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[Intervention Review]

# Pharmacologic interventions for treating phantom limb pain

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## ABSTRACT

### Background

This is an updated version of the original Cochrane review published in Issue 12, 2011. Phantom limb pain (PLP) is pain that arises in the missing limb after amputation and can be severe, intractable, and disabling. Various medications have been studied in the treatment of phantom pain. There is currently uncertainty in the optimal pharmacologic management of PLP.

### Objectives

This review aimed to summarise the evidence of effectiveness of pharmacologic interventions in treating PLP.

### Search methods

For this update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE, and Embase for relevant studies. We ran the searches for the original review in September 2011 and subsequent searches for this update up to April 2016. We sought additional studies from clinical trials databases and reference lists of retrieved papers.

### Selection criteria

We included randomised and quasi-randomised trials studying the effectiveness of pharmacologic interventions compared with placebo, another active treatment, or no treatment, in established PLP. We considered the following outcomes: change in pain intensity, function, sleep, depression or mood, quality of life, adverse events, treatment satisfaction, and withdrawals from the study.

### Data collection and analysis

We independently assessed issues of study quality and extracted efficacy and adverse event data. Due to the wide variability in the studies, we did not perform a meta-analysis for all the interventions and outcomes, but attempted to pool the results of some studies where possible. We prepared a qualitative description and narrative summary of results. We assessed clinical heterogeneity by making qualitative comparisons of the populations, interventions, outcomes/outcome measures, and methods.

### Main results

We added only one new study with 14 participants to this updated review. We included a 14 studies (10 with low risk of bias and 4 with unclear risk of bias overall) with a total of 269 participants. We added another drug class, botulinum neurotoxins (BoNTs), in particular botulinum toxin A (BoNT/A), to the group of medications reviewed previously. Our primary outcome was change in pain intensity. Most studies did not report our secondary outcomes of sleep, depression or mood, quality of life, treatment satisfaction, or withdrawals from the study.

BoNT/A did not improve phantom limb pain intensity during the six months of follow-up compared with lidocaine/methylprednisolone.

Compared with placebo, morphine (oral and intravenous) was effective in decreasing pain intensity in the short term with reported adverse events being constipation, sedation, tiredness, dizziness, sweating, voiding difficulty, vertigo, itching, and respiratory problems.

The N-methyl D-aspartate (NMDA) receptor antagonists **ketamine** (versus placebo; versus calcitonin) and dextromethorphan (versus placebo), but not memantine, had analgesic effects. The adverse events of ketamine were more serious than placebo and calcitonin and included loss of consciousness, sedation, hallucinations, hearing and position impairment, and insobriety.

The results for gabapentin in terms of pain relief were conflicting, but combining the results favoured treatment group (gabapentin) over control group (placebo) (mean difference -1.16, 95% confidence interval -1.94 to -0.38; 2 studies). However, gabapentin did not improve function, depression score, or sleep quality. Adverse events experienced were somnolence, dizziness, headache, and nausea.

Compared with an active control benzotropine mesylate, amitriptyline was not effective in PLP, with dry mouth and dizziness as the most frequent adverse events based on one study.

The findings for calcitonin (versus placebo; versus ketamine) and local anaesthetics (versus placebo) were variable. Adverse events of calcitonin were headache, vertigo, drowsiness, nausea, vomiting, and hot and cold flushes. Most of the studies were limited by their small sample sizes.

### Authors' conclusions

Since the last version of this review, we identified another study that added another form of medical therapy, BoNTs, specifically BoNT/A, to the list of pharmacologic interventions being reviewed for clinical efficacy in phantom limb pain. However, the results of this study did not substantially change the main conclusions. The short- and long-term effectiveness of BoNT/A, opioids, NMDA receptor antagonists, anticonvulsants, antidepressants, calcitonins, and local anaesthetics for clinically relevant outcomes including pain, function, mood, sleep, quality of life, treatment satisfaction, and adverse events remain unclear. Based on a small study, BoNT/A (versus lidocaine/methylprednisolone) does not decrease phantom limb pain. **Morphine, gabapentin, and ketamine demonstrate favourable short-term analgesic efficacy compared with placebo.** Memantine and amitriptyline may not be effective for PLP. However, results must be interpreted with caution, as they were based mostly on a small number of studies with limited sample sizes that varied considerably and also lacked long-term efficacy and safety outcomes. The direction of efficacy of calcitonin, local anaesthetics, and dextromethorphan needs further clarification. Overall, the efficacy evidence for the reviewed medications is thus far inconclusive. Larger and more rigorous randomised controlled trials are needed for us to reach more definitive conclusions about which medications would be useful for clinical practice.

## PLAIN LANGUAGE SUMMARY

### Drugs to treat phantom limb pain in people with missing limbs

#### Background

People can experience pain in a missing body part, for example after limb amputation. This is known as phantom limb pain. Various medications have been tried as treatments for phantom limb pain. It is uncertain whether any of the following medications work: botulinum toxin A, opioids, N-methyl D-aspartate (NMDA) receptor antagonists (e.g. ketamine, memantine, dextromethorphan), anticonvulsants, antidepressants, calcitonin, and local anaesthetics. It is unclear whether these medications can help with pain, function, mood, sleep, quality of life, treatment satisfaction, and safety (e.g. adverse events) in the short and long term.

#### Key results

For this updated review, we repeated the search for relevant clinical trials in April 2016. We found one new trial, including 14 studies with a total of 269 participants. One small initial report showed that botulinum toxin A did not reduce phantom limb pain compared to lidocaine/methylprednisolone. Morphine, gabapentin, and ketamine provided short-term pain relief compared with placebo, but the findings were mostly based on small studies. The results for calcitonin (versus placebo; versus ketamine) and local anaesthetics (versus placebo) were variable. The trials were very different, which made it difficult to combine results for the different drugs. Most studies did not report sleep, depression or mood, quality of life, satisfaction with treatment, or the number of people who did not finish the study.

As they relied on a few small studies, results must be interpreted with caution. There was not enough information about long-term effectiveness and safety. Large, good-quality studies with longer follow-ups and outcomes that are important to patients are needed. Bigger and better studies will help us to make firmer conclusions on the best pain relief available for these patients.

## BACKGROUND

### Description of the condition

This review is an update of a previously published review entitled 'Pharmacologic interventions for treating phantom limb pain' in the Cochrane Database of Systematic Reviews Issue 12, 2011.

Phantom limb pain is pain that is experienced in the missing limb and is a well-recognised phenomenon after amputation. It is a major cause of morbidity and has a profound impact on patients' well-being, activity, lifestyle, functioning, activity, employment, and quality of life (Darnall 2005; Desmond 2010; Ehde 2000; Ephraim 2005; Hanley 2004; Hanley 2009; Millstein 1985; Nikolajsen 2001; Penn-Barwell 2011; Pezzin 2000; Robbins 2009; Sherman 1984; Sin 2013; Sinha 2011a; Sinha 2011b; Whyte 2002). Phantom limb pain is present in more than 70% of amputees (Burgoyne 2012; Clark 2013; Ephraim 2005; Hanley 2009; Reiber 2010; Richardson 2006). About 92% of patients experience the onset of phantom pain within a week following amputation (Richardson 2006). In more than 65% of patients, it occurs within the first six months of amputation (Jensen 1985; Richardson 2006). Approximately 39% of patients report severe pain intensity, and 27% complain that it is "extremely bothersome" (Ephraim 2005). Phantom limb pain has been described as aching, cramping, burning, tingling, sharp, shooting, stabbing, mixed burning-tingling or burning-cramping (Clark 2013; Ehde 2000; Jensen 1983).

The aetiology and pathogenesis of phantom limb pain is complex and not well understood, although there is agreement that peripheral and central mechanisms are involved. A cascade of changes at several levels of the nervous system occur, from the transected afferent fibres that exhibit spontaneous and abnormal evoked activity to the heightened activity in spinal dorsal horn and then to more central relays in the thalamus and cortex. Processes such as central sensitisation, cortical reorganisation, neuroplasticity, and gray matter changes are implicated (Bolognini 2013; Elbert 2004; Flor 1995; Giummarra 2011; Jensen 2000; Montoya 1998; Moseley 2012; Preißler 2013; Woolf 2011). Phantom limb pain is often considered neuropathic pain because of the changes that involve the central and peripheral nervous systems.

### Description of the intervention

Unfortunately, the optimal treatment for phantom limb pain is far from satisfactory and remains a challenge to this day, as the pathomechanism is still unclear. The rationale for the use of various pharmacologic agents lies in the multifactorial theorised origins of phantom pain, chronic and neuropathic pain, as well as the awareness of the affective, cognitive, and biologic triggers of phantom limb pain and chronic pain.

Pharmacologic interventions that have been studied in the treatment of phantom limb pain include beta-blockers, calcitonins, anticonvulsants, antidepressants, selective serotonin-reuptake inhibitors (SSRIs), anaesthetics, opioids, tramadol, analgesics, N-methyl D-aspartate (NMDA) receptor antagonists, non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, nerve blocks, synthetic cannabinoids, and botulinum neurotoxins (BoNTs).

### Why it is important to do this review

There are currently no standard guidelines in the pharmacologic management of phantom limb pain, and therefore a review of all available literature is warranted.

## OBJECTIVES

This review aimed to summarise the evidence of effectiveness of pharmacologic interventions in treating phantom limb pain.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We considered randomised and quasi-randomised studies on pharmacologic agents for treating phantom limb pain (PLP) compared with placebo, another active treatment, or no treatment. We excluded studies with sample sizes of 5 or less. We also excluded short abstracts from conferences or meetings with inadequate or no reporting of data.

#### Types of participants

We included studies that involved participants of any age with established PLP. We excluded studies in which participants had stump pain or residual limb pain alone, or postamputation pain that was not phantom pain, or where phantom pain was mixed with other neuropathic pains. We also excluded studies in which participants with phantom pain were mixed with participants with other postamputation pains if no separate or subgroup analyses were reported for phantom pain.

#### Types of interventions

Pharmacologic agents given singly or in combination, in any dose, by any route were eligible. Preoperative, pre-emptive, intraoperative, and perioperative pharmacologic interventions undertaken to prevent PLP were not eligible.

#### Types of outcome measures

##### Primary outcomes

The primary outcome was change in pain intensity on any standard scale.

##### Secondary outcomes

1. Sleep: changes in sleep as measured on any standard sleep scale.
2. Depression or mood: changes in depression or mood scores as measured on any standard depression or mood scale.
3. Function: changes in function as measured on any standard function scale.
4. Quality of life: changes in quality of life scores as measured on any standard quality of life scale.
5. Adverse events.
6. Satisfaction with treatment.
7. Withdrawals from the study.

We considered short-term (less than or equal to 3 months) and long-term (more than 3 months) outcomes.

### Search methods for identification of studies

#### Electronic searches

For this update we identified studies for inclusion by searching:

- The Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane Library, Issue 3 of 12, 2016 (Cochrane Register of Studies Online) (12 April 2016);
- MEDLINE (OVID): September 2011 to March Week 5 2016 (12 April 2016);
- Embase (OVID): September 2011 to 2016 Week 15 (12 April 2016).

See [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#) for the search strategies used.

For the original review we also searched the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS) Trials Register, but as it is no longer regularly updated it was not searched for this update. There were no language restrictions.

### Searching other resources

We sought additional studies from the following clinical trials registries:

- ISRCTN registry (controlled-trials.com) (14 April 2016);
- ClinicalTrials.gov (clinicaltrials.gov) (14 April 2016);
- World Health Organization International Clinical Trials Registry Platform ([who.int/trialsearch/](http://who.int/trialsearch/)) (14 April 2016).

We also searched reference lists of retrieved papers.

### Data collection and analysis

#### Selection of studies

Initially, we (MJA,TAH, MD) independently reviewed the titles and abstracts of all the articles identified by the literature search for relevance to the research question. From the titles and abstracts, we assessed if the study satisfied the inclusion criteria regarding the design, participants, diagnosis, and interventions. We then retrieved the full text of relevant titles and abstracts, and the non-English language articles were translated. Next, we independently performed a final selection of the studies to be included in the review using a predesigned study eligibility form. We resolved any disagreements by discussion. For clarifications and missing information, we contacted authors of the selected studies.

#### Data extraction and management

We (MJA, TAH) independently extracted the data from the studies that satisfied the inclusion criteria and quality standards. Data extraction included study name; design; sample size; study duration (including follow-up period); participant characteristics (demographic and clinical); intervention including dosage, route, and treatment duration; comparator or control interventions; short- and long-term outcome measures; secondary outcome measures; number of participants analysed and dropouts/withdrawals in the different treatment groups; and duration of follow-up. We extracted data onto a specially designed data extraction form. We resolved differences in data interpretation between review authors through discussion.

#### Assessment of risk of bias in included studies

We (MJA, TAH, MD) independently assessed risk of bias for each included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* with regard to random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and

detection bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other types of biases ([Higgins 2011](#)).

- Random sequence generation (selection bias): We assessed the methods used to generate random sequence and graded the risk as follows: low (e.g. computer-generated random numbers, table of random numbers); unclear (method not clearly stated).
- Allocation concealment (selection bias): We assessed the methods used to implement the sequence. Proper allocation sequence concealment gives the assurance that treatments or interventions were allocated without knowing the intervention assignments ahead of time. We graded the risk as follows: low (e.g. use of a third party; use of consecutively numbered, opaque envelopes); unclear (method not clearly stated).
- Blinding (performance bias and detection bias): We assessed the methods used in blinding the participants and evaluators from knowing which intervention was received. We graded the risk as follows: low (e.g. placebo not distinguishable from treatment in colour, dosage, smell, route; evaluators not the same as those who administered the intervention); unclear (method not clearly stated); high (e.g. no blinding; treatment and placebo are distinguishable in colour, dosage, smell, route; outcome assessors are the same as the treating physician or those who administered the intervention). We excluded studies that were not double-blind.
- Blinding of outcome assessment (detection bias): We assessed methods used in blinding evaluators in outcome assessment. We graded the risk as follows: low (e.g. described as blinded; evaluators not the same as those administering intervention); unclear (method not clearly described or stated); high (e.g. no blinding; outcome assessors are the same as the treating physician or those who administered intervention).
- Incomplete outcome data (attrition bias): We assessed the methods used to handle incomplete outcome data. We graded the risk as follows: low (e.g. all participants accounted for in the analysis; intention-to-treat analysis; less than 10% did not complete study); unclear (method not clearly stated; 'last observation carried forward' analysis); high (exclusion of participants, e.g. those who failed to follow up in the final analysis).
- Selective reporting (reporting bias): We graded the risk as follows: low (results for outcomes intended to be assessed as per methods in the full article or publication are reported); unclear (missing outcomes; results not reported or described for outcomes intended to be assessed as per methods in the full article or publication).
- Other types of biases (such as carry-over effect in cross-over design, baseline characteristics): For carry-over effect in cross-over design, we assessed studies as being at low risk when efforts were made to minimise carry-over effect (e.g. adequate wash-out period); or high risk (e.g. no wash-out period; baseline or starting clinical characteristics, such as pain intensity, are significantly different with each intervention); or unclear (strategies are not described).
- Size of study (checking for possible biases confounded by small size): We assessed studies as being at low risk of bias (i.e. 200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); or high risk of bias (fewer than 50 participants per treatment arm).

## Measures of treatment effect

We initially intended to analyse continuous outcomes using mean differences (MD) in the outcome measures with standard deviations (SDs) to quantify the effects of the pharmacologic intervention (change in pain intensity, sleep, mood, depression, function, quality of life, satisfaction); and dichotomous outcomes using risk ratio (RR) and number needed to treat for an additional beneficial outcome (NNTB) for 50% pain relief. However, due to the extensive variation in the outcomes/outcome measures, analyses, follow-ups, study designs, interventions, and the reporting of results in the 14 studies included in the review, pooling of the results into a fully satisfactory meta-analysis was not possible. For some outcomes in a few studies, we combined results where possible.

## Unit of analysis issues

We incurred a unit of analysis error for combining the results of some cross-over studies (Maier 2003; Wiech 2004), which we acknowledged in the Discussion. For the mentioned studies, we considered all measurements from treatment (memantine) periods and all measurements from control periods and analysed as if the trial was a parallel-group study of treatment versus control. With this approach, the number of observations in the analysis did not correspond to the number of 'units' (participants) that were randomised. In these cross-over studies (Maier 2003; Wiech 2004), a participant underwent more than one intervention (treatment and control), and therefore there is not just one but two measurements for each outcome from each participant analysed. There was thus doubling of the sample size in the analysis. However, as the studies combined using this approach were underweighted, this unit of analysis error may be regarded as less serious than other types of unit of analysis error (Higgins 2011).

## Dealing with missing data

We encountered missing data for some cross-over studies that we were attempting to combine. For example, in the case of the gabapentin studies (Bone 2002; Smith 2005), standard errors (for treatment effects) were not reported. We performed imputations to enable pooling of results of these studies in a meta-analysis.

## Assessment of heterogeneity

We also initially intended to assess the amount of statistical heterogeneity among the studies by computing the  $I^2$  statistic. However, this was not possible for all studies and outcomes due to the differences in the methods as well as in the reporting and presenting of outcomes and results that could not be combined and analysed. We therefore assessed clinical heterogeneity by making qualitative comparisons in terms of the populations, interventions, outcomes/outcome measures, and methods.

## Assessment of reporting biases

We did not perform assessment of publication bias because tests are unreliable. Excluding non-published studies - particularly those with negative results - may overestimate treatment effects, which we acknowledged in the Discussion.

## Data synthesis

Due to the extensive variation in the outcomes/outcome measures, analyses, follow-ups, study designs, interventions, and reporting of the results in the 14 included studies, pooling of the results into a fully satisfactory meta-analysis was not possible. We primarily prepared a qualitative description or narrative summary of the results. We grouped the studies by drug class, namely botulinum neurotoxins, NMDA receptor antagonists, anticonvulsants, antidepressants, calcitonins, opioids, and local anaesthetics. For a few studies, we combined results of outcomes where possible.

## Subgroup analysis and investigation of heterogeneity

We did not perform subgroup analysis, as there were only a few studies included, with one to two studies per drug class. Furthermore, the differences in the methods and analyses, and reporting and presenting of outcomes and results precluded performance of subclass analyses.

## Sensitivity analysis

We planned no sensitivity analysis because the evidence base was known to be too small to permit reliable analysis.

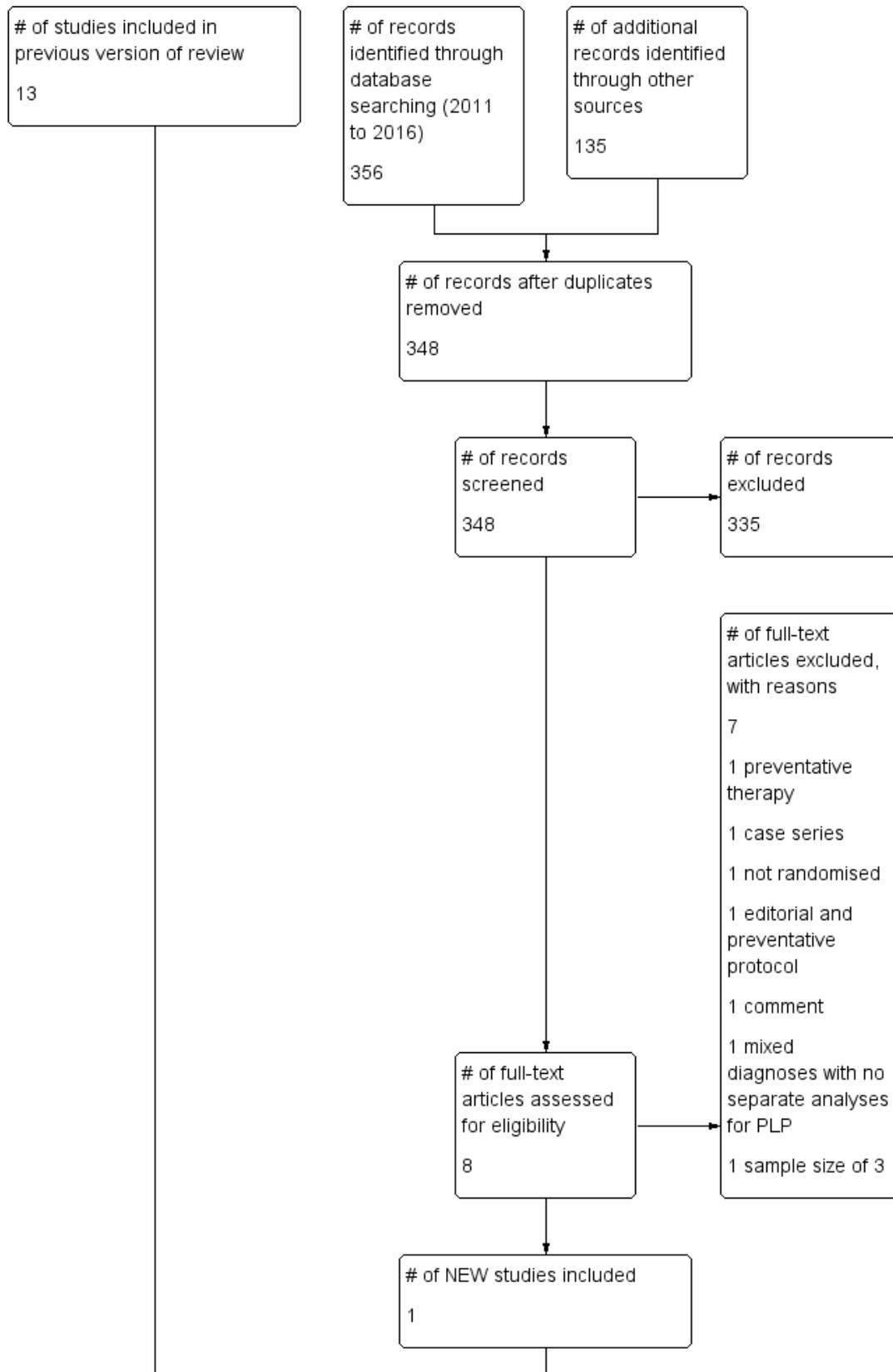
# RESULTS

## Description of studies

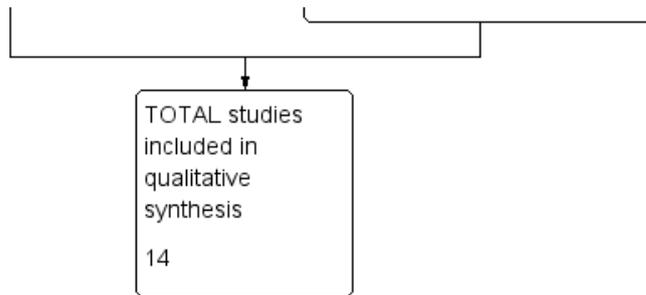
### Results of the search

We included 14 studies with a total of 269 participants in this update. The original version of the review identified 13 studies from 583 titles and abstracts from electronic database searches. For this update, we identified 348 titles and abstracts from the new searches. After initial screening, we excluded 335, as these were irrelevant to the research question, case series, non-pharmacologic, preventive, preoperative and pre-emptive, protocols and ongoing trials, reviews, descriptions of programs and interventions for phantom pain, comments, letters, editorials, conference abstracts, and conference proceedings. We selected eight potentially eligible studies for further scrutiny. We performed the final selection using a predesigned study eligibility form, which resulted in one eligible study. Figure 1 shows the results of the search. Figure 2 and Figure 3 show the 'Risk of bias' graph and summary, respectively.

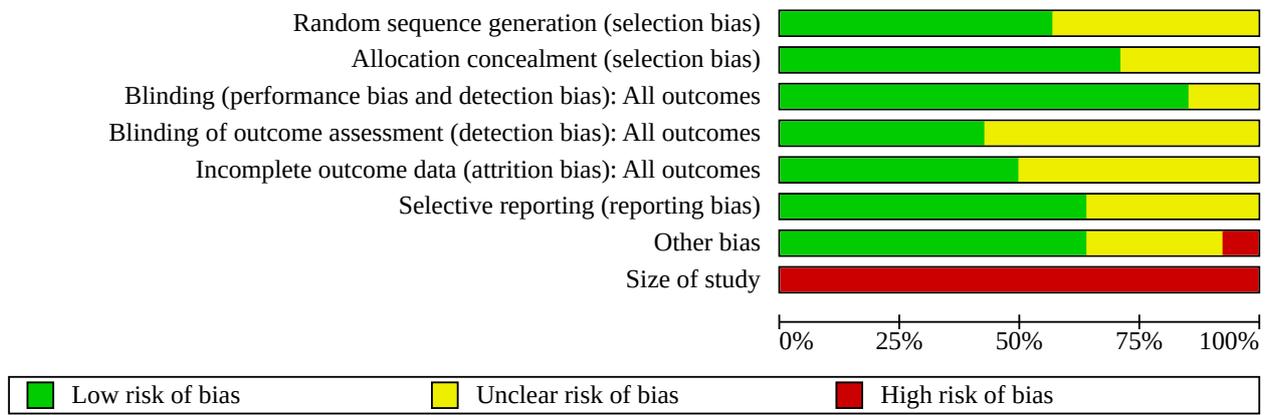
**Figure 1. Study flow diagram.**



**Figure 1. (Continued)**



**Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**



**Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias	Size of study
Abraham 2003	?	+	+	?	+	?	-	-
Bone 2002	+	+	+	?	+	+	+	-
Casale 2009	+	+	+	+	+	+	+	-
Eichenberger 2008	+	+	?	?	?	+	?	-
Huse 2001	?	+	?	?	+	+	+	-
Jaeger 1992	?	?	+	?	?	?	?	-
Maier 2003	+	+	+	?	?	+	?	-
Nikolajsen 1996	?	+	+	?	+	?	+	-
Robinson 2004	+	+	+	+	?	+	+	-
Schwenkreis 2003	+	+	+	+	?	+	+	-
Smith 2005	+	?	+	+	?	?	+	-
Wiech 2004	?	+	+	?	+	+	+	-
Wu 2002	+	?	+	+	+	?	+	-
Wu 2012	?	?	+	+	?	+	?	-

## Included studies

We included 14 studies in this update ( [Abraham 2003](#); [Bone 2002](#); [Casale 2009](#); [Eichenberger 2008](#); [Huse 2001](#); [Jaeger 1992](#); [Maier 2003](#); [Nikolajsen 1996](#); [Robinson 2004](#); [Schwenkreis 2003](#); [Smith 2005](#); [Wiech 2004](#); [Wu 2002](#); [Wu 2012](#) ). We added only one study to the original group of studies reviewed ([Wu 2012](#)). We included another class of drugs, botulinum neurotoxins, in particular botulinum toxin A (BoNT/A), to the six classes of drugs previously reviewed, namely, NMDA receptor antagonists, opioids, anticonvulsants, antidepressants, calcitonins, and local anaesthetics.

Ten studies were cross-over sequences ([Abraham 2003](#); [Bone 2002](#); [Casale 2009](#); [Eichenberger 2008](#); [Huse 2001](#); [Jaeger 1992](#); [Nikolajsen 1996](#); [Smith 2005](#); [Wiech 2004](#); [Wu 2002](#)), and four were parallel, including the newly identified study ([Maier 2003](#); [Robinson 2004](#); [Schwenkreis 2003](#); [Wu 2012](#)). Eleven studies compared the intervention with placebo alone ([Abraham 2003](#); [Bone 2002](#); [Casale 2009](#); [Huse 2001](#); [Jaeger 1992](#); [Maier 2003](#); [Nikolajsen 1996](#); [Robinson 2004](#); [Schwenkreis 2003](#); [Smith 2005](#); [Wiech 2004](#)). Three studies had more than two treatment arms ([Abraham 2003](#); [Eichenberger 2008](#); [Wu 2002](#)). The newly identified study looked at BoNT/A injections ([Wu 2012](#)). Eight studies examined oral medications ([Abraham 2003](#); [Bone 2002](#); [Huse 2001](#); [Maier 2003](#); [Robinson 2004](#); [Schwenkreis 2003](#); [Smith 2005](#); [Wiech 2004](#)); four studies investigated intravenous drugs ([Eichenberger 2008](#); [Jaeger 1992](#); [Nikolajsen 1996](#); [Wu 2002](#)); and one examined myofascial injections ([Casale 2009](#)).

All studies measured pain relief. Four studies assessed change in function or disability ([Bone 2002](#); [Maier 2003](#); [Robinson 2004](#); [Smith 2005](#)). Five studies examined change in mood or depression scores ([Bone 2002](#); [Huse 2001](#); [Maier 2003](#); [Robinson 2004](#); [Smith 2005](#)). One study looked at change in sleep quality ([Bone 2002](#)). One study measured treatment satisfaction ([Wu 2002](#)). Assessment points following application of interventions in the double-blind phase ranged from 30 minutes to 6 months. See [Characteristics of included studies](#).

A total of 269 participants were included in this updated review, with ages ranging from 19 to 81 years. The number of participants per study ranged from 8 to 36. The reasons for the amputations were traumatic, vascular, neoplastic, infectious, and chronic pain syndromes (reflex sympathetic dystrophy). Of these, trauma was most common. The time since amputation varied from within a week to 57 years, while the duration of PLP ranged from less than a week to 49 years. The baseline pain intensity varied from mild to severe.

## Excluded studies

For this update, we excluded seven studies for the following reasons: one was preventative or pre-emptive therapy ([Karanikolas 2011](#)); one was a case series ([Licina 2013](#)); one was not randomised ([Cohen 2011](#)); one was an editorial for a preventative protocol ([Lirk 2012](#)); one was a comment ([Neil 2012](#)); one had a sample size of 3 ([Ilfeld 2013](#)); and one involved people with mixed neuropathic pain diagnoses without separate analyses for PLP ([Van Seventer 2010](#)). See [Characteristics of excluded studies](#).

## Risk of bias in included studies

Sequence generation, blinding of outcome assessment, and completeness of outcome data were most often inadequately reported. Another important source of bias in the review was the small size of studies. See [Characteristics of included studies](#). Overall, we considered 10 studies to be at low risk of bias and 4 to be at unclear risk of bias. See review authors' judgement of 'Risk of bias' items ([Figure 2](#)) and 'Risk of bias' summary for each study ([Figure 3](#)).

### Allocation

Eight studies described the method of random sequence generation ([Bone 2002](#); [Casale 2009](#); [Eichenberger 2008](#); [Maier 2003](#); [Robinson 2004](#); [Schwenkreis 2003](#); [Smith 2005](#); [Wu 2002](#)), and we judged them to be at low risk of bias. The remaining studies did not report the method of random sequence generation, and we judged them to be at unclear risk of bias. Ten studies described the method of treatment allocation (low risk of bias) ([Abraham 2003](#); [Bone 2002](#); [Casale 2009](#); [Eichenberger 2008](#); [Huse 2001](#); [Maier 2003](#); [Nikolajsen 1996](#); [Robinson 2004](#); [Schwenkreis 2003](#); [Wiech 2004](#)), while the remainder of the studies were unclear about their method (unclear risk of bias).

### Blinding

We judged 12 studies to be at low risk for blinding (performance bias) ([Abraham 2003](#); [Bone 2002](#); [Casale 2009](#); [Jaeger 1992](#); [Maier 2003](#); [Nikolajsen 1996](#); [Robinson 2004](#); [Schwenkreis 2003](#); [Smith 2005](#); [Wiech 2004](#); [Wu 2002](#); [Wu 2012](#)). We judged two studies to be at unclear risk ([Eichenberger 2008](#); [Huse 2001](#)). We judged six studies to be at low risk for blinding outcome assessment ([Casale 2009](#); [Robinson 2004](#); [Schwenkreis 2003](#); [Smith 2005](#); [Wu 2002](#); [Wu 2012](#)), while the remainder had an unclear risk ([Abraham 2003](#); [Bone 2002](#); [Eichenberger 2008](#); [Huse 2001](#); [Jaeger 1992](#); [Maier 2003](#); [Nikolajsen 1996](#); [Wiech 2004](#)).

### Incomplete outcome data

We judged seven studies to be at low risk for attrition bias ([Abraham 2003](#); [Bone 2002](#); [Casale 2009](#); [Huse 2001](#); [Nikolajsen 1996](#); [Wiech 2004](#); [Wu 2002](#)), while the remaining studies had an unclear risk ([Eichenberger 2008](#); [Jaeger 1992](#); [Maier 2003](#); [Robinson 2004](#); [Schwenkreis 2003](#); [Smith 2005](#); [Wu 2012](#)).

### Selective reporting

We judged nine studies to have a low risk of reporting bias ([Bone 2002](#); [Casale 2009](#); [Eichenberger 2008](#); [Huse 2001](#); [Maier 2003](#); [Robinson 2004](#); [Schwenkreis 2003](#); [Wiech 2004](#); [Wu 2012](#)), while the remaining studies had an unclear risk ([Abraham 2003](#); [Jaeger 1992](#); [Nikolajsen 1996](#); [Smith 2005](#); [Wu 2002](#)).

### Other potential sources of bias

We judged one study to have a high risk of bias for carry-over effect due to lack of a wash-out period ([Abraham 2003](#)). Three studies had an unclear risk ([Jaeger 1992](#); [Maier 2003](#); [Wu 2012](#)), as the baseline characteristics of the intervention groups were not similar.

### Size of study

All studies had small sample size (fewer than 50 participants per treatment arm), so we judged them to be at high risk of bias.

## Effects of interventions

Table 1 contains a summary of the results for the effects of interventions. Analysis 1.1 and Analysis 2.1 show results for the outcome change in pain intensity for memantine and gabapentin, respectively.

### 1. Botulinum neurotoxins (BoNT/A injections)

The newly identified study in this update is a pilot study investigating the effectiveness of BoNT/A injections in PLP or residual limb pain (RLP), or both (Wu 2012). Fourteen participants with PLP or RLP, or both were randomised into two groups to receive either BoNT/A injections or lidocaine/methylprednisolone injections. The intensity of the phantom limb pain was not improved with either BoNT/A (at 1 ml equivalent to 50 units for each injection site) ( $P = 0.49$ ) or lidocaine/methylprednisolone (1 mL mixture of 0.75 mL lidocaine and 0.25 mL methylprednisolone 40 mg/mL for each painful site) injections ( $P = 0.42$ ). The outcomes sleep, depression or mood, function, quality of life, adverse events, satisfaction with treatment, and withdrawals from the study were not described or reported.

### 2. Opioids

Two cross-over studies investigated the effectiveness of morphine in treating phantom pain (Huse 2001; Wu 2002). One compared oral morphine with placebo (Huse 2001), and the other compared morphine infusion with lidocaine and placebo (Wu 2002).

The pain intensity (mean (SD)) on a 0-to-100 visual analogue scale (VAS) was significantly reduced during the oral morphine phase compared with the placebo phase ( $P = 0.036$ ) at four weeks (3.26 (1.59) versus 3.99 (1.23)). About 42% (5) of participants experienced equal to or greater than 50% pain relief (considered responders in study) with morphine versus one participant in placebo ( $P < 0.05$ ) (Huse 2001). Significantly lower pain intensity was also seen with intravenous morphine compared to placebo ( $P < 0.01$ ) in the other study (Wu 2002). Furthermore, subjective, self reported percentage pain relief was significantly higher with morphine. The NNTB for 30% pain relief for morphine in this study was 1.9 (95% confidence interval (CI) 1.3 to 3.7) (Wu 2002).

As for secondary outcomes, scores on self rating depression scale, West Haven-Yale Multidimensional Pain Inventory, and Brief Stress Scale were not significantly associated with pain reduction (Huse 2001). Treatment satisfaction scores (mean (SD)) were significantly higher in the morphine group compared with placebo (45.9 (35.5) versus 9.6 (21);  $P < 0.01$ ) (Wu 2002).

Adverse events were classified as moderate and were significantly more frequent with morphine. These were tiredness, dizziness, sweating, constipation, micturition difficulties, nausea, vertigo, itching, and short of respiration, but a difference between treatment and placebo groups was only found for constipation (Huse 2001). One participant dropped out due to absence of pain before the start of treatment (Wu 2002).

The outcomes sleep, function, and quality of life were not described or reported in these studies.

### 3. NMDA receptor antagonists

Six studies investigated the effectiveness of NMDA receptor antagonists in established PLP: memantine versus placebo (Maier

2003; Schwenkreis 2003; Wiech 2004); dextromethorphan versus placebo (Abraham 2003); ketamine versus placebo (Nikolajsen 1996); and ketamine versus calcitonin, combination ketamine and calcitonin, and placebo (Eichenberger 2008).

Pain intensity was not significantly decreased with 30 mg/day of memantine for three to four weeks in traumatic amputees with chronic pain (Maier 2003; Schwenkreis 2003; Wiech 2004). Combining the results of two memantine studies for the outcome change in pain intensity showed a standardised mean difference (SMD) 0.24 (95% CI -0.31 to 0.79) (Maier 2003; Wiech 2004), which is an overall effect of no difference between treatment and control groups (Analysis 1.1). In so doing, however, a unit of analysis error was incurred. The cross-over study was treated as though it was a parallel study by taking all measurements from memantine periods and all measurements from placebo periods and analysing these data as in a parallel study comparing memantine versus placebo (Wiech 2004).

In the dextromethorphan study, 4 participants on 120 mg dextromethorphan/day and 1 participant on 180 mg/day reported 50% pain relief compared with placebo ( $P = 0.01$ ) after 10 days of treatment in the double-blind phase (Abraham 2003).

Ketamine at 0.5 mg/kg given once as intravenous infusion significantly reduced pain intensity in a population of 11 participants with chronic phantom pain that was mostly malignant in aetiology ( $P < 0.05$ ) compared with placebo. In another study, pain intensity was significantly decreased with ketamine alone at 0.4 mg/kg and combination ketamine-calcitonin after infusion compared with placebo ( $P < 0.05$ ) in a group of 20 participants with chronic phantom pain of various aetiologies. Ketamine alone and its combination with calcitonin had significant pain reduction of greater than 50% versus placebo (Eichenberger 2008).

Two studies assessed change in mood (depression scores and feelings of well-being scores) (Abraham 2003; Maier 2003). One study found no significant difference in the change in depression scale score between memantine and placebo (Maier 2003). On the other hand, the scores of feelings of well-being were significantly better in the dextromethorphan group compared with placebo ( $P = 0.025$ ) (Abraham 2003). Only one study assessed change in function or disability, where the pain disability index (recreation, social activity, family and home responsibilities, sexual behaviour, occupation, life support) did not change significantly in either group (Maier 2003).

Severe adverse events such as loss of consciousness and other mild/moderate effects such as light sedation, light visual hallucination, hearing impairment, and position impairment were reported with ketamine in one study (Eichenberger 2008). Insobriety, discomfort, and mood elevation were described in another (Nikolajsen 1996). Adverse effects such as nausea, fatigue/tiredness, dizziness/vertigo, agitation/restlessness, and headaches were observed with memantine (Maier 2003; Wiech 2004). No adverse events were observed in any of the participants during dextromethorphan treatment and at one-month follow-up (Abraham 2003). No dropouts or withdrawals were reported in the NMDA antagonists studies, except in one study, where two participants dropped out in the memantine group due to adverse events and three from the placebo group due to insufficient analgesia (Maier 2003).

The outcomes depression or mood, function, and quality of life were reported in some studies. The outcomes sleep and satisfaction with treatment were not described or reported.

#### 4. Anticonvulsants

Two studies examined the effectiveness of gabapentin in treating phantom pain in placebo-controlled, cross-over trials of six weeks' duration (Bone 2002; Smith 2005). In the first study, pain intensity difference on the 100-millimetre VAS (mean (SD)) (converted and presented as centimetre VAS in Bone 2002) was significantly higher with gabapentin at 2.4 g/day at the end of six weeks compared with placebo in a population of 19 participants with chronic phantom pain (3.2 (2.1) versus 1.6 (0.7),  $P = 0.03$ ) (Bone 2002). In the second study of 24 participants with chronic phantom and stump pain following amputation of various aetiologies, average phantom pain intensity differences on the 0-to-10 numerical rating scale (mean (SD)) in the gabapentin phase did not differ significantly from placebo (0.94 (1.98) versus 0.49 (2.20),  $t = 0.70$ ) (Smith 2005). Combining the results of these two studies using the generic inverse variance method for the outcome change in pain intensity showed a mean difference of -1.16 (95% CI -1.94 to -0.38) ( $P = 0.004$ ), favouring gabapentin (Analysis 2.1).

Change in mood/depression and function were evaluated using different outcome scales, so the results could not be combined. The end-of-treatment median (interquartile range) Hospital Anxiety and Depression Scale, Barthel Index, and Sleep Interference Scale were not significantly different between gabapentin and placebo (12 (4 to 22) versus 14 (5 to 25); 85 (70 to 105) versus 87 (65 to 105); 3 (1 to 5) versus 4 (1 to 5)) (Bone 2002), respectively. Average scores for Center for Epidemiologic Studies Depression Scale (CES-D) (mean (SD)) were not significantly different between gabapentin and placebo (4.22 (9.20) versus 3.78 (10.13),  $t = -0.11$ ), respectively (Smith 2005). Craig Handicap Assessment and Reporting Technique (CHART) and Satisfaction With Life Scale (SWLS) change scores were not significant (no values shown) (Smith 2005). Somnolence ( $n = 7$ ), dizziness ( $n = 2$ ), headache ( $n = 2$ ), and nausea ( $n = 1$ ) reported in the gabapentin group were not significantly different from control group (Bone 2002).

The outcomes quality of life and treatment satisfaction were not described or reported in any of the studies.

#### 5. Antidepressants

The only eligible study determined the effectiveness of a 6-week course of amitriptyline in treating phantom pain (versus an active control of benzotropine mesylate) in 39 participants with at least 3 months of phantom or residual limb pain after amputations for various causes (Robinson 2004).

The average PLP on the 0-to-10 numerical rating scale (mean (SD)) was not significantly different between the amitriptyline and active placebo groups at the end of 6 weeks (3.1 (2.7) versus 3.1 (2.9)). The CES-D, Functional Independence Measure, CHART, and SWLS scores (mean (SD)) were not significantly different between amitriptyline and placebo (12.9 (8.5) versus 16.1 (13.1); 74.5 (18.8) versus 79.1 (3.3); 360 (142) versus 417 (75); 21.2 (6.4) versus 21.8 (8.7)), respectively. Mouth dryness, drowsiness, blurred vision, constipation, dizziness, altered sleep, nausea, vomiting, urinary retention, diarrhoea, and tinnitus were reported in the amitriptyline group.

The outcomes sleep, quality of life, and treatment satisfaction were not described or reported.

#### 6. Calcitonins

Two studies examined the effectiveness of s-calcitonin infusion in treating phantom pain (Eichenberger 2008; Jaeger 1992). One study compared it to saline placebo in a group of 21 participants with severe phantom pain developing within a week after amputations of various aetiologies (Jaeger 1992). Another study compared it to ketamine, combination ketamine and calcitonin, and placebo in 20 participants with chronic phantom pain (Eichenberger 2008).

Median pain intensity on a 0-to-10 numerical analogue scale (NAS) was significantly reduced 24 hours after 200 international units (IU) calcitonin infusion ( $P < 0.001$ ) (Jaeger 1992). Four participants in the group where calcitonin infusion was the first of the matched pair of infusions given (one consisting of calcitonin and the other of saline placebo) did not require a second infusion, as they had a NAS of less than 3. In the other study, pain intensity on the 10-centimetre VAS did not significantly decrease with 200 IU calcitonin infusion compared with placebo at 48 hours. Also, the number of responders (equal to or greater than 50% pain relief) to calcitonin did not differ significantly from placebo (2 of 20 versus 1 of 19) (Eichenberger 2008).

Both studies described adverse events. With calcitonin, 2 participants had facial flushing, 5 had nausea, 1 had sedation, and 1 had dizziness (Eichenberger 2008). Twelve of 21 participants experienced one or more of the following adverse events: headache ( $n = 2$ ), vertigo ( $n = 2$ ), nausea ( $n = 6$ ), vomiting ( $n = 5$ ), augmentation of phantom sensation ( $n = 4$ ), drowsiness ( $n = 2$ ), and hot/cold flushes ( $n = 4$ ) (Jaeger 1992). As for withdrawals, no participants withdrew during the double-blind phase in the two-arm study (Jaeger 1992). Dropouts were not described in the calcitonin group in the multi-arm study (Eichenberger 2008).

The outcomes sleep, depression or mood, function, quality of life, and satisfaction with treatment were not described or reported.

#### 7. Local anaesthetics

Two studies examined the effectiveness of local anaesthetics in treating phantom pain. Bupivacaine at 0.25%, 1 mL, as contralateral myofascial injection given once was compared with placebo (0.9% saline) in a randomised cross-over trial (Casale 2009). Lidocaine at 4 mg/kg given as intravenous infusion over 40 minutes was compared with morphine (intravenous infusion) and placebo (diphenhydramine) (Wu 2002).

Contralateral myofascial injection of bupivacaine given once to 8 participants with chronic phantom pain following amputations of various aetiologies afforded significantly greater pain reduction (VAS from 0 no pain to 10 worst pain ever experienced) (mean (SD)) versus placebo one hour after the injection (-5.3 (1.4) versus -1.5 (1.3),  $P = 0.003$ ) (Casale 2009). Phantom pain relief with lidocaine was not significantly different from placebo ( $P > 0.05$ ) in 31 participants with chronic phantom pain (Wu 2002). There were no reported cardiovascular or respiratory problems or any reports of a stinging sensation after the injection (Casale 2009).

The outcomes sleep, depression or mood, function, and quality of life were not described or reported. Only one study reported adverse events.

See [Table 1](#) for a summary of the results.

## DISCUSSION

### Summary of main results

In this update we added another class of drugs, botulinum neurotoxins, in particular botulinum toxin A (BoNT/A), to the list of pharmacologic interventions for treating established phantom limb pain. However, the results of the lone eligible investigation on BoNT/A did not substantially change the main results of the original version of the review.

Firstly, the short- and long-term effectiveness of most pharmacologic interventions in established PLP remains unresolved for clinically relevant outcomes that include pain, function, mood or depression, sleep, quality of life, satisfaction, and safety. Botulinum toxin A was ineffective in phantom limb pain (based on a pilot study) in both short- and long-term (up to six months) time frames. Of the remaining six drug classes reviewed, only morphine consistently demonstrated short-term analgesia (based on two studies:  $n = 12$  (Huse 2001);  $n = 31$  (Wu 2002)), although only one study was adequately powered. The various NMDA receptor antagonists had differential efficacy, in that ketamine and dextromethorphan provided pain relief, and memantine did not. Gabapentin was shown to be beneficial with the pooled results, but these results should be interpreted with caution as computations were based on approximations. The studies on calcitonin and local anaesthetics had conflicting results.

Secondly, there was extensive variation in the methods, interventions, outcomes, outcome measures/scales, follow-ups, data analyses, and reporting and presenting of results. This limited the pooling of results. Clinically relevant outcomes that include function, mood, sleep, quality of life, and satisfaction were missing in the majority of the studies, including the newly identified study.

### Overall completeness and applicability of evidence

Botulinum toxin A injections did not lower phantom limb pain intensity assessed monthly for six months. Botulinum neurotoxins comprise a group of nerve-blocking biologic agents that exert their blocking effect at the neuromuscular junction by preventing the release of acetylcholine (Aoki 2001a; Aoki 2001b). Of the existing seven serotype botulinum toxins, BoNT/A and botulinum toxin B have been studied in amputation-related complications such as pain, hyperhidrosis, and involuntary movements (Charrow 2008; Jin 2009; Kern 2003; Kern 2004a; Kern 2004b; Kern 2011). The rationale for using BoNT/A in phantom limb pain relates to the peripheral mechanisms contributing to PLP. Phantom limb pain is often associated with neuroma, excessive muscle tightness, and spasm. Botulinum toxin A reduces muscular activity as a result of the neuromuscular blockade (Aoki 2001b; Brin 1997; Silberstein 2001). The negative results of this pilot study, Wu 2012, are not congruent with earlier studies (Jin 2009; Kern 2003; Kern 2004a; Kern 2004b). The authors of the study cited the small sample size, low baseline VAS scores, and the heterogeneous patient population included in the study. As this was only a preliminary study, it is difficult to make a definitive conclusion regarding the effectiveness and clinical applicability of BoNT/A in phantom limb pain.

Both oral and intravenous forms of morphine significantly reduced pain intensity. The percentage of participants responding to oral morphine in Huse 2001 was comparable to that of another

study on morphine for postamputation pains (Wu 2008). As for adverse events, reviews on opioids for chronic non-cancer and neuropathic pain also found constipation, along with nausea, vomiting, dizziness, and drowsiness as the most common and significant adverse events (Furlan 2006; Furlan 2011; McNicol 2013; Moore 2005).

The rationale for the use of opioids in PLP stems from the observed efficacy of these medications in neuropathic pain states. As with neuropathic pain, peripheral and central neural mechanisms have been implicated in the pathogenesis of PLP. Also, reviews investigating the prescription and use of opioids, in Hall 2013, as well as the effectiveness of opioids in neuropathic pain conditions (e.g. diabetic neuropathic pain, postherpetic neuralgia) included evidence from PLP trials, albeit results on their effectiveness including long-term adverse events in these conditions have not been strong and conclusive (Finnerup 2015; Furlan 2006; Furlan 2011; Kalso 2004; McNicol 2013). The reasons why opioids might work in phantom pain are not well-understood. Peripherally and at the spinal level, opioids act via presynaptic nerve terminals and postsynaptic neurons involved in pain transmission. Centrally, these drugs may decrease cortical reorganisation, a phenomenon where the topographic representation of lost extremity is shifted to other areas of the cortex and taken over by sensory input from other areas of the body, leading to perceptual remapping following the amputation (Birbaumer 1997; Elbert 1994; Flor 1995; Ramachandran 1992).

The results for the NMDA receptor antagonists as a group were at best equivocal. Blocking the NMDA receptors in the dorsal horn, which play a significant role in central sensitisation, hyperexcitability, and wind-up phenomenon, can decrease pain manifestations. Among the NMDA receptor antagonists, dextromethorphan and ketamine had short-term analgesic effects compared with placebo, but these findings were based on underpowered studies. On the other hand, memantine did not have the same positive effects (Maier 2003; Wiech 2004). The issues raised were low drug dosage, short run-in period, other probable mechanisms that maintain phantom pain aside from the NMDA receptor activation (Maier 2003), time-dependent effect of memantine on neural transmission via NMDA receptor pain maintenance, and the differential affinity of the various NMDA receptor antagonists (Wiech 2004).

The differences in the results for ketamine and memantine are not easily explained. Firstly, the type of neuropathic pain involved could be a factor. Ketamine significantly decreased pain evoked by mechanical stimulation and increased pressure pain thresholds (Nikolajsen 1996). Conversely, memantine in neuropathic pain after amputation, surgery, and postherpetic neuralgia neither decreased mechanical and cold allodynia, mechanical hyperalgesia, and wind-up-like pain nor increased thresholds to mechanical pressure (Eisenberg 1998; Nikolajsen 2000). However, in the included memantine studies, the detailed characteristics of the neuropathic pain were not explicit nor were there outcomes on allodynia, hyperalgesia, wind-up-like pain and pressure pain thresholds. Secondly, the timing of the intervention might be important. Memantine given in combination with brachial plexus blockade in the early postoperative stage significantly decreased the intensity and prevalence of PLP at four weeks and six months (Schley 2007). On the other hand, memantine given in established PLP in the current review led to negative findings. A characteristic of the

populations was continuous pre-existing pain of at least 12 months. Pre-existing pain results in the formation of a somatosensory “pain memory” that indicates long-term changes in the central nervous system (Katz 1990). When this pain memory is in place, functional and structural changes in nociceptive structures have already occurred (Lei 2004). NMDA antagonism might thus no longer be useful in longstanding phantom pain where the neuroplastic changes are already fixed. Thirdly, the route of administration might also be an issue. In this review, intravenous ketamine during the chronic phase of phantom pain altered the pain intensity favourably. On the other hand, all three memantine studies used the oral preparation and demonstrated consistent negative findings.

The results for the analgesic efficacy of gabapentin were contradictory. An earlier study, Bone 2002, indicated positive findings in favour of gabapentin, while a later study, Smith 2005, showed otherwise. Combining the results of the two studies entailed estimating certain parameters that include the treatment effect and its standard error (SE) from each study (Bone 2002; Smith 2005). We approximated the SE in one study given the standard deviations of the pain intensity differences and *n* for treatment and placebo (Bone 2002). In the later study, we computed the SE by dividing the mean difference between placebo and treatment by the given value of the *t* statistic (Smith 2005). We performed the generic inverse variance method for pooled analysis. The pooled estimate suggested a trend favouring gabapentin, but this should be interpreted with caution for reasons mentioned above. A recent review on gabapentin for chronic neuropathic pain that included PLP found that gabapentin was better than placebo and that 34% to 38% of participants experienced at least 50% pain relief with the drug (Moore 2014). Adverse events were also significantly more frequent with gabapentin in this review (Moore 2014), compared to the Bone study.

The negative results for amitriptyline (based on only one study) were attributed to a missed a small treatment effect, insufficient duration of treatment (six weeks), and the type of participants included (Robinson 2004). Tricyclic antidepressants including amitriptyline have been considered first-line drugs for neuropathic pain (Finnerup 2015; Moulin 2014; Tan 2010). However, a recent meta-analysis that focused on amitriptyline in neuropathic pain showed a lack of good-quality studies to support its beneficial effects or lack of effect (Moore 2015). Furthermore, the review suggested that it may benefit a few and select group of patients, but not the majority (Moore 2015).

The findings on the analgesic action of calcitonin were contrasting. The earlier study involved participants with acute phantom pain (developing within seven days after amputation) (Jaeger 1992), whereas the later study included participants with years of history of phantom pain (Eichenberger 2008). The mechanism involved in the analgesic action of calcitonin is unclear, although its direct central action is likely the main mechanism, as suggested by its inhibitory effect on the neuronal firing in response to peripheral stimulation and the finding of its receptors in the central nervous system structures (Azria 2002). The ineffectiveness of calcitonin in one study was attributed to its possible lack of effect on central sensitisation processes, which are important in phantom pain pathophysiology (Eichenberger 2008).

The results for the local anaesthetics (lidocaine, bupivacaine) were variable. While both are sodium channel blockers, they

were administered via different routes. Lidocaine at 4 mg/kg was administered systemically as an infusion, whereas bupivacaine at 2.5 mg was given locally as an injection. Lidocaine infusion was ineffective in PLP, as the mechanisms responsible for PLP are primarily considered to be central, although peripheral inputs are important in maintaining pain. Lidocaine is considered to act for the most part in the periphery by decreasing ectopic discharge following peripheral nerve injury (Wu 2002). Conversely, bupivacaine injection to contralateral myofascial hyperalgesic areas decreased phantom pain intensity (Casale 2009). The mechanism of pain relief from local anaesthetic contralateral injection is not clear. In animal experiments, blocking afferent inputs on the contralateral side can decrease the spontaneous hyperactivity and after discharges following noxious evoked responses in the wide dynamic response neurons in the ipsilateral (injured) side (Bileviciute-Ljungara 2001).

Aside from the type of medication, the dosing, route, and ease of administration are also of clinical importance. While some of the drugs were given for a period of days to weeks (oral medications), others were administered as a single dose via relatively more invasive manner (e.g. infusion, injection) such as ketamine, calcitonin, intravenous morphine, and bupivacaine injection. Thus far, outcome assessment, including adverse events, for these single-dose drugs given intravenously or as injections, have been within short time frames (e.g. at the end of infusion, within 30 minutes to 48 hours). Also, the duration of their analgesic effects has not been documented. This may put some degree of uncertainty on the clinical value of such drugs at this stage for this type of pain, which is generally considered chronic.

Other issues that can impact on applicability of evidence are the characteristics of the population and the phantom limb pain. The majority of studies included populations with mixed amputation aetiologies, although predominantly traumatic. In the United States, dysvascular disease accounts for most amputation cases, followed by trauma (motor vehicular accidents) (Sheehan 2014; Ziegler-Graham 2008). Also, as aftermath of the Afghanistan and Iraq wars, major limb amputations constitute 7.4% of major limb injuries, and about 88% of these are attributed to explosive device (Stansbury 2008). Phantom limb pain is more likely in traumatic amputees (Ephraim 2005).

Phantom limb pain chronicity (four months to 12 years) was a feature of the included studies, except for one that dealt with acute phantom pain. None of the studies provided analyses that explored the relationship between chronicity and treatment response, although in general, people with chronic pain usually have a more protracted course of treatment, as there are other associated problems such as mood and sleep disorders. Furthermore, none of the studies described the phantom pain in detail (e.g. frequency, quality, mechanism, severity, etc.). The association between characteristics of the phantom limb pain and response to particular drugs needs further investigation.

The second main finding in this review relates to heterogeneity. The study populations varied, from acute PLP to chronic phantom pain, although most were of the chronic type. Seven groups of interventions examining 10 individual drugs of dissimilar doses (e.g. gabapentin at 2.4 g/day or 3.6 g/day; single intravenous morphine infusion), of differing routes (e.g. oral morphine versus morphine infusion; intravenous lidocaine versus myofascial injection of bupivacaine), and of variable duration of

administration (minutes versus weeks or months) were studied. A wide range of pain scales and measures were utilised (e.g. 11-point numerical rating scale, 0-to-100 VAS, NNTB for 30% or 50% pain relief, McGill Pain Questionnaire). A variety of scales were used to assess secondary outcomes as well (e.g. Functional Independence Measure or Barthel Index for function; the Hospital Anxiety and Depression Scale or Center for Epidemiologic Studies Depression Scale for depression). Outcomes were measured at different time points ranging from 30 minutes to 6 months. The majority of studies had a cross-over design that differed in number of treatment arms, phases (blinded and open), and analyses of the data. The results for outcomes were reported and presented in various ways.

### Quality of the evidence

Studies were generally small and of short duration. Adequately powered studies yield more accurate and reliable estimates of treatment effect. The clinical applicability of interventions for phantom limb pain that is considered chronic would rely on the assessment of clinically relevant outcomes including adverse events over the long term. Also, the completeness of outcome data was questionable in some studies, as the attrition and exclusions from the analyses were not explicit. Another issue was that the majority of the studies had a cross-over design, and the possibility of carry-over effects could not be entirely eliminated. Evaluation of carry-over effects is not straightforward, as statistical techniques to analyse such effects are far from satisfactory and rely for the most part on judgement (Higgins 2011). To reduce the risk of carry-over effects, most of the studies utilised sufficient wash-out periods between treatment periods, except for the dextromethorphan study, which did not report any wash-out periods. Some studies also reported no significant differences in the baseline pain intensity levels between the start of each treatment period to indicate that carry-over effect was unlikely.

### Potential biases in the review process

This review has several limitations. Firstly, all of the included studies had small sample sizes, which made it problematic to form generalisations and conclusions. Secondly, we did not include studies where populations included participants with a diagnosis of postamputation pains with analyses that did not distinguish PLP from the other pains (e.g. postoperative pain, stump pain, etc.). One study found oral morphine to be more effective than placebo and mexiletine in improving pain but not function in people with postamputation pains (Wu 2008). The exclusion of such a study might have led to an underestimation of the analgesic effect of oral morphine in this review. Also, we did not include a negative study on another class of drugs being investigated for phantom limb pain, synthetic cannabinoids, due to the lack of information regarding methods, data, and actual study results, as it was published only as an abstract (Khanahmadi 2012). Thus, the possibility of publication bias thus cannot be entirely discounted. However, the general results of that study based on the abstract would not have changed the main conclusions of this update. Thirdly, we were not able to do a fully satisfactory meta-analysis due to the variability in designs, outcomes and outcome measures, and analyses and reporting of the results. For example, for the opioid and anaesthetic studies, different routes of administration were studied. By combining the results of the memantine studies (Maier 2003; Wiech 2004), we incurred a unit of analysis error, as we treated the cross-over study, Wiech 2004, as though it was a parallel study by taking all measurements from memantine periods and all measurements

from placebo periods and analysing these data as in a parallel study. The analysis assumed that this study had 16 participants, when in reality it had only 8. We thus see in the forest plot that the confidence interval is very wide and that the study has very little weight (Analysis 1.1). But to start with, the trial has a very small sample size, so the presentation of forest plot here does not in fact add more to what the individual results show. The strategy of combining the two gabapentin studies was also not without shortcomings (Analysis 2.1). Ideally, the estimates of the treatment effect with their SEs are available in the study, but in this case, they were not; we therefore performed imputations. We noted, however, that the SE estimate of the positive study with the smaller sample, Bone 2002, was slightly smaller, and hence the weight was larger than that of the study with a slightly bigger sample size. It is possible that there was a little more variability in measurement in the other study (Smith 2005). These pooled results should therefore be interpreted with caution.

### Agreements and disagreements with other studies or reviews

Several reviews have also identified and discussed various modalities of treatment in phantom pain but without firm recommendations on which is the best for clinical use (Foell 2011; Halbert 2002; Manchikanti 2004; Sherman 1980; Wolff 2011). A recent systematic review identified level 2 evidence (classified as "one or more well-powered randomized, controlled trials") for the efficacy of intravenous ketamine and intravenous morphine in phantom limb pain in the short term (McCormick 2014). This shows some agreement with the findings of our review.

A recent meta-analysis on medications for neuropathic pain of various causes including postamputation pain found moderate to strong evidence of efficacy for tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, pregabalin, gabapentin, tramadol, strong opioids, capsaicin patches, and BoNT/A (Finnerup 2015).

## AUTHORS' CONCLUSIONS

### Implications for practice

Since the last version of this review, only one new study representing another class of drugs, botulinum neurotoxins, in particular botulinum toxin A (BoNT/A), has been added to this update. However, the results of the BoNT/A study did not substantially change our conclusion that the short- and long-term effectiveness of pharmacologic interventions for phantom limb pain (PLP) remains unclear.

### For people with phantom limb pain

The information from the studies included in this update is not sufficient to support any particular medication for established PLP. The short- and long-term effectiveness of BoNT/A, opioids, NMDA receptor antagonists, anticonvulsants, antidepressants, calcitonins, and local anaesthetics for clinically relevant outcomes that include pain, function, mood, sleep, quality of life, satisfaction, and adverse events remains unclear. Morphine, gabapentin, and ketamine demonstrate favourable short-term analgesic efficacy, with the caveat that these results were mostly based on small studies that varied considerably and also lacked long-term efficacy and safety outcomes.

### For clinicians

The information from the studies included in this update is not sufficient to support any particular medication for established PLP. The short- and long-term effectiveness of BoNT/A, opioids, NMDA receptor antagonists, anticonvulsants, antidepressants, calcitonins, and local anaesthetics for clinically relevant outcomes that include pain, function, mood, sleep, quality of life, satisfaction, and adverse events remains unclear. Morphine, gabapentin, and ketamine demonstrate favourable short-term analgesic efficacy, with the caveat that these results were mostly based on small studies that varied considerably and also lacked long-term efficacy and safety outcomes. More data are needed to clarify the direction of efficacy of BoNT/A, calcitonins, dextromethorphan, local anaesthetics, and other types of antidepressants. Larger and more rigorous randomised controlled trials are needed to make stronger recommendations about which medications would be useful for clinical practice.

### For policymakers

While the evidence regarding effective treatment in PLP is weak at this stage, pharmacologic interventions such as morphine, gabapentin, ketamine, and amitriptyline are worth considering as treatment given the potential severity of PLP in people with limb loss.

### For funders

While the evidence regarding effective treatment in PLP is weak at this stage, pharmacologic interventions such as morphine, gabapentin, ketamine, and amitriptyline are worth considering as treatment given the potential severity of PLP in people with limb loss.

### Implications for research

The following are research directions that would help in studies on pharmacologic interventions in PLP.

#### General

More data are needed to clarify the direction of efficacy of BoNT/A, calcitonins, dextromethorphan, anaesthetics, and other types of antidepressants. Larger and more rigorous randomised controlled trials are needed to make stronger recommendations about which medications would be useful for clinical practice.

#### Design

Larger (e.g. ideally at least 200 participants per treatment arm) and more rigorous randomised controlled trials with longer duration

(at least 12 weeks) are needed to make stronger recommendations about which medications would be useful for clinical practice.

#### Measurement (endpoints)

Assessment of clinically relevant outcomes, including pain, function, mood, sleep, quality of life, satisfaction with treatment, safety and tolerability, and withdrawals from the study, in longer time frames, would be important and helpful.

#### Others

Evaluation of combination pharmacologic interventions would be worthwhile.

Further investigations of drugs for their effectiveness in people with PLP depending on factors such as PLP chronicity (acute or chronic), patient age, and amputation aetiology (dysvascular, traumatic, or other) are needed. Also, analysis of different sensory profiles (burning pain, sharp pain, stabbing pain, or other) in these patients and response to particular drugs would be useful (pain phenotype).

A register for people with limb loss may be helpful, as this could facilitate research by providing more information about patients such as demographic and clinical characteristics, clinical course, and response to therapy. As such, it could aid in determining evidence-based therapy for this population's medical problems, including phantom limb pain.

Clinical trials evaluating other anticonvulsants and antidepressants that have been found to be effective in other neuropathic pain states would be beneficial.

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**CHARACTERISTICS OF STUDIES**
**Characteristics of included studies [ordered by study ID]**
**Abraham 2003**
**Study characteristics**

Methods	Controlled clinical trial; DB followed by open phase, 3-period, cross-over; no wash-out period; non-involved doctor prepared drugs and order of administration  Ff-up after 10 days of each treatment period (DB phase)
Participants	Severe phantom pain for at least 1 month despite extensive pain therapy; majority of upper and lower extremity amputations of cancer aetiology, rest due to vascular and trauma; 10 participants, 5 males; mean age in yrs (SD): 50 (14); duration of phantom pain, months: 4.8
Interventions	1. dextromethorphan 60 mg for 10 days, oral 2. dextromethorphan 90 mg for 10 days, oral 3. placebo
Outcomes	Number of participants with $\geq$ 50% pain relief on subjective pain intensity score 0 to 100;  Feeling of well-being from 0 to 100;  Sedation score from 0 to 100;  Adverse events;  Dropouts/withdrawals

**Abraham 2003** (Continued)

Notes Limitations related to dosing and small sample size; n = 10

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Physician not involved in study prepared batches of medications and order of administration
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical capsules; outcomes assessed at the medical centre acute pain service
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes assessed at the medical centre acute pain service but not clear if blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data for all
Selective reporting (reporting bias)	Unclear risk	Results in the DB phase reported in graphical form noting level of significance but without numerical results; the results for the specified outcomes in the methods section of the published study were reported, although not necessarily as our preferred outcomes
Other bias	High risk	no wash-out period; carry-over effect not addressed
Size of study	High risk	n = 10

**Bone 2002**
**Study characteristics**

Methods	Randomised, DB, cross-over; 6 weeks each treatment arm; 1 week wash-out period; computer-generated randomisation  Ff-up at 6 wks
Participants	Phantom pain of at least 6 months with pain intensity of at least 40 mm on 100-millimetre VAS scale; majority with lower limb amputations; time since amputation is 18 months; 19 participants, 15 males; mean age, yrs (SD): 56.25 (17.5); baseline mean pain intensity (SD) (converted and presented in cm VAS by Bone 2002 study authors): treatment group 6.1 (1.8); placebo 6.7 (1.9)
Interventions	1. gabapentin titrated in increments of 300 mg up to 2400 mg or maximal tolerable dose for 6 weeks; oral 2. placebo
Outcomes	Change in pain intensity 100-millimetre VAS at end of treatment week 6 vs baseline (converted and presented in cm VAS by Bone 2002 study authors);  Mean pain intensity difference at end of treatment week 6;

**Bone 2002** (Continued)

Categorical phantom pain intensity (0 = none, 1 = mild pain, 2 = moderate pain, 3 = severe pain) end of treatment to baseline;

Change in mood on HADS;

Change in function on BI;

Change in sleep on SIS;

Number of rescue tablets;

Adverse events;

Dropouts/withdrawals

Notes For lifestyle indices, sample size may be too small to rule out type 2 error; used between-group analysis for comparisons; n = 19

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Organized remotely (hospital pharmacist)
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical coded medication bottles containing identical tablets of gabapentin and placebo"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described who assessed and if blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Data from these 19 patients were included in the results presented, using intention-to-treat analysis"
Selective reporting (reporting bias)	Low risk	All specified outcomes in methods section of published study were reported, although not necessarily as our preferred outcomes
Other bias	Low risk	(+) wash-out period; baseline VAS pain score before placebo/gabapentin not significantly different
Size of study	High risk	n = 19

**Casale 2009**
**Study characteristics**

Methods Randomised, DB, cross-over with 72-hour wash-off period; computer-generated randomisation

Ff-up at 60 min after injection

**Casale 2009** (Continued)

Participants	PLP of at least 6 months, lower extremity amputation of traumatic and vascular aetiology; 8 participants, 6 males; mean age, yrs (SD): 70.1 (7.7); baseline pain intensity on VAS from 0 no pain to 10 worst pain ever experienced, mean (SD): 7.9 (0.8) treatment group; 7.6 (0.7) control group
Interventions	1. contralateral myofascial injection with local anaesthetic bupivacaine at 2.5 mg/mL, 1 mL, given once 2. placebo (saline)
Outcomes	Pain intensity on VAS from 0 no pain to 10 worst pain ever experienced;  Mean difference pain intensity;  Adverse events;  Dropouts/withdrawals;  Other outcomes: phantom sensation, mirror displacement in healthy limbs
Notes	Small number of participants; n = 8; preliminary results

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation (confirmed through email correspondence with author)
Allocation concealment (selection bias)	Low risk	"saline or local anaesthetic solutions prepared in a separate room by a nurse"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Syringes of same size; an independent physician blinded to contents of syringe performed injections"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The same physician who performed the basal clinical examination blinded to the treatment, visited the patients collecting number of painful muscle areas present within 1 hr of injection. The intensity of the phantom pain was evaluated before and after treatment by means of the VAS from 0 (no pain) to 10 (worst pain)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Low risk	All specified outcomes in methods section of published study were reported, although not necessarily as our preferred outcomes
Other bias	Low risk	(+) wash-out period; baseline pain intensity during anaesthetic and saline not significantly different
Size of study	High risk	n = 8

**Eichenberger 2008**
**Study characteristics**

Methods	Randomised, DB, cross-over, 1 hr each treatment arm; time between infusions 48 hours; Randomisation by drawing lots by person not involved in study
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**Pharmacologic interventions for treating phantom limb pain (Review)**

**Eichenberger 2008** (Continued)

Ff-up at 30, 60 min, 48 hrs after infusion

Participants	Chronic phantom pain > 6 months' duration; upper and lower extremity amputation of vascular, traumatic, cancer, chronic pain in aetiologies, mean pain intensity $\geq 3$ on 10-centimetre VAS scale; 20 participants; 15 males; median age, yrs (range): 57 (19.3 to 72.7); mean baseline pain intensity on 10-centimetre VAS: 4.32; duration of phantom pain, yrs: 12.41
Interventions	<ol style="list-style-type: none"> <li>1. ketamine at 0.4 mg/kg, once, 1-hour intravenous infusion</li> <li>2. calcitonin at 200 IU once, 1-hour intravenous infusion</li> <li>3. combination ketamine/calcitonin at 200 IU calcitonin and 0.4 mg/kg ketamine once, 1-hour intravenous infusion</li> <li>4. placebo (saline)</li> </ol>
Outcomes	Number of participants with $\geq 50\%$ pain reduction on 10-centimetre VAS; Change in pain intensity on 10-centimetre VAS; Adverse events: Dropouts/withdrawals; Other outcomes: basal sensory assessments
Notes	Relatively small sample size; n = 20; wide range in duration of phantom pain; ketamine alone was given to only 10 participants

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Drawing of lots
Allocation concealment (selection bias)	Low risk	Person not involved in study randomised and prepared solutions
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"neither investigator performing experiment nor the patients were aware of the solutions infused" "In some cases, drug-related side effects occurred which rendered blinding of physician performing the tests and patients questionable"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"In some cases, drug-related side effects occurred which rendered blinding of physician performing the tests and patients questionable"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing outcome data in 1 group, but not related to outcome
Selective reporting (reporting bias)	Low risk	All specified outcomes in methods section of published study were reported, although not necessarily as our preferred outcomes
Other bias	Unclear risk	Carry-over effect
Size of study	High risk	n = 20

**Huse 2001**
**Study characteristics**

Methods	<p>Randomised, cross-over, 4-week double-blinded phase with 1 to 2 weeks' wash-out period; a long-term open phase for responders to intervention; physician with no contact with participants randomised and kept code</p> <p>Ff-up: hourly for pain and adverse event; weekly during 4 weeks of DB phase; long term 6, 12 mos (open)</p>
Participants	Phantom pain at least 3 in 10-centimetre VAS; with upper and lower extremity amputations; 12 participants, 10 males; mean age, yrs (SD): 50.58 (14.01); mean baseline pain intensity on 10-centimetre VAS (SD): 4.65 (1.06); time since amputation, years (SD): 16.49 (14.01)
Interventions	<ol style="list-style-type: none"> <li>morphine sulfate titrated from 70 mg/day up to 300 mg/day or max tolerable dose for 4 weeks, oral</li> <li>placebo</li> </ol>
Outcomes	<p>Change in pain intensity on 0-to-10-centimetre VAS;</p> <p>Number of participants with pain reduction of &gt; 50% (10-centimetre VAS);</p> <p>Change in mood/depression on Self-Rating Depression Scale;</p> <p>Long-term outcomes (6 months, 12 months): only with morphine sulfate; n = 9</p> <p>Other outcomes: pain-related self-assessment scale; active coping and catastrophising using West Haven-Yale Multidimensional Pain Inventory; Brief Stress Scale; psychophysical thresholds, 2-point discrimination; attentional performance with d2 Test of Attention, magnetoencephalography</p>
Notes	Small sample size (n = 12); cortical reorganisation results based on 3 participants (open phase)

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Physician with no contact with participants randomised and kept code.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as a double-blind study; efforts were made to blind participants (e.g. treatment and placebo preparations were "put into exactly identical pills by the pharmacy"; identical treatment phases). The authors of the study acknowledged in their discussion that the participants were able to guess the morphine medication (but not the placebo) due to side effects, but there was no mention of feedback as to the correctness of their guess. Also, pain reduction scores with the morphine treatment were not significantly correlated with participant-assessed treatment expectancy outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blind study; while there was mention of psychologist (not involved in giving treatment to the participant) who administered psychological assessment scales, it was unclear who assessed pain intensity and side effects
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in analysis of outcomes

**Huse 2001** (Continued)

Selective reporting (reporting bias)	Low risk	All specified outcomes in methods section of published study were reported, although not necessarily as our preferred outcomes.
Other bias	Low risk	(+) wash-out period
Size of study	High risk	n = 12

**Jaeger 1992**
**Study characteristics**

Methods	Controlled clinical trial, cross-over; 2-hour wash-out period; double-blind phase, then an open phase with the intervention (s-calcitonin) for longer-term assessment; drawing of lots by person not involved in study  Ff-up: short-term: 24 hrs before and after treatment (double-blind); long-term: 6 mos, 1 to 2 yrs (open phase)
Participants	Phantom pain 0 to 7 days following amputation; all except one are lower limb amputations of vascular, traumatic, malignancy, and infectious aetiology, at least 3 on 0-to-10 numerical analogue scale; 21 participants, 12 males; median age yrs (range): 59 (20 to 78)
Interventions	1. s-calcitonin at 200 IU, once, 20-minute intravenous infusion 2. saline
Outcomes	Change in pain intensity on 0-to-10 numerical analogue scale;  Number of participants with pain reduction of > 50%;  Long term (at 1 yr): number of participants with reduction of > 75%;  Adverse events;  Dropouts/withdrawals;  Other outcomes: number of phantom pain attacks, number of participants requiring second infusion for phantom pain recurrence
Notes	n = 21

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"patients with PLP exceeding 3 on NAS were randomly divided into 2 groups"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"double-blind"
Blinding of outcome assessment (detection bias)	Unclear risk	Not described

**Jaeger 1992** (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some missing data, as some participants did not have the second infusion, placebo, as their NAS did not exceed 3
Selective reporting (reporting bias)	Unclear risk	Numerical results for pain intensity on NAS not reported, although out in graphical form and noted significance; all specified outcomes in methods were reported, although not necessarily our preferred outcomes
Other bias	Unclear risk	Unclear if baseline pain characteristics were not significantly different in treatment and placebo interventions
Size of study	High risk	n = 21

**Maier 2003**
**Study characteristics**

Methods	Randomised, DB, parallel; computer-generated randomisation Ff-up at end of 3 wks
Participants	History of PLP of at least 12 months; PLP of at least 4 on 11-point numeric rating scale; majority of upper and lower extremity amputations of traumatic aetiology; 36 participants, 29 males; median age in years (range): 62 (28 to 76) in memantine group; 61 (35 to 77) placebo; baseline average pain intensity on 11-point numeric rating scale (SD): 5.1 (2.13) in memantine group; 5.2 (2.02) placebo
Interventions	1. memantine at 30 mg/day, once a day, for 3 weeks, oral 2. placebo
Outcomes	Change in pain intensity on 11-point numeric rating scale; Number of participants with > 50% mean pain reduction on 11-point numeric rating scale; NNTB for 50% pain reduction (95% CI); Change in mood/depression score on German validated depression scale; Change in PDI; Adverse events; Dropouts/withdrawals
Notes	Low-powered study; dosage too low, however this is the limit of clinical tolerability as seen in studies; n = 36

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Doctor not involved in study prepared randomisation; medications prepared in hospital pharmacy

**Maier 2003** (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo and memantine (treatment intervention) had the same colour and size (5 mg/capsule)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Last observation carried forward
Selective reporting (reporting bias)	Low risk	All specified outcomes in methods section of published study were reported, although not necessarily as our preferred outcomes
Other bias	Unclear risk	Baseline characteristics, e.g. time since amputation, dissimilar; longer time period since amputation in the memantine group, but the duration of phantom pain comparable
Size of study	High risk	n = 36

**Nikolajsen 1996**
**Study characteristics**

Methods	Controlled clinical trial, DB, cross-over; 3-day wash-out period; non-involved doctor prepared sealed, numbered envelope for each participant containing order of drugs  Ff-up at end of infusion: 45 min
Participants	Postamputation stump and phantom pain; upper and lower extremity amputation mostly malignancy in aetiology, rest trauma and infection, reflex dystrophy; 11 participants, 8 male; mean age, yrs (range): 47 (32 to 78); baseline pain intensity on 100-millimetre VAS: 30.2; median duration of phantom pain, yrs (range): 4 (0.75 to 14)
Interventions	1. ketamine at 0.5 mg/kg once for 45 minutes, intravenous infusion 2. placebo (saline)
Outcomes	Change in pain intensity on 0-to-100-millimetre VAS;  Adverse events;  Dropouts/withdrawals;  Other outcomes: McGill Pain Questionnaire, pressure pain threshold, wind-up-like pain, thermal stimulus response, temporal summation of heat-induced pain, reaction time
Notes	Small sample size; n = 11

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described

**Nikolajsen 1996** (Continued)

Allocation concealment (selection bias)	Low risk	"doctor not involved in study prepared, sealed and numbered envelope for each patient containing order of ketamine and saline administration"
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind design; ketamine and saline same form (IV) and amount; probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were analysed as to outcomes
Selective reporting (reporting bias)	Unclear risk	Numerical results for pain intensity in VAS not reported but presented in graph as % of baseline values and noted significance; all specified outcomes in methods section of published study were reported, although not necessarily as our preferred outcomes
Other bias	Low risk	(+) wash-out period; baseline pain characteristics basically similar in treatment and control periods
Size of study	High risk	n = 11

**Robinson 2004**
**Study characteristics**

Methods	Randomised, DB, parallel; randomisation by central pharmacy  Ff-up at 6 wks
Participants	PLP or residual limb pain; upper and lower limb amputation of vascular, traumatic, cancer, infectious aetiologies; amputation at least 6 months, pain at least 3 months, at least 2 on 0-to-10 numerical rating scale; 39 participants, 17 males; mean age, yrs (SD): 44.4 (9.4) in amitriptyline group; 45.3 (13.3) in control; time since amputation, yrs (SD): 11.3 (10.9) in amitriptyline; 10.6 (9.1) control; baseline mean pain intensity on 0-to-10 NRS (SD): 3.6 (2.4) amitriptyline; 3.1 (2.6) in control
Interventions	1. amitriptyline at 10 mg/d titrate each week to max of 125 mg/day for 6 weeks, oral 2. benzotropine mesylate at 0.5 mg/day for 6 weeks, oral
Outcomes	Mean change in pain intensity on 0-to-10 NRS;  Change in mood/depression on CES-D;  Change in function on FIM;  Change in QOL/handicap on CHART;  Adverse events;  Dropouts/withdrawals;  Other outcomes: MPQ, Modified Brief Pain Inventory, satisfaction

**Robinson 2004** (Continued)

Notes Sample represents only 18% of eligible and may have only selected those refractory to standard treatment; n = 39

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by pharmacy investigational drug service; probably appropriate random sequence generation
Allocation concealment (selection bias)	Low risk	Random assignment and preparation of medication by hospital pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	"a 7 day supply of medication provided to each participant each week in identical gelatin capsules in plastic holder so that study personnel and participants were blind to medication assignment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"all pre and post treatments measures were administered by research assistant blinded to the subject assignment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not all randomised participants were included in analysis (2 (10%) in amitriptyline group excluded)
Selective reporting (reporting bias)	Low risk	All specified outcomes in methods section of published study were reported, although not necessarily as our preferred outcomes
Other bias	Low risk	Similar baseline characteristics between 2 groups (see characteristics of population above)
Size of study	High risk	n = 39

**Schwenkreis 2003**
**Study characteristics**

Methods	Randomised, DB, parallel, computer-generated randomisation by doctor not involved in study  Ff-up at end of treatment at 21 days
Participants	Chronic PLP of at least 12 months; traumatic upper limb amputations; 16 participants, 14 males; median age 62 (35 to 71)
Interventions	1. memantine titrated up to 30 mg/day x 3 weeks 2. placebo
Outcomes	Pain intensity;  Dropouts/withdrawals;  Other outcomes: intracortical inhibition; intracortical facilitation
Notes	Small number of participants; n = 16

**Schwenkreis 2003** (Continued)

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Doctor not involved in study performed randomisation; hospital pharmacy prepared medication
Blinding (performance bias and detection bias) All outcomes	Low risk	"the study medication was produced in hospital pharmacy using capsules of same colour and size for placebo and memantine"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigator who undertook the TMS and data analysis was blinded to participants' treatment allocation and assessed pain intensity at same time
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 participant in memantine group who did not continue with drug due to adverse events was excluded from study and not included in analysis
Selective reporting (reporting bias)	Low risk	All specified outcomes in methods section of published study were reported, although not necessarily as our preferred outcomes
Other bias	Low risk	Baseline characteristics between 2 groups similar
Size of study	High risk	n = 16

**Smith 2005**
**Study characteristics**

Methods	Randomised, DB, cross-over; 6 weeks each treatment arm; wash-out period of 5 weeks; computer-generated randomisation  Ff-up at 6 wks
Participants	PLP and residual limb pain, with upper and lower extremity amputations of vascular, traumatic, cancer, infectious aetiology; time since amputation at least 6 months; with average pain intensity of at least 3 on 0-to-10 numerical rating scale; 24 participants, 18 males; mean age, yrs (SD): 52.1 (15.5); baseline mean pain intensity on 0-to-10 numerical rating scale (SD): 4.38 (2.57)
Interventions	1. gabapentin titrated from 300 mg to 3600 mg per day for 6 weeks, oral 2. placebo
Outcomes	Mean change in pain intensity on 0-to-10 NRS;  Mean change in mood/depression on CES-D;  Change in function on FIM;  Change in QOL/handicap on CHART;  Adverse events;  Satisfaction;

**Smith 2005** (Continued)

Other outcomes: participant rating of global improvement; Modified Brief Pain Inventory; SF-MPQ sensory score; SF-MPQ affective score

Notes Underpowered study; n = 24

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"pharmacy compounded gabapentin and placebo capsules that were identical in appearance so that study investigators and participants could not determine study assignment by the capsules"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Research study nurse contacted each participant to assess pain intensity; probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not all randomised participants were included in final analysis
Selective reporting (reporting bias)	Unclear risk	Adverse events not described in detail/not specified; withdrawals and dropouts not described
Other bias	Low risk	(+) wash-out period; within-subject analysis
Size of study	High risk	n = 24

**Wiech 2004**
**Study characteristics**

Methods	Randomised, DB, cross-over, 4 weeks each treatment arm; 2-week wash-out phase; randomisation by central pharmacy  Ff-up at end of treatment at 30 days
Participants	Chronic PLP; all upper extremity amputations of traumatic aetiology; 8 participants, 7 males; mean age in years (SD): 45 (12.51); baseline pain intensity on 0-to-100 VAS endpoints (SD): 46.98 (20.38)
Interventions	1. memantine from 10 mg/day 1st week titrated to 30 mg/day 3rd to 4th week, for 4 weeks oral 2. placebo
Outcomes	Change in pain intensity on 0-to-100 VAS endpoints;  Pain in residual limb;  Adverse events;  Dropouts/withdrawals;

**Wiech 2004** (Continued)

Other outcomes: magnetoencephalography recording

Notes Small sample size; n = 8

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"the order of treatment was randomised" but not described
Allocation concealment (selection bias)	Low risk	"scientist not involved in study kept a record of treatment assignment"
Blinding (performance bias and detection bias) All outcomes	Low risk	Member of central pharmacy provided the blinded tablets; placebo substance of identical appearance following same dosage scheme
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in analysis
Selective reporting (reporting bias)	Low risk	All specified outcomes in methods section of published study were reported, although not necessarily as our preferred outcomes
Other bias	Low risk	(+) wash-out period
Size of study	High risk	n = 8

**Wu 2002**
**Study characteristics**

Methods	Randomised, DB, 40 minutes each treatment arm; cross-over with interval of 24 hours for each infusion; block randomisation  Ff-up at 30 min after end of infusion
Participants	Persistent postamputation pains > 6 months, lower and upper extremity amputations; 31 participants, 19 males; mean age, yrs (SD): 54 (13); time since amputation in months (SD): 81 (87.4)
Interventions	1. morphine at 0.2 mg/kg, once given over 40 minutes of intravenous infusion 2. lidocaine at 4 mg/kg, once given over 40 minutes of intravenous infusion 3. placebo (diphenhydramine)
Outcomes	Pain intensity on computerised 0-to-100 VAS;  Subjective self reported % pain relief on 0%-to-100% numeric scale;  NNTB for 30% PLP pain reduction (95% CI);  Treatment satisfaction scores on 0-to-100 numeric scale;

**Wu 2002** (Continued)

Adverse events;  
Dropouts/withdrawals;  
Other outcomes: sedation scores

Notes Study has a power of 80%; carry-over effects possible, but baseline pain scores in both groups similar as well as short duration of action of drugs; n = 31

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	All study medications were identical in appearance; investigator administering study medication blinded from intervention; participant and research co-ordinator blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"during the infusion, the investigator administering the study medication was blinded from the outcome assessment (pain and sedation) and the subject and research coordinators were blinded to the exact timing of study medication administration"
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant dropped out from study due to absence of pain before start of infusion and was not included in analysis
Selective reporting (reporting bias)	Unclear risk	Actual numerical VAS values for pain intensity not reported but presented in graph form and noted significance; all specified outcomes in methods section of published study were reported, although not necessarily as our preferred outcomes
Other bias	Low risk	Carry-over effects addressed and discussed; relatively short duration of action of study medications, use of good active placebo, and baseline pain and sedation scores did not differ significantly between 3 days of infusion
Size of study	High risk	n = 31

**Wu 2012**

**Study characteristics**

Methods	Randomised, DB, pilot, parallel sequence; 1 group receiving BoNT/A injections and another group receiving combination lidocaine and methylprednisolone injections; "one physician was chosen to implement the treatment protocol for all patients after randomisation."  Ff-up at 1, 2, 3,4 ,5,6 mos
Participants	Adult lower extremity amputees with PLP or RLP, or both with VAS > 5/10 and unresponsive to conventional treatment

**Wu 2012** (Continued)

Interventions	<ol style="list-style-type: none"> <li>1. Injections of BoNT/A with dosage of 1 mL equal to 50 units of BoNT/A into painful sites; 1 treatment episode</li> <li>2. Injections of 1 mL mixture of 0.75 mL of 1% lidocaine and 0.25 mL of lidocaine/methylprednisolone 40 mg/mL into painful sites; 1 treatment episode</li> </ol>
Outcomes	Pain intensity by 0-to-10 VAS;  Changes in pressure pain tolerance;  Dropouts/withdrawals
Notes	Study has a small size; n = 14

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Technique of allocation not clearly described
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants were blinded to the type of treatment they received; medications same in appearance, dosage amount, and route
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluators were blinded to the type of treatment participants received
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study described the dropouts and withdrawals during the course of the study, but unclear whether these were included in the analysis
Selective reporting (reporting bias)	Low risk	All specified outcomes in methods section of published study were reported, although not necessarily as our preferred outcomes
Other bias	Unclear risk	Uncertain if baseline characteristics similar in both groups
Size of study	High risk	n = 14 (but only an initial report)

BI: Barthel Index; BoNT/A: botulinum toxin A; CES-D: Center for Epidemiologic Studies Depression Scale; CHART: Craig Handicap Assessment and Reporting Technique; CI: confidence interval; DB: double-blind; FIM: Functional Independence Measure; ff-up: follow-up; HADS: Hospital Anxiety and Depression Scale; ICF: intracortical facilitation; ICI: intracortical inhibition; IU: international unit; IV: intravenous; max: maximum; mos: months; MPQ: McGill Pain Questionnaire; n: number of participants; NNTB: number needed to treat for an additional beneficial outcome; NAS: numerical analogue scale; NRS: numerical rating scale; PDI: Pain Disability Index; PLP: phantom limb pain; RLP: residual limb pain; QOL: quality of life; SD: standard deviation; SF-MPQ: Short-Form McGill Pain Questionnaire; SIS: Sleep Interference Scale; TMS: transcranial magnetic stimulation; VAS: visual analogue scale; wks: weeks; yrs: years.

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

Study	Reason for exclusion
<a href="#">Abraham 2002</a>	Sample size of 3

Study	Reason for exclusion
<a href="#">Atesalp 2000</a>	Not reported as randomised or quasi-randomised; no mention of treatment allocation; no description of double-blinding
<a href="#">Borghi 2010</a>	Not established PLP/pre-emptive therapy
<a href="#">Cohen 2011</a>	Not randomised
<a href="#">Elizaga 1994</a>	Not established PLP
<a href="#">Elrazek 2005</a>	Population composed of participants with stump pain; none had PLP
<a href="#">Grant 2008</a>	Pre-emptive/preventative therapy
<a href="#">Ilfeld 2013</a>	Sample size of 3
<a href="#">Jacobson 1989</a>	Case series
<a href="#">Jacobson 1990</a>	Not established PLP but stump pain
<a href="#">Jaeger 1988</a>	Mixed group of phantom pain and causalgias; no control
<a href="#">Jin 2009</a>	Case series
<a href="#">Karaniokolas 2011</a>	Pre-emptive therapy
<a href="#">Kessel 1987</a>	Non-randomised, open study
<a href="#">Kukushkin 1996</a>	Pre-post study; no control group
<a href="#">Licina 2013</a>	Case series
<a href="#">Lirk 2012</a>	Editorial and preventive therapy protocol
<a href="#">Neil 2012</a>	Comment on a study done in 2011
<a href="#">Nikolajsen 1997</a>	Case report
<a href="#">Nikolajsen 2006</a>	Pre-emptive therapy
<a href="#">Panerai 1990</a>	Mixed diagnoses for central pain
<a href="#">Pinzur 1996</a>	Pre-emptive therapy
<a href="#">Rogers 1989</a>	Case report
<a href="#">Sato 2008</a>	Case report
<a href="#">Scadding 1982</a>	Mixed diagnoses with no separate analyses for PLP
<a href="#">Van Seventer 2010</a>	Mixed diagnoses with no separate analyses for PLP
<a href="#">Vorobeichik 1997</a>	No description of randomisation, allocation, double-blinding, who assessed outcomes, withdrawals/dropouts

Study	Reason for exclusion
Wilder-Smith 2005	Non-randomised after day 3, where treatment assignment was changed based on response; not all participants were blinded; numerical results for initial responders (first 3 days) not reported
Wu 2008	Included all postamputation pains; did not distinguish PLP from other postamputation pains; no separate analysis for PLP

PLP: phantom limb pain

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

**Buch 2019**

Methods	Randomized, double-blind, placebo-controlled crossover study
Participants	Amputees with constant postamputation pain. Sample size of 12 (but only 9 were analysed)
Interventions	Peripheral nerve block
Outcomes	The primary outcome was the difference in absolute change between worst pain intensity, either phantom or stump pain, at baseline and at 30 minutes after lidocaine or saline injection.
Notes	

**DATA AND ANALYSES**

**Comparison 1. Memantine versus placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Change in pain intensity	2	52	Std. Mean Difference (IV, Fixed, 95% CI)	0.24 [-0.31, 0.79]

**Analysis 1.1. Comparison 1: Memantine versus placebo, Outcome 1: Change in pain intensity**

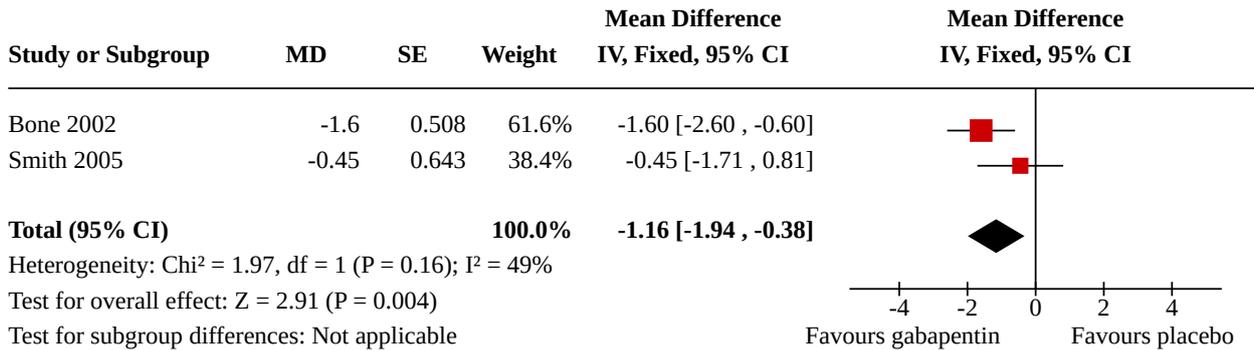
Study or Subgroup	Experimental			Control			Weight	Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Maier 2003	3.8	2.3	18	3.2	1.46	18	69.0%	0.30 [-0.35, 0.96]	
Wiech 2004	51.51	20.61	8	49.46	21.11	8	31.0%	0.09 [-0.89, 1.07]	
<b>Total (95% CI)</b>			<b>26</b>			<b>26</b>	<b>100.0%</b>	<b>0.24 [-0.31, 0.79]</b>	

Heterogeneity: Chi<sup>2</sup> = 0.12, df = 1 (P = 0.73); I<sup>2</sup> = 0%  
 Test for overall effect: Z = 0.86 (P = 0.39)  
 Test for subgroup differences: Not applicable

**Comparison 2. Gabapentin versus placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Change in pain intensity	2		Mean Difference (IV, Fixed, 95% CI)	-1.16 [-1.94, -0.38]

**Analysis 2.1. Comparison 2: Gabapentin versus placebo, Outcome 1: Change in pain intensity**



**ADDITIONAL TABLES**
**Table 1. Summary of results**

Author, year	Intervention	Treatment duration	Follow-up	Outcomes	Results	Overall direction of efficacy	Adverse events
<b>BoNTs</b>							
<b>BoNT/A</b>							
Wu 2012	1. BoNT/A, 1 mL = 50 units for each injection site 2. combi l/m, 1 mL = 0.75 mL of 1% lidocaine and 0.25 mL methylprednisolone 40 mg/mL for each painful site	1 tx episode	At 1, 2, 3, 4, 5, 6 mos	Change in VAS, change in pressure pain tolerance	No significant change in phantom pain and pressure pain tolerance	-	Not described
<b>NMDA antagonists</b>							
<b>Memantine</b>							
Maier 2003	1. memantine 30 mg/d; oral 2. placebo	3 weeks	At end of 3 weeks	Pain intensity 11-point NRS; number of participants with > 50% pain reduction; NNTB; mood; disability; adverse events	No sig diff in change in pain level, in number of participants with > 50% pain relief; depression scores; disability indices  in 2 grps; overall number severe events higher in memantine grp	-	Vertigo, tiredness, headache, nausea, restlessness, excitation, cramps

**Table 1. Summary of results** (Continued)

Wiech 2004	1. memantine titrated up to 30 mg/d; oral 2. placebo	4 weeks each treatment arm	At end of 4 weeks of each arm	Pain intensity 0-to-100 VAS; MEG recording; adverse events	No sig diff in change in pain intensity, cortical reorganisation in both grps	-	Nausea, fatigue, dizziness, agitation, headaches
Schwenkreis 2003	1. memantine titrated up to 30 mg/d; oral 2. placebo	3 weeks	At end of 3 weeks	Pain intensity 11-point NRS; ICI; ICF	No sig diff in pain intensity; enhanced ICI; reduced ICF	-	Not described
<b>Dextromethorphan</b>							
Abraham 2003	1. dextromethorphan 120 mg/d; oral 2. dextromethorphan 180 mg/d; oral 3. placebo	10 days each treatment arm	At end of 10 days of each arm	Number of participants with ≥ 50% pain relief; feeling of well-being; sedation score; adverse events	Dextromethorphan grps with ≥ 50% pain relief; with sig better feeling of well-being scores; with sig lower sedation scores	+	None reported
<b>Ketamine</b>							
Nikolajsen 1996	1. ketamine 0.5 mg/kg once, IV infusion 2. placebo	45 min each treatment arm	At end of IV infusion	Pain intensity 0-to-100-millimetre VAS; adverse events; McGill; pressure pain threshold; wind-up like pain; thermal stimulus response; temporal summation of heat-induced pain; reaction time	Sig dec in pain intensity; in pain evoked by mechanical stimulation; inc in pressure pain threshold; no alteration in temperature sensitivity in ketamine group	+	Insobriety, discomfort, elevation of mood
Eichenberger 2008	1. ketamine 0.4 mg/kg once, IV infusion 2. calcitonin 200 IU, once, IV infusion	1 hour each arm	At 30, 60 mins, 48 hours after infusion	Pain intensity; number of participants with ≥ 50% pain reduction on 10-centimetre VAS; basal sensory assessment; adverse events	Sig dec pain intensity in ketamine alone and combination vs placebo and calcitonin; sig inc in number of responders in ketamine alone and combination vs placebo and calcitonin; sig	+	Loss of consciousness, light sedation,

**Table 1. Summary of results** (Continued)

	3. combination ketamine/calcitonin, IV				inc in electrical thresholds with combination treatment but no change in pressure or heat thresholds		light visual hallucination, hearing impairment, position/feeling impairment
<b>Anticonvulsants</b>							
<b>Gabapentin</b>							
<a href="#">Bone 2002</a>	1. gabapentin titrated up to 2400 mg or max tolerable dose; oral 2. placebo	6 weeks each arm	Weekly and at end of 6 weeks	Pain intensity 100-millimetre VAS; pain intensity difference; depression score (HADS); function (BI); sleep (SIS); no. of rescue tabs; adverse events	Significantly greater pain intensity diff with gabapentin at end of treatment; no sig diff in depression score, function, sleep, no. of rescue tablets with the treatments	+a ..b	Somnolence, dizziness, headache, nausea
<a href="#">Smith 2005</a>	1. gabapentin titrated up to 3600 mg/d; oral 2. placebo	6 weeks	At end of 6 weeks of each arm	Pain intensity 0-to-10 NRS; depression score (CES-D); function (FIM); handicap (CHART); satisfaction; global improvement rating; pain inventory; McGill	No sig group diff on any outcomes at end of treatment	..c	Not described
<b>Antidepressants</b>							
<b>Amitriptyline</b>							
<a href="#">Robinson 2004</a>	1. amitriptyline 10 mg/d titrated to max of 125 mg/d; oral	6 weeks	At end of 6 weeks	Pain intensity 0-to-10 NRS; depression score (CES-D); function (FIM); handicap	No sig group diff on any outcomes at end of treatment	-	Dry mouth (more severe),

**Table 1. Summary of results** (Continued)

	2. benzotropine mesylate 0.5 mg/d; oral				(CHART); pain inventory; McGill; satisfaction		dizziness
<b>Calcitonins</b>							
<a href="#">Jaeger 1992</a>	1. s-calcitonin 200 IU, IV infusion 2. saline	20-minute IV infusion; once	24 hours after infusion (DB); 7 to 152 days, weekly (open phase)	Pain intensity 0-to-10 NAS in open phase/long term; number of participants with > 50%, 75% pain relief; adverse events	Sig dec in median pain intensity with s-calcitonin at 24 hours after infusion; at 1 yr, 62% of participants with 75% pain reduction	+	Headache, vertigo, nausea, vomiting, phantom sensation, drowsiness, hot/cold flushes
<a href="#">Eichenberger 2008</a>	1. ketamine 0.4 mg/kg, once, IV infusion 2. calcitonin 200 IU, once, IV infusion 3. combination ketamine/calcitonin, IV 4. placebo	1 hour each arm	At 30, 60 mins, 48 hours after infusion	Pain intensity; number of participants with ≥ 50% pain relief on 10-centimetre VAS; basal sensory assessments; adverse effects	No sig dec in pain intensity with calcitonin vs placebo at 48 hrs; number of responders not significantly different from placebo	-	Drowsiness, nausea, facial flushing, hot/cold flushes, dizziness
<b>Opioids</b>							
<b>Morphine</b>							
<a href="#">Huse 2001</a>	1. Morphine sulfate titrated up to 300 mg/d or max tolerable dose; oral 2. placebo	4 weeks each arm (DB)	End of each treatment phase of 4	Pain intensity 10-centimetre VAS; number of participants with > 50% pain reduction; depression score; pain-related self assessment scale;	Sig pain reduction during morphine; 42% with > 50% pain relief; 8% with 25% to 50% pain relief during morphine; no sig change in perception and	+	Constipation only sig adverse effect among

**Table 1. Summary of results** (Continued)

				weeks	WHYMPI; BSS; psycho-physical thresholds; 2-point discrimination; attentional performance; MEG	pain thresholds; significantly lower attentional performance during morphine; scores on pain experience scale, depression score, WHYMPI, BSS with no sig relationship with pain reduction; 2 of 3 with clear cortical reorganisation		others, e.g. tiredness, dizziness, sweating, micturition difficulty, vertigo, itching, respiration
<a href="#">Wu 2002</a>	1. morphine 0.2 mg/kg, IV infusion 2. lidocaine 4 mg/kg, IV infusion 3. placebo (diphenhydramine)	0.2 mg/kg, IV infusion	40 mins of IV infusion	30 mins after end of infusion	Pain relief 0-to-100% numeric scale; NNTB for 30% pain reduction; satisfaction; sedation scores; adverse events	Sig dec in phantom and stump pain intensity during IV morphine; NNTB 1.9 (95% CI 1.3 to 3.7); significantly higher satisfaction with morphine; no sig diff in sedation scores	+	Sedation (but no sig diff with other groups)
<b>Local anaesthetics</b>								
<b>Lidocaine</b>								
<a href="#">Wu 2002</a>	1. morphine 0.2 mg/kg, IV infusion 2. lidocaine 4 mg/kg, IV infusion 3. placebo (diphenhydramine)	0.2 mg/kg, IV infusion	40 mins of IV infusion	30 mins after end of infusion	Pain relief 0-to-100% numeric scale; NNTB for 30% pain reduction; satisfaction; sedation scores; adverse events	No sig dec in PLP vs placebo; NNTB 3.8 (95% CI 1.9 to 16.6); significantly higher satisfaction with lidocaine vs placebo; no sig diff in sedation scores	-	Sedation scores not significantly different from placebo
<b>Bupivacaine</b>								

**Table 1. Summary of results** (Continued)

Casale 2009	1. bupivacaine 2.5 mg/mL, 1mL, contralateral myofascial injection 2. placebo (saline)	Injections given once	After 1 hour	Pain intensity 0-to-10 VAS from 0 no pain to 10 worst pain ever experienced;  pain intensity difference;  phantom sensation;  mirror displacement  in healthy limbs; adverse effects	Sig pain relief with bupivacaine; + reduction in phantom sensation in 6 of 8 participants	None
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BI, Barthel Index; BoNT/A, botulinum toxin A; BSS, Brief Stress Scale; CES-D, Center for Epidemiologic Studies Depression Scale; CHART, Craig Handicap Assessment and Reporting Technique; CI, confidence interval; combo, combination; d, day; DB, double-blind; dec, decrease; diff, difference; dx, diagnosis; FIM, Functional Independence Measure; grp, group; grps, groups; HADS, Hospital Anxiety and Depression Scale; ICI, intracortical inhibition; ICF, intracortical facilitation; inc, increase; IU, international units; IV, intravenous; l/m, lidocaine/methylprednisolone; max, maximum; MEG, magnetoencephalography; min, minutes; mos, months; NAS, numerical analogue scale; NNTB, number needed to treat for an additional beneficial outcome; NRS, numerical rating scale; PLP, phantom limb pain; sig, significant; SIS, Sleep Interference Scale; tx, treatment; VAS, visual analogue scale; WHYMPI, West Haven-Yale Multidimensional Pain Inventory; yr, year; <sup>a</sup>pain intensity; <sup>b</sup>mood, sleep, function; <sup>c</sup>pain intensity, mood, function, handicap, satisfaction

## APPENDICES

### Appendix 1. Cochrane Library (CENTRAL) search

#1 MeSH descriptor Phantom Limb, this term only

#2 phantom or fantom

#3 MeSH descriptor Pain explode all trees

#4 pain\* or discomfort\* or sensation\* or sore\* or ache\* or tender\* or irritat\* or feel\* or syndrome\*

#5 (#1 OR #2)

#6 (#3 OR #4)

#7 stump near/6 pain\*

#8 (( #5 AND #6 ) OR #7)

### Appendix 2. MEDLINE OVID

1 Phantom Limb/

2 (phantom or fantom).mp.

3 exp Pain/

4 (pain\* or discomfort\* or sensation\* or sore\* or ache\* or tender\* or irritat\* or feel\* or syndrome\*).mp.

5 or/1-2

6 or/3-4

7 (stump adj6 pain\*).mp.

8 (5 and 6) or 7

9. randomized controlled trial.pt.

10. controlled clinical trial.pt.

11. randomized.ab.

12. placebo.ab.

13. drug therapy.fs.

14. randomly.ab.

15. trial.ab.

16. or/9-15

17. exp animals/ not humans.sh.

18. 16 not 17

19. 8 and 18

Key

mp=title, original title, abstract, name of substance word, subject heading word, unique identifier

### Appendix 3. Embase OVID

1 Agnosia/

- 2 (phantom or fantom).mp.
- 3 exp Pain/
- 4 (pain\* or discomfort\* or sensation\* or sore\* or ache\* or tender\* or irritat\* or feel\* or syndrome\*).mp.
- 5 or/1-2
- 6 or/3-4
- 7 (stump adj6 pain\*).mp.
- 8 (5 and 6) or 7
9. random\$.tw.
10. factorial\$.tw.
11. crossover\$.tw.
12. cross over\$.tw.
13. cross-over\$.tw.
14. placebo\$.tw.
15. (doubl\$ adj blind\$).tw.
16. (singl\$ adj blind\$).tw.
17. assign\$.tw.
18. allocat\$.tw.
19. volunteer\$.tw.
20. Crossover Procedure/
21. double-blind procedure.tw.
22. Randomized Controlled Trial/
23. Single Blind Procedure/
24. or/9-23
25. (animal/ or nonhuman/) not human/
26. 24 not 25
27. 8 and 26

key:

mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer

## WHAT'S NEW

Date	Event	Description
7 August 2020	Review declared as stable	See <a href="#">Published notes</a> .

## HISTORY

Protocol first published: Issue 1, 2007

Review first published: Issue 12, 2011

Date	Event	Description
3 July 2018	Review declared as stable	See <a href="#">Published notes</a>
29 October 2015	New search has been performed	We updated the searches in April 2016. We updated the results, 'Risk of bias' tables, flow of study selection, summary tables, and discussion.
29 October 2015	New citation required but conclusions have not changed	We added one new study with 14 participants, but the conclusions remain unchanged. Previous readers of the review should re-read this update because we added another form of medical therapy to the pharmacological interventions.
16 December 2011	Amended	Changes to presentation of Table 3 and <a href="#">Table 1</a> .
18 February 2009	Amended	Minor revisions made to the protocol text by the author
29 May 2008	Amended	Converted to new review format.

## CONTRIBUTIONS OF AUTHORS

MJA was responsible for the first draft of the protocol. MJA and TAH revised the protocol. MJA, MD, and TAH examined the studies for eligibility and assessed the quality of the studies. MJA and TAH extracted the data. MJA and TAH analysed the data. MJA wrote the review. TAH and MD independently checked data analysis. MJA and TAH made revisions to the manuscript. MJA, TAH, and MD approved the final version.

For this update, MJA, TAH, and MD examined the eligibility and risk of bias of the studies, and MJA and TAH extracted and analysed the data. MJA wrote the review. MJA and TAH made revisions to the manuscript. MJA, TAH, and MD approved the final version.

## DECLARATIONS OF INTEREST

MJA: none known. MJA is a Rehabilitation Medicine specialist and has completed PhD Research in Orthopaedic Rehabilitation.

TAH: none known. TAH is a Rehabilitation physician and manages patients with amputations and complications including phantom limb pain.

MD: none known. MD is a Rehabilitation Medicine specialist and manages both adult and paediatric patients with musculoskeletal and neurologic conditions including patients with neuropathic pain.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol intended to combine and summarise the outcome measures across the studies into quantitative analyses, but due to the variations in study characteristics and reporting and presenting of results, this was not possible. Nevertheless, we made attempts to pool the results of some studies where possible in the review. We have provided a qualitative description and narrative summary as stated in the protocol for the results that could not be combined.

For the 2016 update, we clarified the term 'satisfaction' in the secondary outcomes in the protocol as 'satisfaction with treatment'. We also relied solely on the Cochrane 'Risk of bias' tool to assess the likely impact of various study characteristics on the strength of the evidence. We furthermore elaborated on how we graded the risk of bias for the included studies and added size of study to the 'Risk of bias' assessment.

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## NOTES

### Assessed for updating in 2018

A restricted search in June 2018 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. The review will be re-assessed for updating in two 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 necessitate major revisions.

### Assessed for updating in 2020

A restricted search in June 2020 identified one potentially relevant study ([Buch 2019](#)), but it was unlikely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in two 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 necessitate major revisions.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Analgesics, Opioid [therapeutic use]; Anesthetics [therapeutic use]; Anticonvulsants [therapeutic use]; Antidepressive Agents [therapeutic use]; Botulinum Toxins, Type A [therapeutic use]; Calcitonin [therapeutic use]; Neurotoxins [therapeutic use]; Phantom Limb [\*drug therapy]; Randomized Controlled Trials as Topic; Receptors, N-Methyl-D-Aspartate [antagonists & inhibitors]

### MeSH check words

Humans