no additivity or synergy for adverse effects). It must be emphasised that, in most situations, a clinically useful two-drug (A + B) combination should be superior to either drug alone (i.e. A + B > A and A + B > B) and should contain agents both of which are efficacious on their own (i.e. A > placebo and B > placebo). Furthermore, if both drugs share common adverse effects (e.g. sedation), what is necessary for a drug combination to be useful is that pain-relieving effects are more additive than are adverse effects, i.e. synergy for pain reduction is not absolutely necessary (Gilron 2005a). Combination pharmacotherapy in acute pain results in an additive, not synergistic, effect (Moore 2012a); there was no evidence for synergy, if defined as interaction or co-operation of two or more drugs to produce a combined effect greater than the sum of their separate effects.

Why it is important to do this review

Identification of favourable analgesic combinations will promote their more widespread use with the end result of improving population effectiveness of neuropathic pain pharmacotherapy. Identification of analgesic combinations associated with an unfavourable therapeutic ratio (i.e. balance between analgesia and side effects) will discourage their subsequent use and ultimately reduce the population toxicity, and improve the cost-effectiveness of neuropathic pain pharmacotherapy. Finally, given these important objectives of analgesic combination trials, detailed review and consideration of methodology of combination trials conducted to date will serve to guide future improvements in the continued evaluation of promising analgesic combinations.

O B J E C T I V E S

The objectives of this review were to evaluate the efficacy (primary), tolerability (secondary) and safety (secondary) of various drug combinations for the treatment of neuropathic pain.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We sought double-blind, randomised controlled trials (RCTs) comparing combinations of two or more drugs to placebo and/or at least one other comparator for the treatment of neuropathic pain. We graded all considered studies for quality as per the 'Risk of bias' tool.

Types of participants

We included studies involving adult participants of 18 years and older with a diagnosis of neuropathic pain.

Types of interventions

We included interventions involving a combination of two or more different drugs.

Types of outcome measures

We included participant-reported measure(s) of pain intensity or pain relief using validated methods.

Primary outcomes

The primary outcome we sought was the proportion of participants reporting ≥ 30% pain reduction from baseline OR ≥ moderate pain relief OR ≥ moderate global improvement. The selection of ≥ 30% pain reduction from baseline was based upon analyses demonstrating a relationship between this degree of pain reduction (≥ 30%) and concurrent patient ratings of 'much improved' or 'very much improved' using a patient global impression of change scale (Farrar 2001). The most recent guidance favours an even more stringent definition of at least 50% pain relief (Moore 2010b) because distribution of pain relief tends to be bimodal, and because high levels of pain relief are strongly associated with improved fatigue, sleep, depression, work ability and quality of life. This outcome tends not to have been reported in older studies, and to be unavailable without access to data at the level of the individual patient.

Secondary outcomes

The secondary outcomes we sought were as follows:

1. Proportion of participants dropping out of the study due to treatment-emergent adverse effects.
2. Proportion of participants reporting each specific adverse effect (e.g. sedation, dizziness) of ≥ moderate severity.

Search methods for identification of studies

Electronic searches

We searched the following databases for studies (most recent search conducted 9 April 2012):

- the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 3 2012);
- MEDLINE (1947 to April 9, 2012); and
- EMBASE (via Ovid, 1980 to April 9, 2012).

In addition to the pre-planned literature search, we further searched the clinical trials.gov and controlled-trials.com trial databases for completed pharmaceutical industry trials which posted their results on the clinicalstudyresults.org website.

We performed a snowballing search to increase the accuracy of the protocol defined search (Greenhalgh 2005).

We developed a search strategy for MEDLINE and also adapted this for the other databases (see Appendix 1).

Searching other resources

We also searched the reference lists of over 50 published systematic reviews on the subject of neuropathic pain pharmacotherapy for eligible studies.

Data collection and analysis

Selection of studies

We selected studies as per the criteria listed above.

Data extraction and management

We extracted the following data from each study included: study drug name(s), dose(s), route(s) and study/treatment duration; proportion of participants a) reporting ≥ 30% pain reduction from baseline OR ≥ moderate pain relief OR ≥ moderate global improvement; b) dropping out of the study due to treatment-emergent adverse effects; c) reporting each specific adverse effect (e.g. sedation, dizziness) of ≥ moderate severity.

Assessment of risk of bias in included studies

We graded all considered studies for quality as per the 'Risk of bias' tool (Higgins 2011). It should be noted that the protocol, and thus the methodology, of this review preceded more recent considerations of bias such as imputation methods for treatment responder analyses (Moore 2012b).

Measures of treatment effect

The primary comparison of interest was between study drug(s) and one or both single-agent comparators. We also searched for comparisons of each two-drug combination and any other placebo and/or active treatment comparators. We combined studies if they evaluated the same drug class combination at roughly similar doses and durations of treatment. We used RevMan 5 (RevMan 2011) to analyse study data for binary outcomes.

Unit of analysis issues

For studies involving more than one active treatment group, we would divide the control treatment group among the active treatment arms.

Dealing with missing data

Analyses were based upon intention-to-treat (ITT). We considered randomised participants receiving assigned treatments and providing at least 50% of the required outcome data in the ITT population.

Assessment of heterogeneity

We only combined studies evaluating similar conditions for analysis so as to avoid clinical heterogeneity. We planned to use visual data assessment with L'Abbé plots (L'Abbé 1987) and to calculate the I² statistic to explore statistical heterogeneity when the I² was greater than 50%.

Assessment of reporting biases

In this review we extracted dichotomous data which are independent of other results that study authors may have chosen to report. The review did not include any evaluation of publication bias.

Data synthesis

We planned to use a fixed-effect model for any meta-analyses conducted.

Subgroup analysis and investigation of heterogeneity

We would group according to specific combinations of drug classes (e.g. opioids and anticonvulsants).

Sensitivity analysis

We planned to use sensitivity analyses to evaluate the robustness of a particular result by repeating primary analyses without studies which were considered to be outliers with respect to study quality, drug dose/duration or pain measurement scales.

R E S U L T S

Description of studies

See the 'Characteristics of included studies' and the 'Characteristics of excluded studies' tables for further information.

We identified 107 relevant citations for this review but found only 21 neuropathic pain RCTs that fulfilled the review inclusion criteria.

Results of the search

On 9 April 2012 we identified 1168 citations, which two of the review authors (IG, LEC) independently screened based on the title and the abstract. The first screening for obvious exclusions yielded 132 records that we further reviewed in more detail. We retrieved and reviewed 107 articles in full text and finally 21 fulfilled the inclusion criteria (see Figure 1).
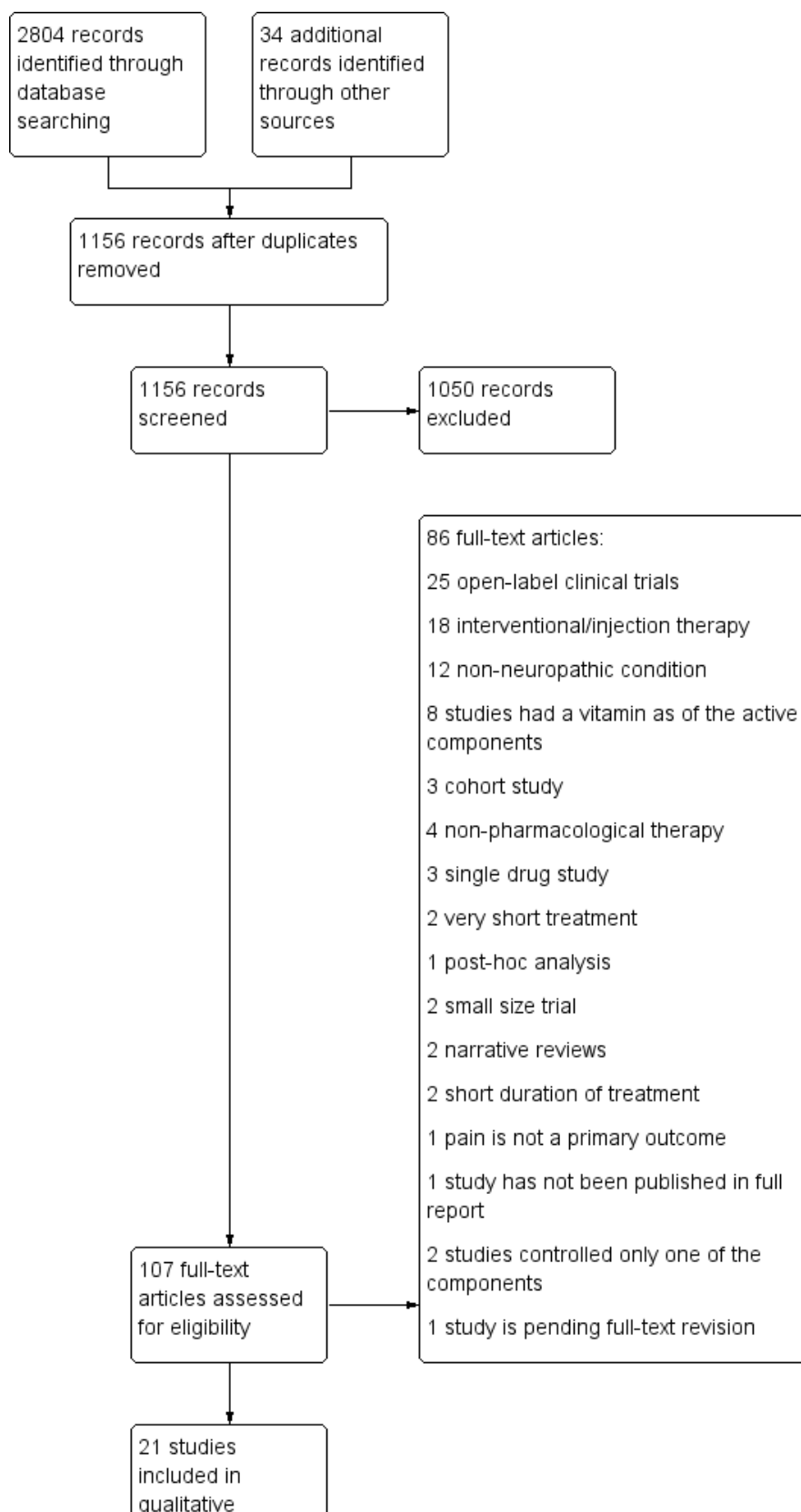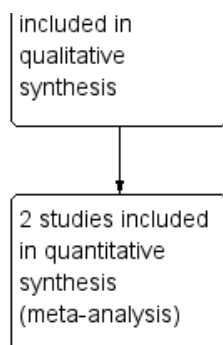
Figure 1. Study flow diagram.

Figure 1. (Continued)

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included in
qualitative
synthesis
        |
        v
2 studies included
in quantitative
synthesis
(meta-analysis)
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Our search for studies registered on the clinicaltrials.gov and controlled-trials.com databases only yielded one recently completed relevant study (http://clinicaltrials.gov/ct2/show/NCT00944697) and another ongoing trial (http://clinicaltrials.gov/ct2/show/NCT00516503); results from these studies were not available at the time of this review.

Study selection

We identified 21 studies that fulfilled the inclusion criteria of the review. Four studies (578 participants) evaluated the combination of an opioid with gabapentin or pregabalin (Caraceni 2004; Gilron 2005b; Hanna 2008; Zin 2010); two studies (77 participants) evaluated the combination of an opioid with a tricyclic antidepressant (Khoromi 2007; Mercadante 2002); one study (56 participants) evaluated the combination of gabapentin and nortriptyline (Gilron 2009); three studies (90 participants) evaluated the combination of fluphenazine with a tricyclic antidepressant (Gomez-Perez 1985; Gomez-Perez 1996; Graff-Radford 2000); three studies (90 participants) evaluated the combination of an N-methyl-D-aspartate (NMDA) blocker with an agent from a different drug class (Amr 2010; Eichenberger 2008; Tonet 2008); five studies (604 participants) evaluated combinations of various topical medications (Agrawal 2009; Barton 2011; Lynch 2003; Lynch 2005; McCleane 2000); one study (313 participants) evaluated the combination of tramadol with acetaminophen (Freeman 2007), another one (44 participants) evaluated the combination of a cholecystokinin blocker (L-365,260) with morphine (McCleane 2003) and a recent trial evaluated the combination of alpha lipoic acid and gabapentin for burning mouth syndrome (Lopez-D'alessandro 2011). Full characteristics are presented in the 'Characteristics of included studies' table.

Study design

Twelve studies (Agrawal 2009; Amr 2010; Barton 2011; Caraceni 2004; Freeman 2007; Graff-Radford 2000; Hanna 2008; Lopez-D'alessandro 2011; Lynch 2005; McCleane 2000; Tonet 2008; Zin 2010) used a parallel design and nine (Eichenberger 2008; Gilron 2005b; Gilron 2009; Gomez-Perez 1985; Gomez-Perez 1996; Khoromi 2007; Lynch 2003; McCleane 2003; Mercadante 2002) used a cross-over design. None of the cross-over trials conducted analyses involving first period data only, likely due to inadequate statistical power.

Nineteen of the included studies evaluated a two-drug combination and only two studies (Barton 2011; Tonet 2008) evaluated a three-

drug combination. Three studies compared the combination of interest to placebo only (Barton 2011; Freeman 2007; Gomez-Perez 1985). Nine double-drug studies compared their combination to placebo and each of the two single agents alone (Agrawal 2009; Eichenberger 2008; Gilron 2005b; Graff-Radford 2000; Khoromi 2007; Lopez-D'alessandro 2011; Lynch 2003; Lynch 2005; McCleane 2000; McCleane 2003). One study compared the combination to the medications alone with no placebo arm (Gilron 2009). Five studies looked at the effect of the combination compared with only one of the two single-agent components (Amr 2010; Caraceni 2004; Hanna 2008; Mercadante 2002; Zin 2010). One study compared the combination to a completely different single-agent drug (Gomez-Perez 1996). Only one study compared the effect of a three-drug combination to two of those drugs (Tonet 2008) and that study did not include a placebo arm.

Outcomes

Only 10 out of 21 studies reported the primary outcome, as defined in the protocol for this review (percentage of pain relief) (Eichenberger 2008; Freeman 2007; Gilron 2005b; Gilron 2009; Gomez-Perez 1985; Gomez-Perez 1996; Hanna 2008; Khoromi 2007; Lynch 2005; Zin 2010). Most of the studies reported pain intensity scores (Agrawal 2009; Amr 2010; Caraceni 2004; Eichenberger 2008; Freeman 2007; Gilron 2005b; Gilron 2009; Graff-Radford 2000; Hanna 2008; Khoromi 2007; Lynch 2003; Lynch 2005; McCleane 2000; McCleane 2003; Mercadante 2002; Tonet 2008; Zin 2010). Patient global impression of change was reported in seven studies (Freeman 2007; Gilron 2005b; Gilron 2009; Hanna 2008; Khoromi 2007; Lopez-D'alessandro 2011; Zin 2010). A number reported the Short Form of the McGill Pain Questionnaire (SF-MPQ) (Agrawal 2009; Freeman 2007; Gilron 2005b; Gilron 2009; Graff-Radford 2000; Hanna 2008; Lynch 2003; Lynch 2005) and/or the Brief Pain Inventory (BPI) (Freeman 2007; Gilron 2005b; Gilron 2009; Hanna 2008). Only three studies measured co-analgesia requirement (Caraceni 2004; McCleane 2003; Tonet 2008). Five studies reported the 36-item Short-Form General Health Survey (SF-36) (Freeman 2007; Gilron 2005b; Gilron 2009; Khoromi 2007; Zin 2010) and four reported sleep interference (Freeman 2007; Hanna 2008; Mercadante 2002; Zin 2010). Seven studies reported a mood state scale (Freeman 2007; Gilron 2005b; Gilron 2009; Graff-Radford 2000; Khoromi 2007; Lopez-D'alessandro 2011; Mercadante 2002; Zin 2010). Additionally, four studies measured the serum levels of the studied drugs (Gilron 2009; Graff-Radford 2000; Lynch 2003; Lynch 2005) and only seven studies reported neuropathy symptoms as well as pain scores (Barton 2011; Caraceni 2004; Lynch 2005; Gomez-Perez 1985; Gomez-Perez 1996; McCleane 2000; Zin

2010). Three studies reported use of sensory tests (Agrawal 2009; Eichenberger 2008; Lynch 2005).

Pain conditions

Painful diabetic neuropathy was explored in 11 studies (Agrawal 2009; Freeman 2007; Gilron 2005b; Gilron 2009; Gomez-Perez 1985; Gomez-Perez 1996; Hanna 2008; Lynch 2003; Lynch 2005; Tonet 2008; Zin 2010); postherpetic neuralgia in seven studies (Gilron 2005b; Gilron 2009; Graff-Radford 2000; Lynch 2003; Lynch 2005; Tonet 2008; Zin 2010); neuropathic cancer pain in three studies (Barton 2011; Caraceni 2004; Mercadante 2002); chronic sciatica in one study (Khoromi 2007); spinal cord injury pain in one study (Amr 2010); another study was developed in patients with burning mouth syndrome (Lopez-D'alessandro 2011) and peripheral nerve injury was the pain condition in three studies (Lynch 2003; Lynch 2005; Tonet 2008). Only one study included participants with complex regional pain syndrome (CRPS) type II (Tonet 2008); in one study, the diagnosis was made based on constituent symptoms (McCleane 2000); and one study included "intractable neuropathic pain of mixed aetiology unresponsive to currently available tricyclic antidepressants, anticonvulsants, opioids and non steroidal anti-inflammatory drugs" (McCleane 2003).

Previous and concomitant pain treatment

We evaluated the analgesic profile previous to participation in the trial for the included studies: patients continued taking at least two additional analgesics during a trial of neuropathic pain in cancer (NPC) (Caraceni 2004); another study in patients with NPC excluded those that were already taking the evaluated drug (antidepressants) (Mercadante 2002); of note, the baseline opioid requirement of the included patients was not stated. In a recent study in chemotherapy-induced peripheral neuropathy, the participants could not be concurrently treated with antidepressants or anticonvulsants (Barton 2011).

Two studies, one evaluating patients with phantom limb pain (Eichenberger 2008) and another one of topical analgesia (Lynch 2005) included participants taking a wide range of number and type of co-analgesics: patients were taking from no medications to three additional drugs, apart from those evaluated in the trial.

The majority of the patients (39/57) in one trial were not taking any concomitant drug or taking acetaminophen or anti-inflammatories only (Gilron 2005b). In a similar trial 28/56 patients were free of analgesics before the trial and 20/56 were taking acetaminophen or anti-inflammatories only (Gilron 2009). One study allowed the concomitant use of any analgesic except for extended-release opioids, which were the studied drug (Hanna 2008). In one study

that evaluated patients with sciatica, most of the participants were taking non-steroidal anti-inflammatory drugs or opioids before the trial (Khoromi 2007). One study evaluating topical analgesics allowed the use of any other analgesic during the trial; however, the report does not show the concomitant analgesia profile of the participants (Lynch 2003).

One study excluded patients who failed treatment with anti-inflammatories or antidepressants (McCleane 2000); another study from the same research group included patients that were unresponsive to any other analgesic scheme (McCleane 2003); however, the concomitant analgesic profile of the participants was not stated in the publication of those studies. The only study that evaluated the combination of three drugs (Tonet 2008) excluded opioid users; however the participants were rescued with 30 mg codeine.

Previous analgesics were stopped before the trial in three studies (Agrawal 2009; Freeman 2007; Zin 2010). Finally, the information concerning concomitant analgesia is not stated in five studies (Amr 2010; Gomez-Perez 1985; Gomez-Perez 1996; Graff-Radford 2000; Lopez-D'alessandro 2011).

Excluded studies

We excluded all studies that used a neuraxial approach (Aldrete 2006; Amr 2011; Autio 2004; Blonna 2004; Braun 1982; Bush 1991; Devulder 1999; Dureja 2010; Glynn 1996; Karppinen 2001; Kotani 2000; Lauretti 2002; Pirbudak 2003; Rodriguez 1999; Schechtmann 2010; Siddall 2000) and targeted injection therapies (Amjad 2005; Eker 2012; Lemos 2008; Martinez 1990; Stajcic 1990), given that they have been recently reviewed elsewhere (Manchikanti 2010; Patel 2009) and because our search strategy was not designed to detect all studies of injection therapies. We excluded two studies combining transcutaneous electrical stimulation plus systemic analgesia (Alvaro 1999; Barbarisi 2010). One study for CRPS patients included a low proportion of CRPS type II (documented nerve injury) (Gustin 2010). One study adding immunoglobulins to carbamazepine in patients suffering from trigeminal neuralgia has published the protocol (Goebel 2003). We also excluded studies evaluating the effectiveness of combined treatments including vitamins (Abbas 1997; Fliege 1966; Goldberg 2009; Kottschade 2009; Lagalla 2002; Levin 2009; Tian 2005). For other reasons for exclusion (e.g. methodological flaws) see the 'Characteristics of excluded studies' table.

Risk of bias in included studies

See 'Risk of bias' table in Figure 2 for summary information.

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

Two of the review authors (LC and IG) assessed each study independently for quality using the 'Risk of bias' tool (ROB) (Higgins 2011). Ten out 21 studies had at least four out of seven items qualified as low risk of bias. Most of the studies did not adequately describe methods of blinding of outcomes assessors. Since most study medications were associated with recognisable adverse effects (e.g. sedation), methods to prevent and/or evaluate (e.g. blinding questionnaires) quality of blinding of outcomes assessors were not adequately addressed. Details are in the 'Characteristics of included studies' table. 'Risk of bias' tables are presented (Figure 2; Figure 3).

Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
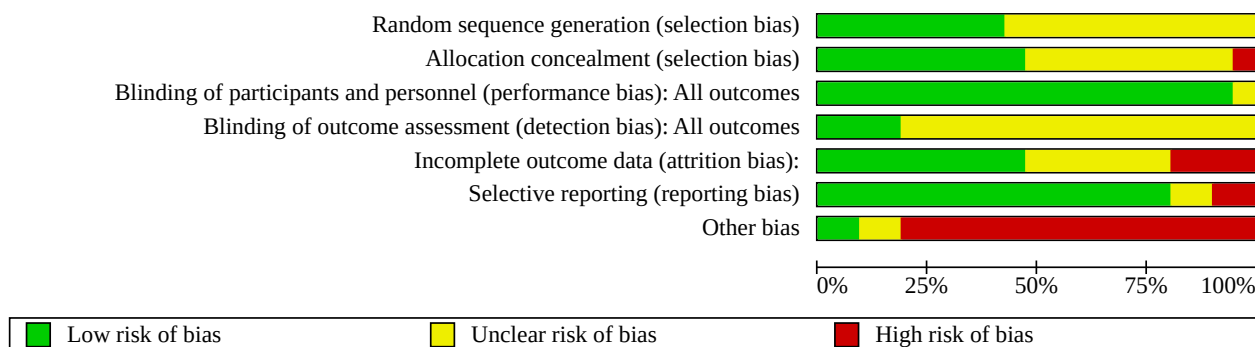
Random sequence generation and allocation concealment (selection bias)

Only six out of 21 studies reported the method used to generate a random sequence and to keep the allocation concealed (Gilron 2005b; Gilron 2009; Hanna 2008; Khoromi 2007; Lynch 2005; Zin 2010) and seven additional studies (Amr 2010; Barton 2011; Caraceni 2004; Eichenberger 2008; Freeman 2007; Lopez-D'alessandro 2011; McCleane 2000) appropriately reported one or the other item.

Blinding

All studies except one reported how participants were blinded; however, only four of the 21 adequately described methods for blinding the outcomes assessors (see Figure 2).

Incomplete outcome data

Eight of the 21 studies did not provide information about trial dropouts (Agrawal 2009; Amr 2010; Lopez-D'alessandro 2011; Lynch 2003; Lynch 2005; McCleane 2000; McCleane 2003; Mercadante 2002). We qualified attrition bias as 'low risk' for studies where the dropout rate was below 20% (Bhandari 2005). We qualified studies with higher dropout rate but including ITT analysis as 'unclear' or 'high risk of bias'.

Selective reporting

Although few studies indicated pre-trial registration on a clinical trial registry, all reported at least one of the outcomes that are considered to be clinically relevant (Dworkin 2005).

Other potential sources of bias

We assessed the 'other bias' item as high risk in studies where the follow-up was shorter than eight weeks (Moore 2010a; Moore 2010b) and/or the study had fewer than 50 participants per arm or period of treatment in parallel or cross-over studies, respectively (Moore 1998).

Effects of interventions

Please see Table 1 for more information.

We included 21 studies with a total of 1972 participants in this review; 966 participants were exposed to a combination of drugs.

Tricyclic antidepressants combined with morphine

Two clinical trials (Khoromi 2007; Mercadante 2002) were identified. Using a cross-over design, Khoromi 2007 evaluated the combination of nortriptyline and controlled-released morphine versus each medication alone and versus active placebo (benztropine) for chronic lumbar root pain; only 28 out 61 participants completed the four nine-week periods of the study. This study reported no significant differences in the primary outcome, average leg pain, across any of the four study treatments: 13/32 participants during the morphine alone period, 12/31 during the nortriptyline alone period, 18/28 during the combination treatment and 9/37 in the placebo period reported at least moderate pain relief. The most frequent reported side effects were constipation, dry mouth, drowsiness and fatigue. Dropouts due to side effects were as follows: 4/41 participants in the morphine period, 2/34 in the nortriptyline period, 4/34 in the combination period and 1/39 in the placebo period.

Mercadante 2002 also used a cross-over design to evaluate the effect of adding amitriptyline or placebo in patients that were already on morphine therapy for neuropathic cancer pain; 15/16 participants completed the two one-week periods of treatments. No significant differences were reported between groups for the primary outcome, global pain intensity. Primary outcomes, as defined in the protocol for this review, were not reported as such in this study. Additionally, no differences in opioid requirement were observed. Only one participant dropped out from the study during the amitriptyline period due to severe confusion and drowsiness. Significant differences in side effects against adding amitriptyline to morphine treatment were reported, such as drowsiness, confusion and dry mouth.

We did not combine these two studies in a meta-analysis because they involved diverse pain conditions (e.g. lumbar radiculopathy versus neuropathic cancer pain) and outcome measures.

Gabapentin or pregabalin combined with opioids

Four clinical trials (Caraceni 2004; Gilron 2005b; Hanna 2008; Zin 2010) were identified. Caraceni 2004 used a parallel design to evaluate the effectiveness of adding titrated doses of gabapentin in patients that were receiving opioid therapy for neuropathic cancer pain; a significant proportion (> 10% per group) of the participants were also receiving non-steroidal anti-inflammatories, antidepressants and/or steroid therapy. Primary outcomes, as defined in the protocol for this review, were not reported as such in this study. Twenty-one out of 79 participants in the gabapentin group and 9/41 in the placebo group dropped out of the study due to the need for prohibited therapy. Reduction in the primary outcome, average pain score, was statistically superior for the gabapentin group. The number of participants that discontinued the study due to side effects was 6/79 in the combination arm and 3/41 in the opioid alone group.

Gilron 2005b used a four-period cross-over design to evaluate the effectiveness of titrated doses of gabapentin and morphine versus each drug alone and versus active placebo (lorazepam) in population with post-herpetic neuralgia or painful diabetic neuropathy. Forty-one out of 57 participants completed all four treatment periods. The trial's primary outcome, mean daily pain score at maximal tolerated dose, was significantly lower for the combination versus placebo and versus either drug alone; 27/44 participants during the gabapentin alone period, 13/42 during the placebo period, 35/44 during the morphine period and 32/41 during the gabapentin + opioid period reported at least moderate pain relief. Forty-eight participants received gabapentin and 3/4 withdrawals were due to treatment-emergent side effects; 49 participants received morphine and 5/5 withdrawals were due to treatment-emergent side effects; 47 participants received gabapentin + morphine and all withdrawals were due to treatment-emergent side effects; 44 participants received placebo and 0/1 withdrawal was due to treatment-emergent side effects. The combination increased the frequency of constipation compared with gabapentin alone and that of dry mouth compared with morphine alone.

Hanna 2008 used a parallel-design clinical trial to compare the effectiveness of adding increasing doses of controlled-release oxycodone versus placebo in participants that were already using varying doses of gabapentin for painful diabetic neuropathy; 48 out of 328 participants were concomitantly taking amitriptyline. Two hundred and forty-nine out of 338 randomised participants completed the study. Based on the primary outcome, 'Box Scale-11' pain scores, the study showed a significant effect favouring the oxycodone treatment over placebo using last observation carried forward (LOCF) imputation for withdrawal, which overestimates treatment effect (Moore 2012b); 52/169 participants in the gabapentin alone group versus 68/169 in the gabapentin + controlled-release oxycodone group reported good or very good pain relief. A significant difference in increasing opioid-related side effects, such as constipation, nausea and vomiting, was observed in the combination treatment group as well as dizziness, fatigue and somnolence; 9/169 participants in the gabapentin alone versus 27/169 in the combined treatment group dropped out from the study due to adverse events.

Zin 2010 conducted a parallel-design clinical trial, where participants were randomised to low-dose oxycodone (10 mg/day) or placebo for one week in a double-blind fashion which continued on during subsequent open-label titration of pregabalin (75 to 600 mg/day). Sixty-two participants were randomised and 51 finished the study. The study did not demonstrate a significant difference between groups based in the primary outcome (2/10 difference in pain intensity). Responder rates based on ≥ 50% pain were reached by 15/26 in the pregabalin/oxycodone and 19/29 in the pregabalin/placebo group. Four participants in the oxycodone/pregabalin versus none in the placebo/pregabalin group discontinued the treatment due to side effects.

A meta-analysis is reported including Gilron 2005b and Hanna 2008. Although both trials evaluated the combination of gabapentin with an opioid, several differences should be noted: 1) Gilron 2005b evaluated morphine whereas Hanna 2008 evaluated oxycodone and 2) Gilron 2005b used a cross-over design to compare a morphine-gabapentin combination to each monotherapy and active placebo (lorazepam), whereas Hanna 2008 used a parallel design to compare an oxycodone-gabapentin to placebo-gabapentin (i.e. no comparison was made between oxycodone-gabapentin and oxycodone). It should be noted that Analysis 1.1 (efficacy) is based on fewer patients than Analysis 1.2 (tolerability) since available data for Analysis 1.1 only allowed for a completer analysis for Gilron 2005b, which will make the data look better than in an intention-to-treat analysis. Therefore, some caution is necessary when interpreting the results of this meta-analysis. Caraceni 2004 was not included in the analysis given that the authors did not report the primary outcome for this review. Zin 2010 reported not 30% but 50% of responder rate; furthermore, this study used a very small (10 mg) and fixed dose of oxycodone; this dosage is well below the minimum 40 mg recommended for neuropathic pain (Furlan 2010).

In this analysis, gabapentin plus opioid (48% moderate or good pain relief) was significantly, yet modestly, better than gabapentin alone (37%), with a risk ratio (RR) of 1.3 (95% confidence interval (CI) 1.04 to 1.61) and with a number needed to treat for one patient to benefit (NNTB) of 9.5 (95% CI 5.0 to 86) (Analysis 1.1; Figure 4). More participants dropped out of the study because of side effects with gabapentin plus opioid (15%) than with gabapentin alone (6%); the RR was 2.8 (95% CI 1.5 to 5.2) and number needed to treat to harm (NNTH) was 10 (6.5 to 25) (Analysis 1.2; Figure 5).

Figure 4. Forest plot of comparison: 1 Anticonvulsants and opioids versus anticonvulsants alone, outcome: 1.1 At least moderate/good pain relief.
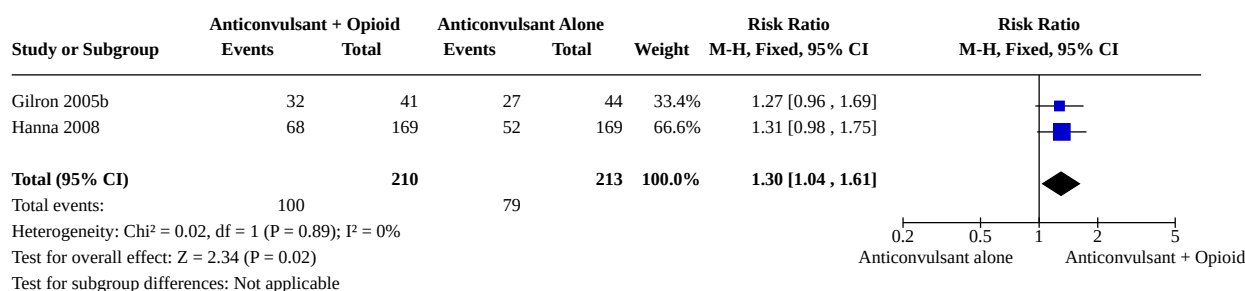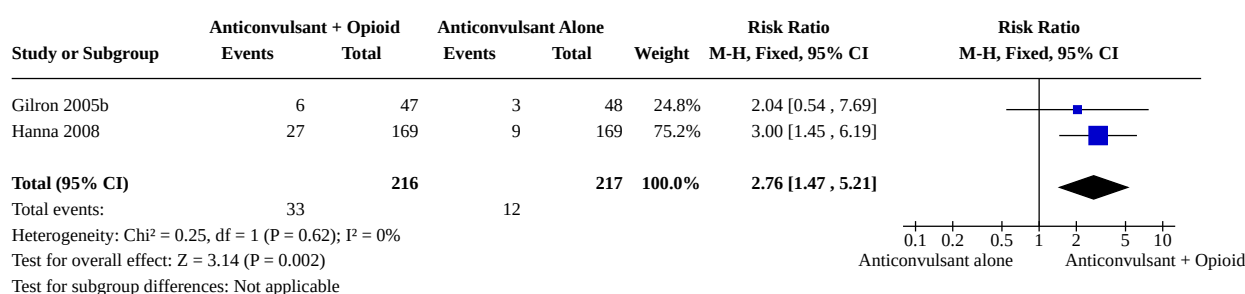

Figure 5. Forest plot of comparison: 1 Anticonvulsants and opioids versus anticonvulsants alone, outcome: 1.2 Proportion of patients who dropped out due to side effects.

Gabapentin combined with nortriptyline

We identified only one clinical trial in this category that fulfilled the inclusion criteria of this review (Gilron 2009). Gilron et al used a three-period, cross-over design to compare the effectiveness of the combination of titrated doses of nortriptyline and gabapentin versus each drug alone in a mixed neuropathic pain population of participants with painful diabetic polyneuropathy or postherpetic neuralgia. Forty-five out of 56 participants completed all three treatment periods. The primary outcome, mean daily pain at maximum tolerated dose, was significantly lower during combination treatment versus either drug alone; 30/46 participants during the gabapentin alone period, 38/50 during the nortriptyline period and 42/50 during the combination treatment period reported at least moderate pain relief. Severe dry mouth was reported more frequently during the combination and nortriptyline treatment periods, compared with the gabapentin treatment period; 5/54 participants that received gabapentin withdrew due to treatment-emergent side effects. The same situation occurred in only 1/52 of the participants during the combined treatment. No participants in the nortriptyline period dropped out due to treatment-emergent side effects.

Tricyclic antidepressants combined with fluphenazine

Three clinical trials were identified (Gomez-Perez 1985; Gomez-Perez 1996; Graff-Radford 2000) for the review. Graff-Radford 2000 reported a parallel-design trial evaluating the effectiveness of combining titrated doses of amitriptyline (up to 200 mg) and fluphenazine (up to 3 mg) versus each drug alone and active placebo (glycopyrrolate) in patients with postherpetic neuralgia. Based on the pain intensity by visual analogue scale

(VAS) a significant reduction from baseline was observed with amitriptyline-fluphenazine combination and amitriptyline alone but not fluphenazine alone or placebo. However, no significant changes from baseline were reported with any of the four treatments according to McGill Pain Questionnaire scores. Primary outcomes, as defined in the protocol for this review, were not reported as such in this study. Only 1/49 participants dropped out of the study due to side effects. The participant had been allocated to the amitriptyline only group. Sleepiness was more frequently reported in the fluphenazine group and the incidence of dry mouth was higher in the amitriptyline group.

Gomez-Perez reported two cross-over design studies (Gomez-Perez 1985; Gomez-Perez 1996) in participants with painful diabetic neuropathy. Both studies evaluated the efficacy of combining titrated doses of nortriptyline (up to 60 mg/day) and fluphenazine (up to 3 mg/day) versus placebo (Gomez-Perez 1985) or titrated doses of carbamazepine (up to 600 mg/day) (Gomez-Perez 1996). The mean per cent of change of pain and paraesthesia (considering a value of 100% at baseline) were the reported study outcomes. The combination of drugs produced at least 50% pain reduction in the placebo-controlled study (Gomez-Perez 1985); 17/18 participants during the combined treatment period versus 4/18 during the placebo treatment period reported at least 30% of pain relief. Six out of 24 participants dropped out of this study, but none of the six dropouts were due to side effects of the medications; dry mouth and dizziness were more prevalent in the combined treatment. In the other study (Gomez-Perez 1996) no significant differences, in terms of effectiveness, were reported between groups. Only two out of 16 participants dropped out due upper gastrointestinal bleeding and non-adherence to treatment.

N-methyl-D-aspartate (NMDA) receptor blockers combined with other analgesic drugs

Three clinical trials have evaluated the combination of an N-methyl-D-aspartate (NMDA) receptor blocker with other analgesic drugs for neuropathic pain (Amr 2010; Eichenberger 2008; Tonet 2008).

Amr 2010 conducted a parallel-design clinical trial comparing the effectiveness of combining seven days of intravenous infusions of 80 mg of ketamine and gabapentin 300 mg orally three times a day versus a saline infusion plus gabapentin in participants with spinal cord injury pain. All participants received midazolam prior to the ketamine infusion. Based on the primary outcome, a 0 to 100 visual analogue scale (VAS) pain score, the score was significantly lower within the first week of the ketamine infusion up to the third week of follow-up. Primary outcomes, as defined in the protocol for this review, were not reported as such in this study. Short-lasting delusions were reported in the ketamine-gabapentin group only; two participants in the combined treatment group and one participant in the gabapentin group reported dizziness. The number of participants, if any, that dropped out from the study due to side effects is not stated.

Eichenberger 2008 reported a two-day per period cross-over study that compared the combination of intravenous infusions of ketamine (0.4 mg/kg) and calcitonin (200 IE) versus the infusions of each drug alone versus placebo for participants with chronic phantom limb pain. Based on the primary outcome, a 0 to 10 VAS up to the 48 hours of each period of treatment, a higher rate of responders was reported for the combined treatment and the infusion of ketamine alone compared to calcitonin alone or placebo. Primary and secondary outcomes, as defined in the protocol for this review, were not reported as such in this study. Zero participants discontinued the study due to side effects

Tonet 2008 conducted a parallel-design clinical trial that compared the combination of amitriptyline (25 mg/day), carbamazepine (200 mg TID) and oral ketamine (10 mg three times daily) versus the combination of amitriptyline, carbamazepine and placebo for patients with neuropathic pain of different aetiologies. Based on the primary outcome, a 0 to 10 numerical rating scale for pain intensity and pain relief, no significant differences were recorded between groups. Primary outcomes, as defined in the protocol for this review, were not reported as such in this study. In the trimodal treatment group 5/15 participants were excluded due to treatment-emergent side effects and the same occurred in 2/15 that received the bimodal treatment.

Miscellaneous analgesic combination trials

Freeman 2007 conducted a parallel-design trial that compared the combination of acetaminophen and tramadol (325 mg + 37.5 mg respectively) versus placebo for participants with painful diabetic neuropathy. Based on the primary outcome, mean change of average daily pain scores, the combined treatment was statistically superior to placebo. In the combination group 90/160 participants versus 58/153 participants in the placebo group reported at least 30% of pain reduction; 13/160 in the combination group versus 10/153 in the placebo group dropped out of the study due to side effects. A significant increase in the incidence of nausea (11.9% versus 3.3%), dizziness (6.3% versus 1.3%) and somnolence (6.3 versus 1.3) was reported in the acetaminophen-tramadol group.

McCleane 2003 conducted a cross-over study involving three two-week treatment periods that compared the combination of the cholecystokinin-2 antagonist, L-365,260 (30 or 120 mg daily) and morphine 20 mg twice daily versus morphine alone in chronic neuropathic pain. Thirty-nine out of 44 participants completed the study. Based on the primary outcome, 11-point Likert scale and categorical scale pain scores, no significant differences were detected between treatments. The author evaluated using a standardised scale from "become more intense to completely relieved". No data were reported for dropouts due to adverse effects.

Lopez-D'alessandro 2011 developed a four-arm study in the only clinical trial developed for burning mouth syndrome that fulfilled our inclusion criteria. The participants received for two months of gabapentin alone (300 mg/day) or alpha lipoic acid (600 mg/day) or the combination of these treatments or cellulose starch. The primary outcome, based on a four-level categorical evaluation including worsening, no change, improvement and total recovery, demonstrated a significant benefit from the combination over the interventions alone or placebo. Pain intensity or pain relief scores were not reported. The number of patients who discontinued the treatment was not reported.

Topical analgesics

Five clinical trials evaluated combinations of topical analgesics (Agrawal 2009; Barton 2011; Lynch 2003; Lynch 2005; McCleane 2000).

Agrawal 2009 conducted a parallel trial that evaluated a combination of glyceryl trinitrate spray (0.4 mg/actuation/night) and oral valproate (20 mg/kg/day) versus each treatment alone versus placebo for painful diabetic neuropathy. Based on the trial outcomes, mean VAS pain scores, short form McGill pain questionnaire, present pain intensity and 10-point Likert scale, all active treatments showed a significant difference compared with placebo. Differences between the combination and glyceryl trinitrate spray alone were not significant for any outcome and differences between the combination and oral valproate were only significant based on VAS pain scores. Primary outcomes, as defined in the protocol for this review, were not reported as such in this study. A negligible number of side effects were observed, even in the combined treatment group, but no dropouts were reported.

Lynch 2003 conducted a two-day, four-period, cross-over trial comparing the combination of topical amitriptyline (1%) and topical ketamine (0.5%) versus each single agent versus placebo in participants with chronic neuropathic pain. Eighteen out of 21 participants completed the study. Based on the outcomes, VAS for pain intensity and pain relief as well as Short Form of the McGill Pain Questionnaire (SF-MPQ), no significant differences were reported between groups. Primary outcomes, as defined in the protocol for this review, were not reported as such in this study. No significant side effects were noticed for dropping out from the study.

Subsequently, Lynch 2005 conducted a parallel study comparing the combination of topical amitriptyline (2%) and topical ketamine (1%) versus each single agent versus placebo in a mixed group of participants with postherpetic neuralgia, painful diabetic neuropathy and post-traumatic neuropathic pain with allodynia. Eighty out of 92 participants completed the study. Based on the primary outcome, an 11-point numerical rating scale for pain, no

differences were detected between groups. Six of 22 participants in the amitriptyline group, 4/22 in ketamine, 9/23 in combination treatment and 7/25 in the placebo group exhibited a pain reduction > 30% according to the NRS-PI. Participants that withdrew due to side effects were 2/25 in the placebo, 2/22 in ketamine and 1/22 in the amitriptyline group.

McCleane 2000 conducted a parallel, four-week clinical trial that compared the combination of topical doxepin (3.3%) and topical capsaicin (0.025%) versus each single agent versus placebo in chronic neuropathic pain. One hundred and fifty-one out of 200 participants completed the study. Based on the primary outcome, a 0 to 10 VAS pain score, significant improvements from baseline were observed with all active treatments. However, no statistically significant differences were reported between any of the three active treatments. Primary outcomes, as defined in the protocol for this review, were not reported as such in this study. The number of participants that dropped out from the study due to side effects is not stated.

Barton 2011 conducted a four-week, parallel-design clinical trial in cancer patients who developed moderate or severe pain secondary to chemotherapy. The effectiveness of a compound gel that included ketamine, baclofen and amitriptyline was compared with placebo. One hundred and fifty of 208 patients completed the study. Based on the evaluation of unpleasant sensory symptoms such as cramping, shooting, burning and tingling, this trial demonstrated a significant benefit of the gel over placebo. No significant side effects were reported. More benefit was reported for symptoms in the upper extremities compared to lower extremities. Motor and autonomic subscales were also evaluated and favoured the use of the compound over placebo.

DISCUSSION

Summary of main results

Given the evidence that at least 45% of participants with neuropathic pain concurrently receive two or more drugs to treat their pain (Tarride 2006), it is somewhat surprising that we were only able to identify 107 relevant citations for this review and only 21 high-quality neuropathic pain randomised controlled trials (RCTs) that evaluated the strategy of combination pharmacotherapy. Even these tended to be relatively small, typically of rather short duration for chronic pain, and sometimes had high withdrawal rates, all of which can contribute to overestimation of treatment effects (Moore 2010b). Only one eligible study evaluated a combination of the two most widely used classes of neuropathic pain drugs, i.e. antidepressants and anticonvulsants. Three studies evaluated opioid-anticonvulsant combinations and only two studies evaluated opioid-antidepressant combinations. The remaining dozen studies evaluated combinations involving other drugs including NMDA receptor antagonists, fluphenazine and other miscellaneous agents, including topically applied drugs. Meta-analysis was possible for only one comparison of only one combination, i.e. gabapentin + opioid versus gabapentin alone. This meta-analysis involving 386 participants from two studies (Gilron 2005b; Hanna 2008) demonstrated statistically significant superiority of a gabapentin + opioid combination over gabapentin alone, but with more frequent side effect-related trial dropouts compared to gabapentin alone. The magnitude of the effect was not large, and may have been smaller if it had been possible to perform

other than a completer analysis from data from the multiple cross-over study (Gilron 2005b).

Overall completeness and applicability of evidence

Evaluation and utility of combination pharmacotherapy for neuropathic pain obviously needs to be considered on a combination-specific basis, although it may be reasonable to consider combinations of slightly different drugs which involve agents from common drug classes collectively (e.g. 'gabapentinoid' + 'tricyclic antidepressant' combination). That being said, the dearth of studies currently available for each studied drug class combination precludes any well-founded conclusions about most combinations.

The only combination with more than one study that we found suitable for pooling in a meta-analysis was the gabapentin + opioid combination. In one study, Gilron 2005b reported that the efficacy of the gabapentin + morphine combination was superior to each of the two drugs alone and to active placebo alone (low-dose lorazepam). However, in the other study, Hanna 2008 employed an 'add-on' design whereby patients already receiving gabapentin were randomised to receive either oxycodone or placebo. Therefore, while pooling these studies may provide more robust evidence for the comparison of gabapentin + opioid versus gabapentin alone, only the Gilron 2005b study provides evidence for the comparison of gabapentin + opioid versus *opioid* alone. It should also be emphasised that, while the gabapentin + opioid combination was superior to gabapentin alone for analgesic efficacy, it was also associated with more frequent study dropouts due to treatment-emergent adverse effects.

The search strategy for this review was not designed to capture all studies of drug combinations administered by targeted injection (e.g. epidural or transforaminal nerve block), so any such studies were excluded from this review. Therefore, we point interested readers to other relevant reviews of these interventions (see Manchikanti 2010; Patel 2009).

Quality of the evidence

The 21 included studies were of reasonably good quality with mostly low risks of bias related to treatment randomisation and blinding. Frequent risks of bias in many of these studies were related to small sample size (< 50 participants) (Moore 1998; Nuesch 2010) and/or short trial duration (< 8 weeks) (Moore 2010a; Moore 2010b). Reports of investigations which were insufficiently blinded and/or uncontrolled were excluded as shown in the 'Characteristics of excluded studies' table. Some studies used imputation methods (like last observation carried forward - LOCF) for some pain outcomes, and these are known to confer large positive biases on results (Moore 2012b); we avoided outcomes where this may have been a problem.

Potential biases in the review process

Restriction of this review to double-blind RCTs limits the potential for bias, though the small size of most of the studies, their relatively short duration and the high levels of withdrawals in some studies could all be sources of bias leading to greater treatment effect for combination therapies. Lack of access to negative studies which remain unpublished could be a source of publication bias that our search strategy could not overcome. While unpublished studies are unlikely, even one modest-sized study showing zero effect would

be sufficient to overcome the positive result in our meta-analysis (Moore 2008).

Agreements and disagreements with other studies or reviews

A systematic review in cancer pain (Bennett 2011) included clinical trials and observational studies focused on adding antidepressants or anticonvulsants to opioid therapy, given the considerable incidence of neuropathic pain in this population. They identified five RCTs and three observational studies; we included in our review two of these studies that satisfied our methodological inclusion criteria and were conducted in a neuropathic cancer pain population. A recent meta-analysis (Finnerup 2010), including only 10/19 of the studies that we identified, stressed the paucity of combination studies and modest efficacy of combination as reported by already published clinical trials. However, the most recent version of the European (EFNS) Practice Guideline for neuropathic pain (Attal 2010) gave a Level A to antidepressant-gabapentin or gabapentin-opioid combinations based on three Class I studies that were included in our review. Fourteen of 19 clinical trials that we selected for this review were described/included in this guideline. The combination tramadol/acetaminophen was recommended for pain exacerbations. In the conclusions of the guideline, combination therapy is recommended in the event of partial response to monotherapy, however, larger studies were strongly recommended. Finally, a considerably more inclusive qualitative review was recently published (Vorobeychik 2011). This review included a variety of randomised, double-blind and open-label studies, as well as observational studies.

AUTHORS' CONCLUSIONS

Implications for practice

Multiple, good-quality studies demonstrate the superior efficacy of two-drug combinations. However, the number of available studies for any one specific combination as well as other study factors (e.g. limited trial size and duration) preclude the recommendation of any one specific drug combination for neuropathic pain. Pooled analysis of two studies comparing gabapentin + opioid to gabapentin alone suggested modest analgesic superiority but also reduced tolerability, leaving the overall benefit of this combination unclear. Given that combination pharmacotherapy may increase the risk of toxicity (particularly when the combined drugs produce common adverse effects such as sedation), practical use of analgesic drug combinations requires vigilant risk-benefit assessment during combination treatment. One common clinical approach to minimising combination toxicity is to use sequential combination therapy, i.e. to start treatment with monotherapy and pursue 'add-on' combination therapy in cases of partial treatment response. However, this approach may lead to a different dose-ratio for the combination than might be achieved with simultaneous combination therapy and, possibly, different results (Gilron 2005a).

Implications for research

Demonstration of combination benefits by several individual studies together with reports of widespread clinical polypharmacy for neuropathic pain surely provide a rationale for additional future rigorous evaluations of analgesic drug combinations. Examination of the studies included in this review may serve to guide future improvements in the evaluation of drug combinations for neuropathic pain. It should be noted that, of the 18 included two-drug combination studies (N.B. one of the 19 studies compared a triple combination to two of its components), only nine compared the combination to *both* single-agent components. One problem with this incomplete design is that observed differences between the combination of drugs 'A + B' versus drug 'A' alone could potentially be due strictly to differences in efficacy between drugs 'A' and 'B' and, thus, additional comparison of 'A + B' also with 'B' alone is crucial for the comprehensive evaluation of the combination. Furthermore, nine of the included studies were not placebo-controlled and five of those failed to demonstrate a difference between the combination of interest and its comparator(s). It should be noted that these five negative studies are essentially inconclusive since, without a demonstrable difference between active treatment and placebo, it is not possible to confirm whether those studies had the assay sensitivity to detect a treatment effect (Dworkin 2010; Max 1991). Therefore, we recommend that future trials of two-drug combinations include comparisons with placebo and both single-agent components, as well as reporting outcomes (such as at least 50% pain intensity reduction with tolerable adverse effects) linked to improved functioning over the longer term (at least 12 weeks). In addition to identifying specific drug combinations which provide additional benefit over monotherapy, other objectives to be incorporated into future analgesic combination trials include identification of optimal dose-ratio for a given combination, cost-effectiveness comparisons for combination versus monotherapy and the therapeutic benefits of concurrent versus sequential 'add-on' combination therapy (Gilron 2005a).

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Moore 2011

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Moore 2012a

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Nuesch 2010

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RevMan 2011 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan). Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Tarride 2006

Tarride JE, Collet JP, Choiniere M, Rousseau C, Gordon A. The economic burden of neuropathic pain in Canada. *Journal of Medical Economics* 2006;**9**(1-4):55-68.

Torrance 2006

Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. *Journal of Pain* 2006;**7**(4):281-9.

Vorobeychik 2011

Vorobeychik Y, Gordin V, Mao J, Chen L. Combination therapy for neuropathic pain: a review of current evidence. *CNS Drugs* 2011;**25**(12):1023-34.

CHARACTERISTICS OF STUDIES

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

Agrawal 2009

Study characteristics

Methods	Single-centre, randomised, double-blind, placebo-controlled, parallel design for 12 weeks
Participants	At least > 4/10 and > 3 months painful diabetic neuropathy; 87 participants were screened, 83 randomised and 80 completed the study. Mean age: 59; proportion of female/male was similar. Analgesics for diabetic neuropathy were stopped at least 2 weeks before the trial.
Interventions	Glyceryl trinitrate spray (GTN): 0.4 mg on each leg before going to bed combined with sodium valproate 20 mg/kg/day orally versus placebo + GTN spray versus sodium valproate + placebo spray versus placebo tablets + placebo spray. Supplementary analgesia was not allowed.
Outcomes	This study reported 0 to 10 VAS pain score, Short Form McGill pain questionnaire (SF-MPQ) and present pain intensity in a 10-point Likert scale. All outcomes were recorded at baseline and every 4 weeks up to week 12.
Notes	Small size trial: only 20 participants per arm. Only 3/83 dropouts. The study also explored electrophysiological response to treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation is not stated
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The placebo tablets used were similar in colour, size and texture as well as the placebo spray was identical in colour and odour with that of GTN"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Clinical evaluation, nerve conduction study and pain scoring were done by another member of the team who was completely ignorant about the administration of the drug"
Incomplete outcome data (attrition bias)	Low risk	Minimal missing outcome data
Selective reporting (reporting bias)	Low risk	Not apparent selective outcome reporting. Trial registration number is not stated.
Other bias	High risk	Fewer than 50 participants per arm of treatment

Amr 2010

Study characteristics

Methods	Single-centre, randomised, double-blind, active-controlled, parallel design for 4 weeks

Amr 2010 (Continued)

Participants	> 6 months spinal cord injury pain; 40 participants randomised and completed the trial. Mean age: 48.6 years. 7/40 were female. The information about previous or concomitant analgesic treatments through the trial is not stated.
Interventions	80 mg of ketamine was diluted in 500 ml of saline to be administered for 5 hours daily for 1 week and then once a week for 1 month. Gabapentin 300 mg was administered orally 3 times a day. One group received the ketamine infusion plus gabapentin and the other saline infusion plus gabapentin.
Outcomes	They reported 0 to 100 VAS pain score and drug-related side effects profile
Notes	A minimum baseline pain score for inclusion in the trial was not reported. Small size trial: only 20 participants per arm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation is not stated
Allocation concealment (selection bias)	Low risk	"The envelopes, infusion bottles containing either ketamine or placebo, and coding of these materials were prepared by an anesthesiologist in cooperation with the hospital's pharmacy. This anesthesiologist did not participate in the study, evaluate the patients or the data, or report the findings".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The sealed envelopes were opened by a blinded chief nurse not participating in the study or data collection for the patients to indicate the group in which they were assigned".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	If the same assessors who noticed ketamine-related side effects were also assessing pain outcomes, they might be biased
Incomplete outcome data (attrition bias)	Unclear risk	Dropout rate is not stated
Selective reporting (reporting bias)	Low risk	Not apparent selective outcome reporting. Trial registration number is not stated.
Other bias	High risk	Fewer than 50 participants per arm of treatment and < 8 weeks duration of trial

Barton 2011

Study characteristics

Methods	Randomised and double-blind, parallel, placebo-controlled, clinical trial during 4 weeks
Participants	Participants that had received neurotoxic chemotherapy and developed numbness, tingling or pain for at least 1 month. Pain intensity > 4/10 was required for inclusion. Participants could not be concurrently treated with any agent with suspected efficacy for neuropathy, such as anticonvulsants or tricyclic antidepressants.

Barton 2011 *(Continued)*

Interventions	Participants were randomised to receive 1.31 g of a compounded gel containing 10 mg of baclofen, 40 mg of amitriptyline HCL, and 20 mg of ketamine versus an identical appearing placebo gel. The gel was applied 2 times/day during 4 weeks.
Outcomes	The primary end point for the study was the change in the sensory neuropathy subscale as measured by the European Organization for Research and Treatment of Cancer QLQ-CIPN20 (CIPN-20); profile of mood states, brief pain inventory, and the sensory neuropathy subsection of the NCI common terminology criteria. Side effect profile was also evaluated.
Notes	There were 5 participants who withdrew from the study before starting study medication. There were 26 participants in the baclofen arm and 27 in the placebo arm who did not provide primary endpoint data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was done using dynamic allocation to balance marginal distributions of the stratification factors".
Allocation concealment (selection bias)	Low risk	"Drug assignments to individual patients were accessible only by the North Central Treatment Group randomization office, study pharmacists, and the study statisticians".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Participants were randomised to receive 1.31 g of a compounded gel containing 10 mg of baclofen, 40 mg of amitriptyline HCL, and 20 mg of ketamine versus an identical appearing placebo gel".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants completed questionnaires at baseline and at 4 weeks. Participants rated the severity of these symptoms on a 0 to 10 scale, with 10 being the most severe. Adverse events were evaluated through the patient-reported questions mentioned above as well as being graded through the NCI Common Terminology Criteria, version 3.0".
Incomplete outcome data (attrition bias)	Low risk	Dropouts are balanced across groups: "There were 26 participants in the baclofen arm and 27 in the placebo arm who did not provide primary endpoint data. In the baclofen arm, 11 refused due to experiencing an adverse event and 15 refused for nonspecified reasons. In the placebo arm, eight refused due to an adverse event, one patient died, and 18 refused for nonspecified reasons".
Selective reporting (reporting bias)	Unclear risk	"The study was registered according to current US federal regulations". The instruments for evaluation of the primary and secondary endpoints are valid and clinically relevant.
Other bias	Unclear risk	The study appears to be free of other sources of bias

Caraceni 2004

Study characteristics

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel design study for 10 days only
Participants	Neuropathic pain (≥ 5/10) secondary to tumoral infiltration or compression of neural structures. 691 patients were screened, 121 randomised and 89 completed the trial. Mean age: 59 (SD 11) years. 68/121

Caraceni 2004 *(Continued)*

were female. Average global pain score was 7.0 (SD 1.4) in the gabapentin group and 7.7 (SD 1.3) in the placebo. Previous analgesic (opioids and non-steroidal anti-inflammatory drugs) and adjuvant therapies (i.e. steroids, antidepressants, anticonvulsants, anxiolytics or muscle relaxants) were unchanged throughout the study. One extra dose of opioid medication was available as needed (prn) and it was prescribed at visit 1 based on the previous opioid regimen. Patients needing more than one daily prn. opioid dose during the treatment phase were withdrawn from study. Patients were comparable in their analgesic requirement (based on oral morphine-equivalent pre-trial analgesic requirement). The majority of the patients were taking during the trial anti-inflammatories and steroids. The trial showed a higher analgesic requirement in the placebo versus the gabapentin group.

Interventions	Titrated doses of gabapentin (600 to 1800 mg/day); dose was increased if pain score ≥ 3/10. Placebo capsules were titrated in the same fashion. Previous analgesics were allowed unchanged during the trial. One extra pill of opioid was allowed per day; however, more than one pill request was a reason for exclusion from the study.
Outcomes	The primary outcome was average follow-up pain score and secondary outcomes were subjective rating scale scores for lancinating pain, burning pain, dysaesthesias, presence/absence of allodynia and use of prn. analgesics
Notes	The duration of pain before starting the study was not reported. 21/79 discontinued in the gabapentin + opioid due to the need for prohibited therapy versus 9/41 in the opioid alone arm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation is not stated
Allocation concealment (selection bias)	Low risk	"…random sequence by the pharmacy department of the sponsor's laboratories. All study participants were blinded to allocation sequence".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Study medications were provided as identical capsules containing 300 mg of gabapentin or placebo in numbered containers".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	If the same assessors who noticed gabapentin-related side effects were also assessing pain outcomes, they might be biased
Incomplete outcome data (attrition bias)	Unclear risk	"The main analysis was performed on the intent-to-treat (ITT) population". Substantial dropout rate and we do not know the trial outcomes for these dropouts.
Selective reporting (reporting bias)	Low risk	Not apparent selective outcome reporting. Trial registration number is not stated.
Other bias	High risk	< 8 weeks duration of trial

Eichenberger 2008

Study characteristics

Methods	Single-centre, randomised, double-blind, placebo-controlled, cross-over design study for 2 days only

Eichenberger 2008 (Continued)

Participants	Phantom limb pain (≥ 3/10) due to surgical or traumatic amputation. 20 participants were included and 17 completed the study. 5/20 patients were female. Median age: 57. Median duration phantom limb pain: 10.9 years. The baseline mean pain score was 4.3/10. Medications: 5/20 patients were not taking analgesics before the trial; 3/20 were taking opioids only; 4/20 were taking anti-inflammatories only; 2/20 were taking an anticonvulsant combined with opioid or antidepressant; 5/20 were taking a combination of antidepressant plus anti-inflammatories, opioids or anticonvulsants; finally 4/20 patients were combining 3 analgesics for neuropathic pain during the trial (apart of the evaluated medications).
Interventions	Intravenous infusion of 200 IE of calcitonin versus racemic ketamine 0.4 mg/kg (only 10/20 patients received ketamine alone) versus a combination of the previous interventions versus saline. All medications were diluted in 20 ml and were injected over one hour using an infusion pump. Washout period 48 hours.
Outcomes	The primary outcome was VAS pain 30 minutes after start the infusion, at the end of the infusion and then every 4 hours up to 48 hours; maximal pain experienced during the 48 hours after each session was recorded. Response to therapy was defined as reduction of at least 50% in pain intensity after the end of the infusion. Pain thresholds after electrical, thermal and pressure stimulation were recorded before and during each infusion.
Notes	The baseline VAS mean score was 3.7 only. A carry-over analysis was not performed. Small size trial: 20 participants only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...randomization, which was performed by drawing lots..."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...neither the investigator performing the experiment nor the patients were aware of the solutions infused..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	If the same assessors who noticed ketamine-related side effects were also assessing pain outcomes, they might be biased (this even acknowledged by authors)
Incomplete outcome data (attrition bias)	High risk	50% of the population did not received ketamine
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported. Trial registration number is not stated.
Other bias	High risk	Fewer than 50 participants per arm of treatment and < 8 weeks duration of trial

Freeman 2007

Study characteristics

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group design for 66 days

Freeman 2007 *(Continued)*

Participants	Pain model: > 4/10 distal symmetric painful diabetic neuropathy in the lower extremities on a daily basis for the past 3 months. 313 patients were randomised; 129/160 in the tramadol/APAP arm and 109/153 in the placebo arm completed the study. 41% were female. Mean age: 55.7 (SD 10.32). Average daily pain at baseline was 7.13 and 7.12 in the tramadol/APAP and placebo groups, respectively. Medications: the study excluded patients who failed to the studied medications, previous failures to more than 2 analgesic treatments as well as those using capsaicin, steroids, antidepressants (except for SSRIs prescribed for depression) or anticonvulsants. Topical local anaesthetics and anti-inflammatories were stopped a couple of days before trial.
Interventions	10-day titration period + 8 weeks maintenance period. 37.5 mg tramadol/325 mg APAP tablets or placebo tablets titrated from 1 to 4 tablets prn. Supplemental acetaminophen was allowed during titration. Maintenance period: 1 to 2 tablets as needed 4 times a day. No supplemental analgesics were permitted.
Outcomes	Primary and secondary outcomes: average daily pain, sleep interference and number of study medication. BPI, SF-MPQ, SF-36, patient global impression of change.
Notes	No tramadol or acetaminophen alone groups. 75/313 participants dropped out from the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation is not stated
Allocation concealment (selection bias)	Low risk	"Randomization schedules were prepared for each study center and were balanced with randomly permuted blocks".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...37.5 mg tramadol/325 mg APAP tablets or placebo tablets that were matched in appearance..."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...subjects called the Interactive Voice-Response system every night to report average daily pain, sleep interference, and the number of tablets of study medication taken that day".
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data are balanced across the 2 groups and intention-to-treat analysis was performed
Selective reporting (reporting bias)	Low risk	Outcome measured are standard in pain clinical trials. Registry # NCT-00210847.
Other bias	Low risk	The study appears to be free of other sources of bias

Gilron 2005b

Study characteristics

Methods	Single-centre, randomised, double-blind, active placebo-controlled, 4-period cross-over design for 5 weeks each period
Participants	Pain model(s): at least moderate painful diabetic neuropathy [PDN] (median age: 60 and duration of pain 4.5 ± 3.8 years) and post-herpetic neuralgia [PHN] (median age: 68 and duration of pain 4.6 ± 5.2 years). 86 patients were screened, 57 randomised and 41 completed all 4 treatment periods. 25/57 of

Gilron 2005b *(Continued)*

the participants were female. Baseline pain score (0 to 10) were: 5.5 ± 1.5 (PDN) and 5.0 ± 1.3 (PHN). Medications: patients were allowed to continue taking an stable dose of non-opioid analgesia except for gabapentin.

Interventions	Patients received 25 days of titrated dose, 1 week of maximum tolerated dose, 4-day tapering and 7 days washout. Morphine period: ER morphine 30 mg BID + lactose placebos TID; max. daily dose 120 mg. Gabapentin period: lactose placebos BID + gabapentin 400 mg TID; max. daily dose: 3600 mg. Gabapentin-morphine period: ER morphine 15 mg BID + gabapentin 300 mg TID; max. daily dose: morphine 60 mg and gabapentin 2400 mg. Placebo period: lorazepam 0.2 mg BID + lorazepam 0.1 mg TID; max. daily dose: 1.6 mg. Gabapentin was allowed through the study.
Outcomes	Primary outcome: mean intensity of pain during the maximum tolerated dose period. Secondary: rate of adverse effects, BPI, SF-MPQ, BDI, SF-36, Mini-Mental State examination, patient global impression of change.
Notes	A carry-over effect was noticed for the next treatment when morphine was compared with placebo. 16/57 (28%) participants did not complete the 4 periods of treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"At the commencement of the trial, a pharmacist at the Kingston General Hospital in Kingston, Ontario, Canada, prepared a concealed allocation schedule randomly assigning the four sequences, in blocks of four, to a consecutive series of numbers".
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled central allocation. See above.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Medications were placed in blue and gray gelatin capsules by the investigational pharmacist in order to maintain double-blind conditions".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	If the same assessors who noticed treatment-related side effects were also assessing pain outcomes, they might be biased
Incomplete outcome data (attrition bias)	Unclear risk	Substantial dropout rate
Selective reporting (reporting bias)	Low risk	Protocol appears at clinical trials.gov and the outcomes are identical
Other bias	High risk	Fewer than 50 participants per period of treatment and < 8 weeks duration of trial

Gilron 2009

Study characteristics

Methods	Single-centre, randomised, double-blind, active-controlled, 3-period cross-over design for 6 weeks each period

Gilron 2009 *(Continued)*

Participants	Pain model(s): > 4/10 painful diabetic neuropathy (median age: 61 years and duration of pain 5.2 ± 3.4 years) and post-herpetic neuralgia (median age: 68 years and duration of pain 2.8 ± 4.3 years). 73 participants were screened, 56 randomised and 45 completed all 3 treatment periods. 21/56 were female. Patients taking, and perceiving benefit from, sustained-release opioids, non-steroidal anti-inflammatory drugs or paracetamol were allowed to continue these drugs at a steady dose for the entire study. However, procedural pain treatments (e.g. nerve blocks or acupuncture) were forbidden.
Interventions	Patients received 24 days of increasing doses of the studied medications, 1 week of maximum tolerated dose, 4-day dose tapering and 1-week washout. Nortriptyline period: nortriptyline 10 mg BID + lactose placebos TID; max. daily dose 100 mg. Gabapentin period: lactose placebos BID + gabapentin 400 mg TID; max. daily dose: 3600 mg. Gabapentin-nortriptyline period: nortriptyline BID + gabapentin 400 mg TID; max. daily dose: nortriptyline 100 mg and gabapentin 3600 mg.
Outcomes	Primary outcome: 0 to 10 pain intensity at the maximum tolerated dose. Secondary outcomes: maximum tolerated dose of study drug, serum concentration of study drugs, BPI, patient reported nocturnal pain, SF-MPQ, SF-36 guessing questionnaires, and bodyweight and global impression of change.
Notes	No placebo arm. 19.6% of the participants did not complete the 3 periods of treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A trial pharmacist prepared a concealed allocation schedule by computer randomisation of these three sequences, in blocks of three, to a consecutive number series".
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled central allocation. See above.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Drugs were given as yellow and orange capsules to maintain double-blinding".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	If the same assessors who noticed treatment-related side effects were also assessing pain outcomes, they might be biased
Incomplete outcome data (attrition bias)	Low risk	Non significant dropout rate (< 20%). No patients were excluded from the analysis because of missing data.
Selective reporting (reporting bias)	Low risk	Protocol was published and outcomes measures are identical
Other bias	High risk	< 8 weeks of duration

Gomez-Perez 1985

Study characteristics

Methods	Single-centre, randomised, double-blind, placebo-controlled, 2-period, cross-over design for 30 days each period

Gomez-Perez 1985 *(Continued)*

Participants	Pain model: painful diabetic neuropathy. Mean age: 55 years (30 to 73). 24 participants were randomised and 18/24 completed the 2 periods of treatment. 9/18 were women. Medications: information about concomitant analgesia is not stated.
Interventions	Nortriptyline 10 mg + fluphenazine 0.5 mg: the starting dose was 1 tablet TID for 2 weeks and it was increased 2 tablets TID for another 15 days. Identical tablets and increasing scheme were applied during the placebo period.
Outcomes	The initial level of pain and paraesthesia were given a 100% value and changes were considered positive or negative per cent deviations (mean per cent of change). VAS change from baseline was used in the outcomes assessor's office as well as a side effects record.
Notes	Baseline pain intensity or minimum pain intensity for inclusion in the study was not reported. Small sample size. No carry-over effect analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation is not stated
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The active drugs, 10 mg of nortriptyline and 0.5 mg of fluphenazine, and the placebo, an inactive substance, were supplied as identical tablets under a code unknown to clinicians"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias)	Unclear risk	Substantial dropout rate
Selective reporting (reporting bias)	Low risk	Not apparent selective outcome reporting. Trial was not registered.
Other bias	High risk	Fewer than 50 participants per period and < 8 weeks duration

Gomez-Perez 1996

Study characteristics

Methods	Single-centre, randomised, double-blind, active-controlled, 2-period, cross-over design for 30 days each period
Participants	Pain model: > 6 months of moderate/severe painful diabetic neuropathy. Mean age: 43.1 (nortriptyline + fluphenazine group) and 51.5 (carbamazepine group) years. 9/16 patients were female. Information about concomitant analgesia is not stated.
Interventions	Nortriptyline 10 mg + fluphenazine 0.5 mg: the starting dose was 1 tablet at bedtime; the second day an additional was added at lunch and a third one at breakfast the third day. 12 days later the dose was

Gomez-Perez 1996 *(Continued)*

doubled. Subsequently, a washout period of 2 to 4 weeks until symptoms returned to baseline. Carbamazepine: titrated doses from 100 to 600 mg.

Outcomes	Primary outcomes: mean per cent of change of pain and paraesthesia and side effects profile
Notes	Small sample size (16 in total). Dropouts: 2/16. No carry-over effect analyses. Side effects: 8/16 (N + F) and 3/16 on carbamazepine group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation is not stated
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"An identical placebo tablet of the comparing drug was given simultaneously with the active drug following the same pattern of administration".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias)	Low risk	Dropout rate was not significant
Selective reporting (reporting bias)	Low risk	Not apparent selective outcome reporting. The trial was not registered.
Other bias	High risk	Fewer than 50 participants per period and < 8 weeks duration

Graff-Radford 2000

Study characteristics

Methods	Single-centre, randomised, double-blind, active placebo-controlled, parallel design for 8 weeks
Participants	Pain model: > 6 months post-herpetic neuralgia. Mean age: 72.9 (SD 10.1); duration of pain 33.4 months (SD 29.5)). 92 participants were screened, 50 randomised and 49 completed the study. 22/49 of the participants were female. Baseline pain score (0 to 100) was 55.22 (SD 16.34); baseline MPQ: 23.22 (SD 13.23). Information about pre-trial analgesia is not stated.
Interventions	Patients received increasing doses (every week) of amitriptyline (12.5 to 200 mg), fluphenazine (1 to 3 mg), the medications combined or active placebo (glycopyrrolate)
Outcomes	This study reported visual analogue scale, McGill Pain Questionnaire, amitriptyline serum levels, MMPI, Beck Depression Inventory, Spielberg State Trait Anxiety Inventory and side effects profile
Notes	No description of the minimum pain intensity to be included. Only 1/49 dropouts (amitriptyline group due to sedation). Study granted by the National Institute of Health Research.

Graff-Radford 2000 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation is not stated ("...were randomly assigned to one of four treatment groups...")
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All patients received two different capsules. One capsule (blue) was either amitriptyline or cellulose".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias)	Low risk	Dropout rate was not significant
Selective reporting (reporting bias)	Low risk	Not apparent selective outcome reporting
Other bias	High risk	Fewer than 50 participants per arm of treatment trial

Hanna 2008

Study characteristics

Methods	Multicentre, randomised, double-blind, active placebo-controlled, parallel, add-on, LOCF-analysis, design study for 12 weeks
Participants	Pain model: painful diabetic neuropathy. Median age: 60.1 (SD 10.24). 406 patients were screened, 338 randomised and 249 completed the study. 118/328 (36%) of the participants were female. At least moderate pain was required for inclusion; baseline pain scores (0 to 10) were: 6.4 ± 1.76 (oxycodone group) and 6.5 ± 1.71 (placebo). Medications pre-trial: the study excluded any patients treated with a long-acting opioid in the previous month or who had previously used oxycodone in combination with gabapentin. Stable dose of concomitant analgesics were allowed. Paracetamol was allowed as rescue medication.
Interventions	Subjects on maximum tolerated dose of gabapentin (48% on < 1200 mg/day) were randomly assigned to Controlled-Released oxycodone or placebo. Oxycodone was started at 5 mg BID and titrated during the 12 weeks up to max. 80 mg BID. Acetaminophen (one gram) was the rescue medication. NSAIDs and TCAs were continued in stable dose. 6.4% of the participants were taking concomitantly TCAs, gabapentin and oxycodone.
Outcomes	The primary outcome of the study: Box Scale-11 (BS-11) pain scores (mean reduction in pain scores). Secondary outcomes: acetaminophen request and sleep quality. Exploratory analyses: BPI, SF MPQ, Euro Qol -5D questionnaire, and subject resource utilisation.
Notes	This study was sponsored by Mundipharma Research Limited. 89/338 (26.3%) dropouts.

Risk of bias

Hanna 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was performed using a validated interactive voice response system that automated the assignment of treatment groups to randomisation numbers in accordance with a randomisation schedule".
Allocation concealment (selection bias)	Low risk	"Randomisation data were kept strictly confidential".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients, and all personnel involved in the study, including investigators, site personnel and sponsor's staff, were blinded to the medication codes until the time of unblinding".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias)	Unclear risk	Substantial dropout rate and we do not know the trial outcomes for these dropouts. Missing these data COULD affect the results and lead to bias.
Selective reporting (reporting bias)	Low risk	Not apparent selective outcome reporting
Other bias	Low risk	The study appears to be free of other sources of bias

Khoromi 2007

Study characteristics

Methods	Single-centre, randomised, double-blind, active placebo-controlled, 4-period cross-over design for 9 weeks each period
Participants	Pain model: chronic sciatica (> 4/10 pain intensity). Median age: 52.5 (range 30 to 64) and duration of pain 5 (0.3 to 37) years. 61 patients were screened, 55 randomised and 28 completed all 4 treatment periods. 14/28 of the completers were female. Baseline pain score (average leg) was: 4.9 ± 2.43. Medications: before the beginning of the trial, 22/28 of the completers were taking NSAIDs, 8 were taking opioids, 3 anticonvulsants, one antidepressants, 3 muscle relaxants and 15 were taking other drugs.
Interventions	During 5 weeks of dose escalation and 2 weeks of maintenance at the highest tolerated dose patients received BID sustained-released morphine (15 to 90 mg; mean 62 mg), nortriptyline (25 to 100 mg; mean 84 mg), their combination (morphine 49 mg and NT 55 mg) or benztropine-active placebo (0.25 to 1 mg); subsequently, 2 weeks of tapering; next period started one pain score reached > 4/10. Opioids and antidepressants were not allowed. NSAIDs and acetaminophen were used as rescue medications.
Outcomes	The primary outcomes: mean scores for average leg pain during the maintenance weeks. Pain diaries consigned 0 to 10 pain score at bedtime, average back, leg and overall pain, worst back, leg and overall. Secondary: global pain relief scores, Oswestry low back pain disability questionnaire, BDI, SF-36 and general health status instrument.
Notes	A carry-over effect was not noticed between treatments. 27/55 (49%) participants did not complete the 4 periods of treatment.

Risk of bias

Khoromi 2007 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were assigned by random numbers within blocks of four to one of four treatment sequences specified by a Latin square".
Allocation concealment (selection bias)	Low risk	"Randomization was performed by the NIH Pharmaceutical Development Service".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"During the MS Contin treatment period, each blue pill contained MS Contin 15 mg and each pink pill contained inert placebo"...
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The rate of guessing by the nurses was above the rate for chance only (> 25%), but did not reach a high percentage
Incomplete outcome data (attrition bias)	High risk	Substantial dropout rate; however, missing outcome data were balanced across groups
Selective reporting (reporting bias)	Low risk	Not apparent selective outcome reporting. The expected outcomes for a pain clinical trial were reported.
Other bias	High risk	Fewer than 50 participants per period of treatment trial

Lopez-D'alessandro 2011

Study characteristics

Methods	Single-centre, randomised, double-blind, placebo-controlled, clinical trial with 60 days follow-up
Participants	120 patients were selected among those patients with burning mouth syndrome (BMS) who had been treated at the service between March 2003 and March 2008, without responding to the applied treatments. A total of 120 patients with idiopathic BMS of more than 3 months duration that wanted to participate voluntarily were included. Polypharmacy patients using more than 3 systemically daily drugs, those ones taking psychotropic and antihypertensives drugs as well as patients with serious psychiatric conditions previously diagnosed were excluded. Patients with deficiencies of folic acid, vitamin B, carriers of anemias of any kind and patients with Sjögren syndrome were also excluded. The pre-trial analgesic profile of the participants is not described in the publication.
Interventions	6 treatment cycles were determined: cycles A, B, C, D, E and F, so that cycle A (n = 20) corresponded to 600 mg/day of alpha lipoic acid (ALA), the cycle B (n = 20) 300 mg/day of gabapentin (GABA), the cycle C (n = 20) to the combination of both drugs and the cycles D (n = 20), E (n = 20) and F (n = 20) were 100 mg/day of starch and cellulose (placebo). The support staff of our service made a draw with 6 balls to link the groups with the cycles of treatment. After the draw, the 3 groups were combined with cycles D, E and F to be treated with placebo, thus forming a single group for these patients, Group D (n = 60) or control group.
Outcomes	To evaluate the changes that occurred with the taking of the different drugs, it was established that the improvements (positive changes) involved the passage of a certain level or numerical category of burning to a lower one, the deteriorations (negative changes) involved an increase of a certain level of burning to a higher one and the total resolution indicated the total absence of burning, that is to say the transition from any higher value to zero value. In this way 4 categories were obtained for the analysis of the results: Category 1: with negative changes (deterioration), Category 2: no changes; Category 3: with positive changes (improvements) and Category 4: with total recovery.

Lopez-D'alessandro 2011 *(Continued)*

Notes	Pain intensity was not recorded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The support staff of our service made a draw with 6 balls to link the groups with the cycles of treatment. After the draw, the three groups were combined with cycles D, E and F to be treated with placebo, thus forming a single group for these patients..."
Allocation concealment (selection bias)	Unclear risk	"...allocation that was always masked to both patients and researcher, through the use of capsules of similar size and appearance so that just the support staff was the one who recorded the information..." For low risk of bias allocation concealment is required the use of identical appearance containers or to describe the use of a central allocation place (pharmacy).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...through the use of capsules of similar size and appearance so that just the support staff..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	If the same assessors who noticed treatment-related side effects were also assessing pain outcomes, they might be biased
Incomplete outcome data (attrition bias)	Unclear risk	"All subjects were evaluated through an Intention-to-Treat Analysis which would take into account all patients although they could discontinue the treatment".
Selective reporting (reporting bias)	Unclear risk	The study was not registered (to compare protocol and publication outcomes), however the outcomes selected are clinically relevant
Other bias	Unclear risk	Fewer than 50 participants per arm of treatment

Lynch 2003

Study characteristics

Methods	Single-centre, randomised, double-blind, placebo-controlled, 4-period cross-over design, 2 days trial plus 7 days of open-label follow-up for responders
Participants	Pain model: at least moderate chronic neuropathic pain. Mean age: 58.7 (SD 12.9) and duration of spontaneous pain 43.8 months). 21 participants were randomised and 20 completed the study, however, analyses were conducted in 18 due to incomplete data. 12/20 of the completers were female. Baseline pain score ranged between 4.4 (SD 2.0) and 5.0 (2.3). Pre-trial analgesic profile: subjects were permitted to continue using previous analgesics including NSAIDs, opioids, antidepressants, and anticonvulsants.
Interventions	Participants received 5 ml of topical treatment: 1% amitriptyline, 0.5% ketamine, the combination and placebo q6h for periods of 2 days. Creams were identical. A return to baseline pain was required between treatments.
Outcomes	Reported outcomes: McGill Pain Questionnaire, VAS present pain intensity, 0 to 10 pain relief, blood levels of medications and side effects

Lynch 2003 *(Continued)*

Notes	3/21 (14.2%) participants did not complete the 4 periods of treatment. Small size trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation is not stated
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All topical formulations were prepared by the study pharmacist using the same vehicle and were identical in consistency, color, and volume".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessor was not biased by the side effects, given that the incidence of those ones was negligible
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Not apparent selective outcome reporting. Trial registration is not reported.
Other bias	High risk	Fewer than 50 participants per period and < 8 weeks duration of trial

Lynch 2005

Study characteristics

Methods	Multi-centre, randomised, double-blind, placebo-controlled, parallel design for 3 weeks
Participants	Pain model: chronic, > 3 months and moderate-severe, neuropathic pain. Median age: 51 and duration of spontaneous pain: 3 to 264 months. 140 participants were screened, 92 participants were randomised and 80 completed the study; 45/92 were female. baseline pain score ranged between 6.66 (SD 1.22) and 7.38 (1.23). Participants were permitted to continue using pre-study oral analgesics including non-steroidal anti-inflammatory drugs, opioids, antidepressants (including amitriptyline and other tricyclics) and anticonvulsants.
Interventions	Participants received 4 ml of topical treatment: 2% amitriptyline, 1% ketamine, the combination or placebo TID for 3 weeks. Creams were identical. Blood samples were takes for assay of amitriptyline and ketamine.
Outcomes	The primary outcomes were 11-point NRS for pain intensity (daily measures) and SF-MPQ (first visit and at the end of the 3 weeks). Secondary measures: evoked pain: dynamic tactile allodynia, pinprick hyperalgesia, pinprick hyperaesthesia, pain disability index, 0 to 10 patient satisfaction and plasma concentrations.
Notes	12/92 (13%) dropout from the study mostly due to adverse events (5/12)

Risk of bias

Lynch 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence genera-tion (selection bias)	Low risk	"Subjects were randomly assigned to one of four treatment groups using a computer-generated randomization list".
Allocation concealment (selection bias)	Low risk	"The study medication containers were numbered sequentially. The manufac-turing site (Pharmaform LLC, Austin, TX) was separate from the study site".
Blinding of participants and personnel (perfor-mance bias) All outcomes	Low risk	"All topical formulations were identical in consistency, color, and volume".
Blinding of outcome as-sessment (detection bias) All outcomes	Unclear risk	It is unclear if the outcomes assessor was involved in the clinical evaluation. This issue can introduce bias.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (re-porting bias)	Low risk	Outcomes reported are normally used for pain clinical trials
Other bias	High risk	Fewer than 50 participants per period and < 8 weeks duration of trial

McCleane 2000

Study characteristics

Methods	This trial was a single-centre, randomised, double-blind, active and placebo-controlled, parallel design for 4 weeks
Participants	Pain model: neuropathic pain unresponsive or intolerant to codeine, NSAIDs or TCAs. Mean age/dura-tion of pain in months: placebo 45.4 (SD 13.6)/57.9 (SD 54.6); doxepin 47.8 (SD 17.2)/59.6 (SD 62.3); cap-saicin 47.8 (SD 27.8)/59.4 (SD 47.9); combination 43.6 (SD 12.9)/74.9 (SD 66.3). 200 participants were randomised and 151 completed the study. 88/151 were female. Baseline pain score ranged between 7.11 and 7.47.

All patients had pain that was unresponsive to simple or compound codeine-containing analgesics or non-steroidal anti-inflammatory drugs. All patients had tried oral TCAs for their pain and had either been unresponsive or intolerant. |
Interventions	Participants received TID topically: 3.3% doxepin, 0.025% capsaicin, the combination and placebo. Creams were identical.
Outcomes	Primary outcome: 0 to 10 average 24-hour pain intensity on a weekly basis, willingness to continue in the study and side effects profile
Notes	49/200 dropout from the study; reasons are unclear

Risk of bias

Bias	Authors' judgement	Support for judgement

McCleane 2000 *(Continued)*

Random sequence generation (selection bias)	Low risk	"patients were randomly allocated, using a computer generated random number list..."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All study creams were white, odourless, had a similar nongreasy texture and they were contained in identical screw top containers marked with the appropriate randomization letter..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	If the same assessors who noticed drug-related side effects were also assessing pain outcomes, they might be biased
Incomplete outcome data (attrition bias)	High risk	Significant dropout rate and data are not presented
Selective reporting (reporting bias)	High risk	Data are not reported
Other bias	High risk	< 8 weeks duration of trial

McCleane 2003

Study characteristics

Methods	This trial was a single-centre, randomised, double-blind, placebo-controlled, add-on, cross-over design for 3 periods of 2 weeks each
Participants	Pain model: severe chronic neuropathic pain unresponsive or intolerant conventional analgesia. Mean age: 46.8 years (SD 10.3). 52 patients were screened, 44 randomised and 39 completed the 3 periods of treatments. 23/39 completers were female. The study included patients unresponsive to tricyclic antidepressants, anticonvulsants, opioids and non-steroidal anti-inflammatory drugs.
Interventions	2 weeks before starting the double-blind periods, patients started oral morphine 20 mg BID. "If subjects were experiencing pain relief with their morphine or getting intolerable side effects from its use, they were withdrawn from the study"; at day 0, participants were randomised to placebo, L-365,260 30 mg daily or L-365,260 120 mg divided in 3 doses.
Outcomes	Outcomes explored: 0 to 11 Likert scale and categorical pain score. Sedation score. Likert scale for sleep. ECG, renal and liver function, full blood count, return of unused medication. Morphine and rescue medication intake.
Notes	No changes were observed in any of the measured pain parameters during the periods of treatment. 39/44 participants finished the 3 periods of treatment. No data were published.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation is not stated

McCleane 2003 *(Continued)*

Allocation concealment (selection bias)	High risk	Unclear who did the randomisation and whether study personnel were able to predict treatment allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Placebo and L- 365,260 capsules were identical in appearance..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	If the same assessors who noticed drug-related side effects were also assessing pain outcomes, they might be biased. Also, SEs not reported.
Incomplete outcome data (attrition bias)	High risk	Data are not presented
Selective reporting (reporting bias)	High risk	Data are not presented
Other bias	High risk	Fewer than 50 participants per period and < 8 weeks duration of trial

Mercadante 2002

Study characteristics

Methods	This trial was a single-centre, randomised, double-blind, placebo-controlled, add-on, cross-over design for 2 periods of 1 week each
Participants	Pain model: patients on morphine therapy due to neuropathic cancer pain. Mean age: 67.1 years. 16 patients were randomised and 15 completed the 2 periods of treatment. 6/16 patients were female. Participants with at least moderate pain and stable doses of morphine in the last 2 days were included. Participants that were users of treatment failure of antidepressants were not included in the study.
Interventions	Patients received 25 mg of amitriptyline or equivalent drops of placebo at night for 3 days plus 50 mg for the following 4 days. Patients were in stable dose of morphine.
Outcomes	Outcomes reported: pain intensity in a 0 to 10 scale. Adverse effects, mood and sleep were recorded in 0 to 3 scales. Patient's preference was recorded at the end of the study.
Notes	Small size trial (16) and small period of treatment (only 1 week)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation is not stated
Allocation concealment (selection bias)	Unclear risk	Not enough information to determine if the allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information

Mercadante 2002 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	If the same assessors who noticed drug-related side effects were also assessing pain outcomes, they might be biased
Incomplete outcome data (attrition bias)	Low risk	Very low dropout rate
Selective reporting (reporting bias)	Low risk	Pain score is standard in pain clinical trials. The trial does not state if it was registered.
Other bias	High risk	Fewer than 50 participants per period and < 8 weeks duration of trial

Tonet 2008

Study characteristics

Methods	Single-centre, randomised, double-blind, active-controlled, parallel design for 1 month
Participants	Pain model: neuropathic pain including participants diagnosed with sciatica, PHN, PDN, CRPS I, CRPS II and post-traumatic nerve injury. Mean age: group 1, 55.1 ± 15.5 and group 2, 48.5 ± 15.6). The number of participants screened is unclear, 30 participants were randomised and 23 completed the trial. 8/30 of the randomised were female. The minimum pain intensity for inclusion is unclear, however, the baseline pain score (0 to 10) were: 7.7 ± 1.6 (group 1) and 7.1 ± 1.8 (group 2). Opioid users were excluded from the study. Codeine was used for analgesic rescue.
Interventions	The group 1 received oral ketamine 10 mg TID + amitriptyline 25 mg/day + carbamazepine 600 mg/day; the group 2 received oral placebo + amitriptyline 25 mg/day + carbamazepine 600 mg/day; amitriptyline was started at 12.5 mg for 3 days and then increased up to 25 mg. Increasing doses of carbamazepine (every 3 days) were administered, starting at 100 mg TID up to 600 mg/day. Codeine was allowed as rescue medication at a maximum dose of 30 mg q6h.
Outcomes	A numerical 0 to 10 rating scale was used for pain intensity and pain relief. Side effects were recorded too.
Notes	7/30 participants dropout from the study due to side effects of the medications

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Ketamine and placebo bottles were identical in solution".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	If the same assessors who noticed drug-related side effects were also assessing pain outcomes, they might be biased

Tonet 2008 *(Continued)*

Incomplete outcome data (attrition bias)	Unclear risk	Substantial dropout rate
Selective reporting (reporting bias)	Low risk	Outcomes reported are standard in pain clinical trials
Other bias	High risk	Fewer than 50 participants per arm and < 8 weeks duration of trial

Zin 2010

Study characteristics

Methods	Single-centre, randomised, double-blind (for oxycodone only), placebo-controlled, parallel design for 5 weeks
Participants	Pain models: adult participants diagnosed with postherpetic neuralgia (pain duration > 3 months and < 5 years) or painful diabetic neuropathy (pain duration > 1 year and < 5 years); pain intensity ≥ 4/10. Mean age: pregabalin/oxycodone: 70.27 and pregabalin/placebo: 66.8. 134 participants were screened, 62 randomised and 51 completed the trial. 27/62 patients randomised were female. Baseline pain scores were 6.85/10 in the pregabalin/oxycodone group and 6.73 in the pregabalin/placebo group. Medications that might possibly affect painful symptoms including opioid analgesics, anticonvulsants (e.g. gabapentin, pregabalin, sodium valproate, lamotrigine), tricyclic antidepressants, capsaicin, benzodiazepines and skeletal muscle relaxants were gradually withdrawn during the study-washout period. Paracetamol was allowed as rescue medication.
Interventions	randomised, double-blind and fixed dose of oxycodone or placebo mixture for 1 week; subsequently, participants received titrated doses of pregabalin (75 to 600 mg/day) during 4 weeks. Acetaminophen was allowed as rescue medication.
Outcomes	Primary outcome: a 2 cm drop in the pain intensity score and a pain score < 4 cm. Pain reduction > 50% was considered a pain responder. Secondary outcomes: sleep interference score, neuropathic pain scale, SF-36, Profile of Mood States, Trial Making Test B, Patient Global Impression of Change and Clinical Global Impression of Change.
Notes	3/4 dropouts secondary to adverse effects were before starting pregabalin. Significant differences in the duration of PDN between groups being longer in the pregabalin/oxycodone. A small and fixed dose of oxycodone was used.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were assigned to 1 of 2 treatment groups using a computer-generated randomization number".
Allocation concealment (selection bias)	Low risk	"The randomization sequence list was controlled independently by the clinical pharmacist".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"the oxycodone and placebo mixture were identical to ensure that study blinding was maintained..."
Blinding of outcome assessment (detection bias)	Unclear risk	If the same assessors who noticed drug-related side effects were also assessing pain outcomes, they might be biased

Zin 2010 *(Continued)*

All outcomes

Incomplete outcome data (attrition bias)	Low risk	Non-significant dropout rate. All analyses were conducted on an ITT basis.
Selective reporting (reporting bias)	Low risk	Outcomes reported are standard and recommended for pain clinical trials
Other bias	High risk	Fewer than 50 participants per period and < 8 weeks duration of trial

ALA: alpha lipoic acid; APAP: acetaminophen; BDI: Beck Depression Inventory; BID: twice a day; BMS: burning mouth syndrome; BPI: Brief Pain Inventory; CRPS: complex regional pain syndrome; ECG: electrocardiogram; GABA: gabapentin; ITT: intention-to-treat; LOCF: last observation carried forward; MMPI: Minnesota Multiphasic Personality Inventory; NSAID: non-steroidal anti-inflammatory drug; NT: nortriptyline; prn: as needed; PDN: Painful Diabetic Neuropathy; PHN: postherpetic neuralgia; SD: standard deviation; SE: standard error; SF-MPQ: Short Form of the McGill Pain Questionnaire; SSRI: selective serotonin re-uptake inhibitor; TCA: tricyclic antidepressant; TID: three times a day; VAS: visual analogue scale.

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

Study	Reason for exclusion
Abbas 1997	Vitamins are not considered analgesics
Achar 2010	Open-label study
Aldrete 2006	Non-neuropathic pain condition
Alvaro 1999	Non pharmacological therapy; out of the scope of this review
Amjad 2005	Invasive/injection therapy out of the scope of this review
Amr 2011	Invasive/injection therapy out of the scope of this review
Arai 2010	Open-label study
Argoff 2004	Open-label study
Atiyat 2000	Single cohort study
Autio 2004	Invasive/injection therapy out of the scope of this review
Barbarisi 2010	Non pharmacological therapy; out of the scope of this review
Baron 2009b	Open-label study
Battla 1981	Cohort study
Bertolotto 2012	Open-label study
Bestard 2011	Open-label study
Blonna 2004	Invasive/injection therapy and open-label study
Braun 1982	Invasive/injection therapy out of the scope of this review

Study	Reason for exclusion
Bush 1991	Invasive/injection therapy out of the scope of this review
Canovas 2009	Open-label study
De Benedittis 1992	Head to head comparison of single agents
Deshpande 2006	Secondary analysis of Gilron 2005
Devulder 1999	Non-neuropathic pain condition
Dureja 2010	Invasive/injection therapy out of the scope of this review
Eardley 2010	Open-label study
Eker 2012	Invasive/injection therapy out of the scope of this review
Ertas 1998	2 drugs were mixed but only 1 has an active mechanism of action (Levodopa)
Fliege 1966	Vitamins are not considered analgesics
Fromm 1984	Add-on therapy trial. Only one medication (baclofen) was randomised
Galer 2004	Non-neuropathic pain condition
Galer 2005	Non-neuropathic pain condition
Gatti 2009	Open-label study
Gerson 1977	Open-label study
Glantz 2004	Open-label study
Glynn 1996	Invasive/injection therapy out of the scope of this review
Gobel 1995	Open-label study
Goebel 2003	Study was published as a protocol only
Goldberg 2009	Vitamins are not considered analgesics
Guo 2007	Open-label study
Gustin 2010	20 patients diagnosed with complex regional pain syndrome (CRPS). However, only 5/20 had CRPS type II (documented nerve injury)
Irving 2012	The drug that was co-administered/combined with capsaicin was not controlled
Karppinen 2001	Invasive/injection therapy out of the scope of this review
Keskinbora 2007	Open-label study
Ko 2010	Open-label study
Kochar 1998	Open-label study

Study	Reason for exclusion
Kotani 2000	Invasive/injection therapy out of the scope of this review
Kottschade 2009	Vitamins are not considered analgesics. Abstract/poster.
Kukushkin 1996	Clinical individual experience/narrative review
Lagalla 2002	Vitamins are not considered analgesics
Lampl 2010	Observational study
Langohr 1982	Open-label study
Lauretti 2002	Invasive/injection therapy out of the scope of this review
Lemos 2008	Invasive/injection therapy out of the scope of this review
Levin 2009	Vitamins are not considered analgesics
Martinez 1990	Invasive/injection therapy out of the scope of this review
McCleane 1998	Non-neuropathic pain condition
Mendel 1986	Small size trial (6 participants, only)
Mercadante 1998	Open-label study
Mercadante 2000	The treatment was for only 30 minutes
Minotti 1998	Non-neuropathic pain condition
Palangio 2000	Patients with neuropathic pain were a minority in this trial
Patarica-Huber 2011	The study was randomised but apparently open-label (no information regarding blinding process in the publication)
Pieri 2007	Open-label study
Pirbudak 2003	Invasive/injection therapy out of the scope of this review
Rabben 1999	Single-dose infusion
Rehm 2010	Open-label study
Rodriguez 1999	Open-label study
Romano 2009	Nociceptive and neuropathic pain conditions mixed in the same trial
Russo 2006	Narrative review
Ruts 2007	This trial included paediatric patients
Schechtmann 2010	Invasive/injection therapy out of the scope of this review
Shaibani 2012	The study looks like a combination study, however, quinidine has no analgesic properties and it was administered to optimise the pharmacokinetic profile of desmethorphan only
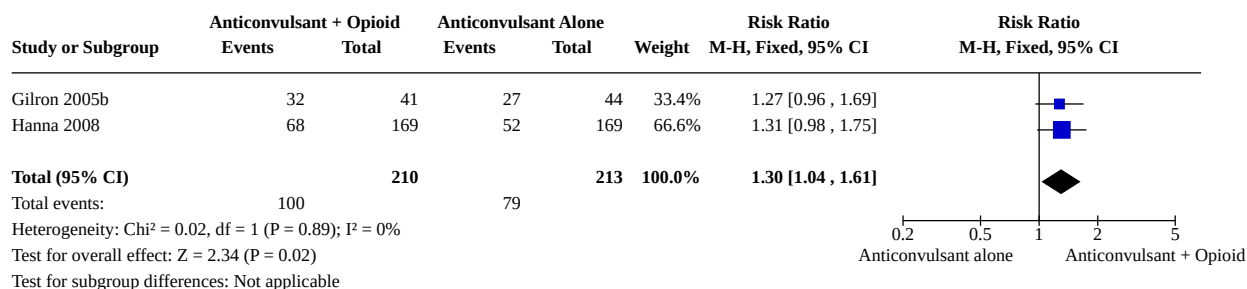
Study	Reason for exclusion
Shlay 1998	Acupuncture plus pharmacological treatment
Siddall 2000	Invasive/injection therapy out of the scope of this review
Silver 2007	This trial included paediatric population
Simpson 2001	A small number of patients completed the study
Stajcic 1990	Invasive/injection therapy out of the scope of this review
Sullivan 2009	Pain intensity was not the primary outcome
Takahashi 2010	Open-label study
Tanenberg 2011	Open-label study
Tian 2005	Chinese medicine plus vitamin trial
Venancio-Ramirez 2004	Open-label study
Wang 2007	Combination including non-pharmacological therapy
Ward 1981	Authors concluded that patients had no neuropathic pain
Winkler 1999	Vitamins are not considered analgesics

DATA AND ANALYSES

Comparison 1. Anticonvulsants and opioids versus anticonvulsants alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 At least moderate/good pain relief	2	423	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.04, 1.61]
1.2 Proportion of patients who dropped out due to side effects	2	433	Risk Ratio (M-H, Fixed, 95% CI)	2.76 [1.47, 5.21]

Analysis 1.1. Comparison 1: Anticonvulsants and opioids versus anticonvulsants alone, Outcome 1: At least moderate/good pain relief

Study or Subgroup	Anticonvulsant + Opioid Events	Total	Anticonvulsant Alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Gilron 2005b	32	41	27	44	33.4%	1.27 [0.96 , 1.69]	
Hanna 2008	68	169	52	169	66.6%	1.31 [0.98 , 1.75]	
Total (95% CI)		**210**		**213**	**100.0%**	**1.30 [1.04 , 1.61]**	
Total events:	100		79				

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.34 (P = 0.02)
Test for subgroup differences: Not applicable

0.2 0.5 1 2 5
Anticonvulsant alone — Anticonvulsant + Opioid

Analysis 1.2. Comparison 1: Anticonvulsants and opioids versus anticonvulsants alone, Outcome 2: Proportion of patients who dropped out due to side effects

Study or Subgroup	Anticonvulsant + Opioid Events	Total	Anticonvulsant Alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Gilron 2005b	6	47	3	48	24.8%	2.04 [0.54 , 7.69]	
Hanna 2008	27	169	9	169	75.2%	3.00 [1.45 , 6.19]	
Total (95% CI)		**216**		**217**	**100.0%**	**2.76 [1.47 , 5.21]**	
Total events:	33		12				

Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 3.14 (P = 0.002)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Anticonvulsant alone — Anticonvulsant + Opioid

ADDITIONAL TABLES

Table 1. Methodology of included analgesic combination trials

Trial ID	Trial comparisons			
	Placebo-controlled	Combination versus only 1 component	Combination versus both components	Combination versus other
Agrawal 2009	+		+	
Amr 2010		+		
Caraceni 2004		+		
Eichenberger 2008	+		+	
Freeman 2007	+			+
Gilron 2005b	+		+	
Gilron 2009			+	
Gomez-Perez 1985	+			
Gomez-Perez 1996				+

Table 1. Methodology of included analgesic combination trials *(Continued)*

Graff-Radford 2000	+	+
Hanna 2008	+	
Khoromi 2007	+	+
Lynch 2003	+	+
Lynch 2005	+	+
McCleane 2000	+	+
McCleane 2003	+	
Mercadante 2002	+	
Tonet 2008	••	
Zin 2010	+	

•• Comparison of amitriptyline + carbamazepine + ketamine versus amitriptyline + carbamazepine + placebo.
'-' No difference between combination and single-agent component.

A P P E N D I C E S

Appendix 1. MEDLINE search strategy

1. Facial Neuralgia/

2. Neuralgia/

3. Causalgia/

4. Hereditary Sensory and Autonomic Neuropathies/

5. neuropath$ or neuralgi$ or radiculopathy

6. or/1-5

7. pain$

8. 6 and 7

9. (combin$ or cotreat$ or co-treat$ or coadministr$ or co-administr$ or synerg$ or isobol$ or add on$ or add-on$)

10. 8 and 9

The search above was combined with the following trial design search filter which was developed for MEDLINE.

Cochrane highly sensitive search strategy for identifying randomised trials in MEDLINE: sensitivity- and, precision-maximising version (2008 revision); OVID format:

1. randomised controlled trial.pt.
2. controlled clinical trial.pt.
3. randomised.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Animals.sh. not (humans.sh. and animals.sh.)
10. 8 not 9"

WHAT'S NEW

Date	Event	Description
30 June 2020	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 1, 2011
Review first published: Issue 7, 2012

Date	Event	Description
7 June 2017	Review declared as stable	See Published notes.
27 June 2012	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

The title was registered by IG. The protocol was developed and written by IG, PW and RAM. IG and LC assessed inclusion of papers and extracted data. LC and IG assumed responsibility for the full review, and write up of the review. PW and RAM contributed to the final draft and approved the final version. LC and IG will be responsible for updating the review.

DECLARATIONS OF INTEREST

In the past five years, IG and RAM have consulted for various pharmaceutical companies. In the past five years, IG and RAM have received lecture fees from pharmaceutical companies that market analgesics and other healthcare interventions. IG and RAM have received research support from charities, government and industry sources at various times, but no such support was received for this work.

Two of the studies included in this review were authored by one of the review authors (IG).

LC has no conflicts to declare.

SOURCES OF SUPPORT

Internal sources

- UK Cochrane Centre, UK

  UK sabbatical residence for IG

External sources

- Canadian Institutes of Health Grant #MCT-94187 and #MSH-55041 to IG, Canada
- IASP J.J. Bonica Trainee Fellowship to LC, USA

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In addition to the pre-planned literature search, we further searched the clinical trials.gov and controlled-trials.com trial databases for completed pharmaceutical industry trials which posted their results on the clinicalstudyresults.org website. We performed a snowballing search to increase the accuracy of the protocol-defined search (Greenhalgh 2005). Given recent updates to the neuropathic pain literature, we also made some revisions to the background section.

NOTES

Assessed for updating in 2017

We performed a full search in May 2017 but we did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

Assessed for updating in 2020

At June 2020 we are not aware of any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be assessed for updating in five years. If appropriate we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitates major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [therapeutic use]; Amines [therapeutic use]; Analgesics [*therapeutic use]; Antidepressive Agents, Tricyclic [therapeutic use]; Benzodiazepinones [therapeutic use]; Cyclohexanecarboxylic Acids [therapeutic use]; Drug Therapy, Combination [methods]; Gabapentin; gamma-Aminobutyric Acid [analogs & derivatives] [therapeutic use]; Morphine [therapeutic use]; N-Methylaspartate [antagonists & inhibitors]; Neuralgia [*drug therapy]; Nortriptyline [therapeutic use]; Phenylurea Compounds [therapeutic use]; Pregabalin; Thioctic Acid [therapeutic use]; Tramadol [therapeutic use]

MeSH check words

Adult; Humans