Interventions for treating pain and disability in adults with complex regional pain syndrome- an overview of systematic reviews (Review)

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[Overview of Reviews]

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ABSTRACT

Background

There is currently no strong consensus regarding the optimal management of complex regional pain syndrome although a multitude of interventions have been described and are commonly used.

Objectives

To summarise the evidence from Cochrane and non-Cochrane systematic reviews of the effectiveness of any therapeutic intervention used to reduce pain, disability or both in adults with complex regional pain syndrome (CRPS).

Methods

We identified Cochrane reviews and non-Cochrane reviews through a systematic search of the following databases: Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Ovid MEDLINE, Ovid EMBASE, CINAHL, LILACS and PEDro. We included non-Cochrane systematic reviews where they contained evidence not covered by identified Cochrane reviews. The methodological quality of reviews was assessed using the AMSTAR tool.

We extracted data for the primary outcomes pain, disability and adverse events, and the secondary outcomes of quality of life, emotional well being and participants' ratings of satisfaction or improvement. Only evidence arising from randomised controlled trials was considered. We used the GRADE system to assess the quality of evidence.

Main results

We included six Cochrane reviews and 13 non-Cochrane systematic reviews. Cochrane reviews demonstrated better methodological quality than non-Cochrane reviews. Trials were typically small and the quality variable.

There is moderate quality evidence that intravenous regional blockade with guanethidine is not effective in CRPS and that the procedure appears to be associated with the risk of significant adverse events.

There is low quality evidence that bisphosphonates, calcitonin or a daily course of intravenous ketamine may be effective for pain when compared with placebo; graded motor imagery may be effective for pain and function when compared with usual care; and that mirror therapy may be effective for pain in post-stroke CRPS compared with a 'covered mirror' control. This evidence should be interpreted with caution. There is low quality evidence that local anaesthetic sympathetic blockade is not effective. Low quality evidence suggests that physiotherapy or occupational therapy are associated with small positive effects that are unlikely to be clinically important at one year follow up when compared with a social work passive attention control.

For a wide range of other interventions, there is either no evidence or very low quality evidence available from which no conclusions should be drawn.

Authors' conclusions

There is a critical lack of high quality evidence for the effectiveness of most therapies for CRPS. Until further larger trials are undertaken, formulating an evidence-based approach to managing CRPS will remain difficult.

PLAIN LANGUAGE SUMMARY

Which treatments are effective for the treatment of complex regional pain syndrome in adults?

Complex regional pain syndrome (CRPS) is characterised by persistent pain, usually in the hands or feet, that is not proportionate in severity to any underlying injury. It often involves a variety of other symptoms such as swelling, discolouration, stiffness, weakness and changes to the skin. This overview sought to summarise and report all of the available evidence arising from systematic reviews for all treatments for this condition regarding how well they work and any potential harm that they might cause.

We identified six Cochrane reviews and 13 non-Cochrane systematic reviews that included evidence relating to a broad range of treatments, from drugs to surgical procedures, rehabilitation and alternative therapies. For most treatments there were only a small number of published trials and the quality of these trials was mixed. As such, most of the evidence for most treatments is of low or very low quality and can not be regarded as reliable.

We found low quality evidence that a daily course of the drug ketamine delivered intravenously may effectively reduce pain, although it is also associated with a variety of side effects. We found low quality evidence that the bisphosphonate class of drugs, calcitonin and programmes of graded motor imagery may be effective for CRPS, and that mirror therapy may be effective in people who develop CRPS after suffering a stroke. Low quality evidence suggested that physiotherapy and occupational therapy did not lead to clinically important benefits at one year follow up, and that blocking sympathetic nerves with local anaesthetic is not effective. There is moderate quality evidence that an intravenous regional blockade using the drug guanethidine is not effective and may be associated with complications.

For a range of other interventions we found only very low quality evidence or no evidence at all. No conclusions should be drawn regarding the value of these interventions based on this level of evidence.

Based on the existing evidence it is difficult to draw firm conclusions as to which therapies should be offered to patients with CRPS. Better quality research is vital to reduce uncertainty in this area and is necessary before confident recommendations can be made.

BACKGROUND

The purpose of a Cochrane overview is to systematically compile evidence from more than one systematic review of different interventions for the same condition into one accessible and usable document (Becker 2011).

Description of the condition

Complex regional pain syndrome (CRPS) is an umbrella term for a variety of clinical presentations characterised by chronic persistent pain that is disproportionate to any preceding injury and that is not restricted anatomically to the distribution of a specific peripheral nerve (Bruehl 2010; Marinus 2011). The diagnostic label

of CRPS was introduced in the 1990s by the International Association for the Study of Pain (IASP) (Merskey 1994) and has since been updated in an attempt to improve its specificity (Harden 2006a). These modified diagnostic criteria (the 'Budapest criteria') can be seen in Table 1. CRPS encompasses a variety of existing diagnostic titles including reflex sympathetic dystrophy (RSD), reflex neurovascular dystrophy, Sudeck's atrophy, causalgia and algodystrophy or algoneurodystrophy. CRPS can be subclassified into two diagnostic subtypes: type I (CRPS-I) in which no peripheral nerve injury can be identified, and type II (CRPS-II) where symptoms are associated with a definable nerve lesion, although this distinction is not always easily made (Harden 2006a).

Both subtypes of CRPS are characterised by severe pain that is disproportionate to the inciting event, most commonly affecting the hand or foot but which can spread to other body regions (Stanton-Hicks 2002). Additionally CRPS presents with some or all of the following symptoms in the affected body parts: sensory disturbances, temperature changes, abnormal patterns of sweating, swelling and oedema, reduced joint range of motion, movement abnormalities such as weakness, tremor or dystonia, trophic changes such as skin atrophy or altered hair and nail growth, and localised osteoporotic changes (Bruehl 2010; de Mos 2009; Shipton 2009); and alterations in body perception or schema (Lewis 2007; Lotze 2007; Moseley 2006).

CRPS occurs most commonly following wrist fracture and subsequent immobilisation but may potentially occur after any often relatively minor trauma and, though rare, may also occur spontaneously (de Mos 2007; de Mos 2008; Sandroni 2003). The underlying pathophysiological mechanisms of CRPS are incompletely understood although there is growing consensus that they include an aberrant inflammatory response, autonomic dysfunction and central nervous system (CNS) dysfunction (for review see Marinus 2011). The evidence for these mechanisms includes signs of increased neurogenic inflammation (Birklein 2001; Schinkel 2006; Schmelz 2001), small fibre neuropathy (Oaklander 2009), an altered local immune response (Tan 2005), altered activity in the sympathetic nervous system (SNS) (Drummond 2004; Niehof 2006) or increased sensitivity to normal SNS activity (Albrecht 2006; Ali 2000; Drummond 2001), and local tissue hypoxia (Birklein 2000; Koban 2003). Additionally changes have been demonstrated in the brain in CRPS (Swart 2009), including alterations of the cortical (higher brain) representation of the affected body part (Maihöfner 2004; Pleger 2006), localised reductions in grey matter density and connectivity (Geha 2008) and altered inhibitory control (Schwenkreis 2003).

Description of the interventions

This overview includes systematic reviews of any intervention aimed at treating pain, disability or both in CRPS. An expert panel has emphasised three core elements in treating CRPS that incorporate a broad selection of therapeutic options: rehabilitation (physiotherapy, occupational therapy), psychological therapy (for example cognitive-behavioural therapy (CBT) and educational interventions) and pain management (including orally or topically administered and interventional pharmacological approaches, nerve blocking procedures, surgical approaches such as sympathectomy, and neuromodulation techniques such as spinal cord or brain stimulation techniques) (Stanton-Hicks 2002), although this list is not exhaustive.

Oral pharmacotherapy

A variety of pharmacological interventions have been described for the treatment of CRPS and in practice combinations of these drugs are commonly utilised (Harden 2006b). Oral pharmacologic options can be divided into the following broad categories (Harden 2006b).

- Anti-inflammatory drugs and immunomodulators, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, cyclooxygenase-2 (Cox-2) inhibitors, free radical scavengers (e.g. vitamin C) and biologics (e.g. tumour necrosis factor-α (TNF-α) inhibitors).
- Anticonvulsants, neuromodulators (e.g. carbamazepine, gabapentin).
- Antidepressants and anxiolytics (e.g. amitriptyline, doxepin).
- Opioids.
- N-methyl d-aspartate (NMDA) antagonists (e.g. ketamine, dextromethorphan).
- Antihypertensives and α-adrenergic antagonists (e.g. clonidine, phentolamine).
- Bisphosphonates (e.g. alendronate).
- Calcitonin.

Topical pharmacotherapy

Topical drug treatments include patch treatments and creams that deliver medication to the affected skin and soft tissues local to the site of application (Harden 2006b). They include lidocaine patches, mixed local anaesthetic creams, capsaicin and dimethyl sulphoxide (DMSO).

Interventional procedures

Intravenous regional anaesthetic blocks commonly involve the infusion of pharmacological agents whilst the affected limb is tourniqueted and may use one of a variety of agents, such as guanethidine, lidocaine, clonidine and others (Burton 2006). Blocking of sympathetic nervous activity may also be achieved by injection directly into sympathetic neural structures such as the stellate ganglion or the lumbar sympathetic chain (Nelson 2006). Sympathectomy involves the destruction of sympathetic neural pathways through the injection of poisonous agents such as phenol, or by

surgical methods such as surgical excision or electrocoagulation (Nelson 2006).

Neurostimulation may involve the surgical implantation of electrodes into areas of the brain or spinal cord to allow electrical stimulation of local neural tissue in order to modulate neural signals or processing. Non-invasive forms of brain stimulation have also been developed and used to treat chronic pain conditions, such as repetitive transcranial magnetic stimulation (rTMS) (Lefaucheur 2008; Prager 2010).

Rehabilitation

Both occupational and physiotherapy rehabilitation are frequently used to treat CRPS and these incorporate a variety of approaches, sometimes used in isolation but more commonly delivered in a multi-modal format that includes manual therapy, electrotherapy (including transcutaneous electrical nerve stimulation (TENS)), massage and therapeutic exercise (Daly 2009). Vocational and recreational rehabilitation approaches are also described in recent clinical guidelines (Harden 2006c).

Psychological therapies

Psychological therapies include cognitive-behavioural therapy (CBT), operant conditioning (OC), counselling, pain education and relaxation techniques (Bruehl 2006).

How the intervention might work

Such a broad range of potential treatments incorporates a multitude of possible therapeutic mechanisms. Orally administered pharmacologic options aim to target and alter physiological pathways involved in the generation of pain, inflammation, abnormal sympathetic activity or bone loss (Harden 2006b).

Sympathetic nerve blocks or sympathectomy aim to reduce sympathetic neural activity by temporarily or permanently disrupting the sympathetic nervous system to the affected body area (Burton 2006). Neuromodulation approaches, such as spinal cord or brain stimulation techniques, seek to reduce pain by altering neural processing within the central nervous system (Lefaucheur 2008; Nelson 2006).

Psychological therapies primarily aim to improve function and disability, rather than pain, by patient education. They address unhelpful pain-related behaviours and beliefs and teach pain coping and management strategies. Rehabilitation approaches typically include exercise regimes as well as passive techniques such as manual therapy, massage and various forms of electrotherapy to improve range of movement (ROM) and strength and function in the joints of the affected body part. It is common for aspects of psychological approaches to be included within rehabilitation approaches (Daly 2009).

More recently, specific rehabilitation approaches have been developed that aim to improve pain and function by altering cortical (brain) processing specific to the affected body part using strategies such as mirror therapy (McCabe 2008), sensory motor retuning (Pleger 2005), graded motor imagery (GMI) (Moseley 2004) and tactile sensory discrimination training (Moseley 2008).

Why it is important to do this overview

Currently there is no strong consensus regarding the optimal management of this condition and a multitude of therapeutic interventions are currently utilised, including pharmacological, surgical, neurostimulation and physical therapy-based treatments. Clinical guidelines have been produced in the Netherlands (Perez 2010), the USA (Harden 2006a) and the UK (Goebel 2011). One of these (Perez 2010) included a systematic synthesis of the evidence for treatments for CRPS-I but not CRPS-II, although this was based on searches conducted a number of years earlier. While clinical guidelines reflect the evidence and pragmatic considerations such as country-specific policies, access and healthcare pathways, and possibly the interests of key stakeholders, a Cochrane overview provides a critical summary based simply on the evidence for treatments of both CRPS-I and CRPS-II, which will be regularly updated.

OBJECTIVES

To provide an overview of evidence from systematic reviews to determine the efficacy of any intervention used to reduce pain, disability or both in adults with complex regional pain syndrome, and to direct readers to these reviews.

METHODS

Criteria for considering reviews for inclusion

Types of studies

We included all Cochrane reviews of randomised controlled trials that assessed the effects of any intervention used to reduce pain or disability in adults with CRPS. We also chose to consider non-Cochrane reviews as, given the broad range of available treatments, to exclude them might have provided an incomplete summary of the available evidence. We therefore included non-Cochrane systematic reviews where they covered classes of interventions that were not covered by identified Cochrane reviews or where they were more up to date (that is searches performed later with significantly more included studies). To be included, any non-Cochrane

review was required to achieve a judgement of 'Yes' on the third criterion on the AMSTAR tool for assessing the quality of systematic reviews (Shea 2007), that is "Was a comprehensive literature search performed?". We considered this a minimum requirement for a review to be considered systematic. Data from original studies presented in more than one included review were only considered once in any analysis. Where reviews considered all interventions for CRPS, each review was compared to the most recent in order to establish whether the older review identified any RCTs that had not already been identified or data which were not adequately reported in the most recent review. Where this was not the case the older review was excluded. Similarly where more than one review investigated the same intervention, or class of interventions, the equivalent process was followed.

Types of participants

Adults 18 years or older described as suffering from CRPS or an alternative descriptor for this condition (for example reflex sympathetic dystrophy, causalgia). We also included studies with participants with post-stroke shoulder-hand syndrome, which is considered a form of CRPS and is distinct from mechanical post-stroke shoulder pain. The use of formal diagnostic criteria for CRPS is inconsistent within the literature (Reinders 2002). Therefore, to avoid excluding reviews which contained relevant studies we included reviews that did not use formally derived diagnostic criteria for CRPS. We included reviews of interventions for 'neuropathic pain' where studies specific to CRPS were presented and analysed separately, or in a subgroup analysis that was extractable. We did not consider comparisons that included participants with diagnoses other than CRPS.

Types of interventions

Any intervention aimed at reducing pain, disability, or both, for CRPS.

Types of outcome measure

Primary outcomes

1. Pain intensity or severity, as measured using a visual analogue scale (VAS), numerical rating scale (NRS) or Likert scale.
2. Disability, measured through self report scales or functional testing protocols.

These outcomes could be presented and analysed as change on a continuous scale or in a dichotomised format as the proportion of patients in each group who achieved a predetermined threshold of improvement (for example minimal clinically important difference (MCID), or recovery).

3. Adverse events, including the number and nature of adverse event withdrawals and serious adverse events, where possible.

Secondary outcomes

1. Quality of life, measured using any validated tool.
2. Emotional well being, measured using any validated tool.
3. Participant ratings of improvement or satisfaction with treatment, measured using any validated tool.

Search methods for identification of reviews

Electronic searches

We searched electronic databases using a combination of controlled vocabulary (MeSH) and free-text terms. We incorporated search terms to target CRPS and systematic reviews but did not include intervention-specific search terms since we wished to identify reviews of any of the interventions. We incorporated the BMJ Clinical Evidence search filter for systematic reviews. The search strategies for all databases can be found in the appendices. We based all database searches on this strategy but revised them to suit each database. We searched the following databases across all included years (see Appendices):

- Ovid MEDLINE (1948 to September week 4 2011) (Appendix 1);
- Ovid EMBASE (1980 to week 39 2011) (Appendix 2);
- Cochrane Database of Systematic Reviews (Issue 10 2011) and Database of Abstracts of Reviews of Effects (DARE) (Issue 4 2011) (Appendix 3);
- CINAHL (1982 to October 2011) (Appendix 4);
- PEDro (1929 to October 2011) (Appendix 5); and
- LILACS (all years to October 2011) (Appendix 6).

Searching other sources

We handsearched the reference lists of all eligible reviews and relevant clinical guidelines to attempt to identify additional relevant reviews (Appendix 7).

Language

The search attempted to identify and include all relevant studies irrespective of language.

Identification of reviews

Two overview authors independently checked the search results and included eligible reviews. Initially we reviewed the titles and abstracts of identified studies and excluded studies that were clearly not relevant. Where it was not clear from the abstract whether a study was relevant we checked the full review to confirm its eligibility.

Data collection and analysis

Selection of reviews

Two overview authors (NOC and BW) independently applied the selection criteria to the full papers of identified reviews. Disagreement between overview authors was resolved through discussion. Where resolution was not achieved a third overview author (JM) considered the study(ies) in question. The team's content expert (GLM) reviewed a final list of included reviews and it was sent for review by an external expert in the field of CRPS research to attempt to identify any omissions.

Data extraction and management

Two overview authors (NOC and BW) extracted data independently using a standardised form. Discrepancies were resolved by consensus. Where agreement could not be reached a third overview author (JM) considered the paper and we made a majority decision. The data extraction form included the following details:

- assessment of methodological quality of the included review;
- objectives of the review;
- details of the included participants;
- interventions studied;
- outcomes and time points assessed (primary and secondary);
- comparisons performed and meta-analysis details; and
- assessment of the methodological quality and risk of bias of the included evidence.

We contacted the authors of the reviews or the original study reports in the event that the required information could not be extracted from the reports.

Assessment of methodological quality of included reviews

We used the AMSTAR tool to assess the methodological quality of the included reviews (Shea 2007) (see Table 2). We applied this to both Cochrane and non-Cochrane reviews.

Assessment of the quality of the evidence in included reviews

Included reviews assessed the methodological quality and risk of bias of included studies in a variety of ways. Therefore, we used the judgements made by the authors of the original reviews regarding the quality of evidence and risk of bias but we have reported it critically within the context of our assessment of the quality of the review itself. Where possible, we used GRADE (Balshem 2011) to assess the quality of the evidence for each type of intervention, each diagnostic group (CRPS-I and II), and each primary outcome. During discussion with the PaPaS editorial team it was agreed that, given the clear empirical evidence that systematic bias is introduced in pain trials by small sample size and inadequate length of follow up (Moore 2011; Nüesch 2010), we would need to consider these factors within the GRADE judgement. Therefore we added the following criteria post hoc for potentially downgrading the judgement of a body of evidence and applied these criteria consistently across all comparisons.

Sample size: downgrade twice if the pooled sample size was < 50 participants per arm; downgrade once if less than 200 participants per arm. Where conclusions were not made from a pooled analysis the same rule was applied to the sample of the individual studies. We applied this criterion whether or not a positive result was reported for that intervention since while small studies tend to produce positive results through publication biases, they may also return spurious negative results as a result of the play of chance (Moore 2010).

Length of follow up: downgrade twice if the latest duration of follow up was < two weeks; downgrade once if two to six weeks. This was applied only where an effect of the intervention was reported.

Data synthesis

Where possible, we extracted data from the included reviews and presented data in a tabular or figure format. The precise comparisons presented were primarily determined by the content of the included reviews. We presented effect sizes using appropriate metrics including, where possible, the number needed to treat for an additional beneficial outcome (NNT) and number needed to harm for an additional harmful outcome (NNH). In interpreting reductions in pain intensity we considered a $\geq$ 15% reduction in pain as a minimally important benefit, a $\geq$ 30% reduction in pain to represent a moderately important benefit, and a $\geq$ 50% reduction in pain intensity to represent a substantially important benefit, as suggested by the IMMPACT guidelines (Dworkin 2008).

We grouped data, where possible, according to diagnosis (CRPS type I or II), intervention and outcome (pain or disability) clearly stating where results applied to CRPS-I, II or a mixed group. For pharmacologic interventions we aimed to extract separate comparisons, where available, for distinct agents within a class of drug. For complex interventions such as physiotherapy, where studies have taken a multi-modal approach to treatment, we considered these interventions under their broad label (for example 'physiotherapy') unless it was clear that the interventions contained within the comparisons were distinct. In that instance we extracted separate comparisons for distinct treatment approaches (for example range of motion exercises, graded motor imagery or electrotherapy might be considered in separate analyses), where available.

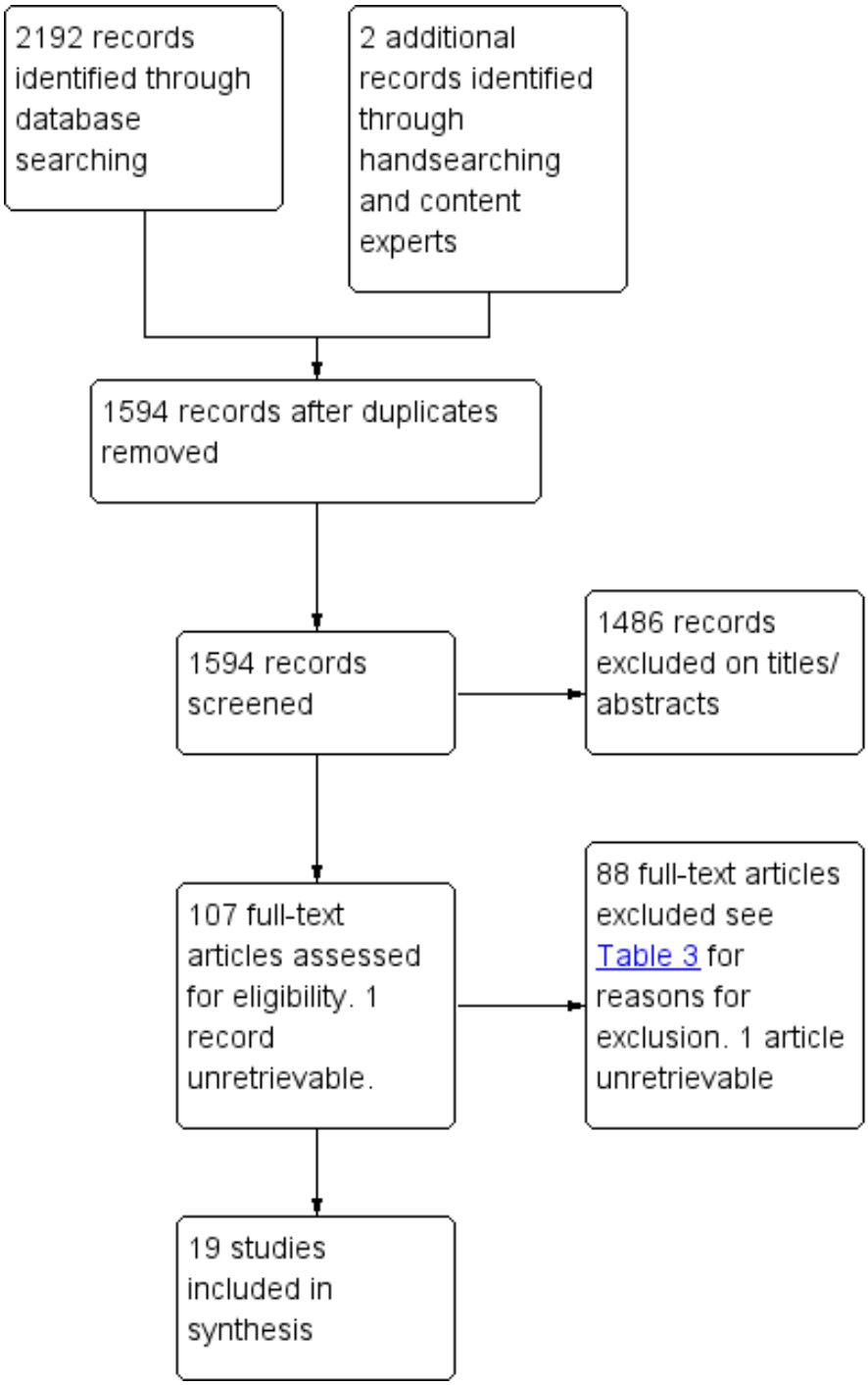
We planned to present and discuss important limitations within the evidence base and to consider the possible influence of publication and small study biases on review findings. Where possible, for studies that utilised dichotomised outcomes, we planned to

test for the possible influence of publication bias on each outcome by estimating the number of participants in the studies with zero effect required to change the NNT to an unacceptably high level (defined as an NNT of 10 or more), as outlined by Moore 2008.

RESULTS

See Figure 1 for a flow diagram of the search process. Database searches identified 2192 records from which 600 duplicates were identified and removed. One additional record was identified from handsearching and one by consulting our content expert (GLM). From the remaining 1594 records, 1486 were removed following screening of the titles and abstracts. The kappa level of agreement for this stage was 0.76. We were unable to retrieve one record for full-text review (see 'Classification pending' references). The remaining 107 full-text articles were assessed for eligibility. Of these 88 were excluded (see Table 3 for the reasons for exclusion). The kappa level of agreement for this stage was 0.83. Nineteen systematic reviews were included in the final overview. For one review (Lu 2009) all data extraction and quality assessment was performed by a lone interpreter.

Figure 1. Study flow diagram.



Description of included reviews

We included six Cochrane reviews (Cepeda 2005; Challapalli 2005; Mailis-Gagnon 2004; Moore 2011; O'Connell 2010; Straube 2010) and 13 non-Cochrane systematic reviews (Brunner 2009; Chauvineau 2005; Collins 2010; Daly 2009; Fischer 2010; Forouzanfar 2002; Jadad 1995; Lu 2009; Perez 2001; Rothgangel 2011; Simpson 2009; Smith 2005; Tran 2010). See Table 4 for a list of the reviews and original trials which have contributed to this review and Table 5 for the characteristics of the included reviews.

CRPS specificity of included reviews

One of the Cochrane reviews (Cepeda 2005) was specific to CRPS. The remaining Cochrane reviews included a mix of chronic or neuropathic pain populations but included studies that were specific to CRPS and reflex sympathetic dystrophy (RSD) populations. Of the non-Cochrane reviews nine were specific to CRPS-I and RSD populations (Brunner 2009; Chauvineau 2005; Daly 2009; Fischer 2010; Forouzanfar 2002; Jadad 1995; Perez 2001; Smith 2005; Tran 2010), one was specific to post-stroke shoulder-hand syndrome (Lu 2009), two included trials of mixed chronic pain conditions (Collins 2010; Simpson 2009) and one review of mirror therapy included any condition (Rothgangel 2011). No reviews were specific to CRPS-II. Only trials specific to CRPS or its alternative diagnostic labels were included in this overview.

Interventions for CRPS covered by included reviews

The included reviews appraised the evidence for a broad range of pharmacologic, surgical or interventional, physical and alternative interventions. Pharmacotherapies evaluated in reviews included bisphosphonates (Brunner 2009; Chauvineau 2005), calcitonin (Perez 2001; Tran 2010), corticosteroids (Fischer 2010), clonidine (Tran 2010), N-methyl-d-aspartate (NMDA) receptor antagonists (Collins 2010), free radical scavengers (Fischer 2010), gabapentin (Moore 2011), sarpogrelate hydrochloride (Tran 2010), tadalafil (Tran 2010) and systematic local anaesthetic agents (Challapalli 2005). Interventional procedures included the following agents delivered using intravenous regional blocks (IVRBs): guanethidine (Jadad 1995; Tran 2010), ketanserin (Forouzanfar 2002; Jadad 1995), droperidol, bretylium (Jadad 1995) and atropine (Tran 2010). Other interventional procedures included local anaesthetic sympathetic blockade (Cepeda 2005; Tran 2010) and surgical sympathectomy (Straube 2010). Neurostimulation interventions included spinal cord stimulation (Mailis-Gagnon 2004; Simpson 2009) and repetitive transcranial magnetic stimulation of the motor cortex (O'Connell 2010). Physical and rehabilitation interventions included physiotherapy and occupational therapy (Daly 2009), pulsed electromagnetic field therapy (Daly 2009), mirror therapy (Rothgangel 2011) and graded motor imagery (Daly 2009; Rothgangel 2011). Alternative therapies included acupuncture, relaxation training and Qigong therapy (Forouzanfar 2002; Smith 2005). See Table 4 for a list of which reviews uniquely contributed to the overview.

Intervention specificity of included reviews

All of the included Cochrane reviews aimed to evaluate the efficacy of a specific class of intervention. Of the non-Cochrane reviews, 10 reviews (Brunner 2009; Chauvineau 2005; Collins 2010; Daly 2009; Fischer 2010; Jadad 1995; Lu 2009; Rothgangel 2011; Simpson 2009; Smith 2005) were concerned with a specific class of intervention and three aimed to include a broad range of interventions for CRPS and RSD (Forouzanfar 2002; Perez 2001; Tran 2010).

Methodological quality of included reviews

See Table 6 for the results of the AMSTAR quality assessment. The kappa level of agreement between the two review authors for the AMSTAR assessment was 0.85. AMSTAR methodological quality scores ranged from 9 to 10 out of 11 (median 10) for Cochrane reviews and from three to eight (median five) for non-Cochrane reviews; this difference was statistically significant (Mann-Whitney U test $P < 0.001$). None of the included reviews met the AMSTAR criterion "Was the conflict of interest stated?" as even in those reviews where review authors declared their own conflicts of interest no review systematically reported author conflicts of interest from the included trials.

Effect of interventions

For a summary of all comparisons for all treatments including quality of evidence judgements see Table 7. Comparisons of the included studies referred to outcomes measured at the end of the intervention period unless otherwise stated.

Pharmacotherapy

Anti-inflammatory treatments

Fischer 2010 specifically investigated the evidence for the efficacy of anti-inflammatory interventions in a non-Cochrane review. This review included both randomised and non-randomised studies, although only evidence from randomised studies was considered here. The heterogeneity of outcomes and interventions has precluded pooling of data. No data were provided on adverse

events. Study quality was assessed with a nine-item tool in which fulfilment of each item scored a point to a total of 9 points. A paper scoring 7 to 9 was assessed as being of high quality, scores between 4 and 6 indicated moderate quality and scores between 0 and 3 indicated poor quality.

Corticosteroids (oral)

Three trials compared varying doses of oral corticosteroids to placebo, of which one trial used pain intensity as a primary outcome and two trials used composite CRPS and RSD scores. One trial was scored as poor quality (Lukovic 2006: 3/9) and the other two as moderate quality (Braus 1994: 4/9; Christensen 1982: 5/9). No effect was observed on pain intensity in one trial (Lukovic 2006, n = 60). Of the two trials which used composite outcome measures, one (Christensen 1982, n = 23) demonstrated positive effects and the other (Braus 1994, n = 36) was suggestive of a positive effect but did not present any data for between-group comparisons of drug versus placebo. All three trials suffered from substantial methodological limitations, which left them at high risk of bias.

One high quality trial (Kalita 2006, n = 60) compared oral corticosteroids with the NSAID piroxicam and used a composite CRPS score as an outcome. This trial demonstrated a positive effect in favour of prednisolone (mean difference in 0 to 14 CRPS score -5.10, 95% CI -6.55 to -3.65) although the methodological assessment by Fischer 2010 suggested that the study groups were not similar at baseline. The baseline data from the groups in this trial suggested differences between groups in the size of haematoma and the presence or absence of sensory loss, while other baseline variables appeared similar.

GRADE quality judgement

There was very low quality evidence (evidence from randomised controlled trial (RCT): high, downgrade once for single trial, twice for sample size and once for methodological quality) that oral corticosteroids did not effectively reduce pain intensity compared with placebo.

There was very low quality evidence (evidence from RCTs: high, downgrade twice for sample size, once for methodological limitations and once for inadequate reporting) that oral corticosteroids improved composite CRPS scores compared with placebo. The size of this effect was not clear.

There was very low quality evidence (evidence from one high quality trial, downgrade twice for sample size, once for single study) that oral prednisolone may be superior to piroxicam for improving composite CRPS scores.

Corticosteroids (IVRB)

One trial assessed as high quality (Taskaynatan 2004, n = 22) compared an IVRB of methylprednisolone and lidocaine with a saline placebo delivered once a week for a total of three procedures. With pain as a primary outcome no significant difference was observed, although the study was small and potentially underpowered.

GRADE quality judgement

There was very low quality evidence (evidence from one RCT: high, downgrade once for single study, twice for sample size) that IVRB with methylprednisolone was not more effective than placebo in reducing CRPS-related pain.

Free radical scavengers (topical)

Four trials investigated the topical application of preparations of the free radical scavenger dimethyl sulphoxide (DMSO). Two trials compared topical DMSO with a placebo preparation, of which one high quality trial (Zuurmond 1996, n = 30) reported a negative result on pain and one low quality trial (Goris 1987, n = 20) reported a positive effect on patients' subjective evaluation of clinical improvement. One moderate quality but unblinded trial (Geertzen 1994, n = 26) compared topical DMSO with IVRB guanethidine and reported a positive result, and one larger high quality trial (Perez 2003, n = 146) compared DMSO with N-acetylcysteine and demonstrated no difference on composite CRPS scores.

Free radical scavengers (intravenous)

One trial (Perez 2008, n = 41) assessed as high quality compared intravenous mannitol versus placebo and found no improvement in pain, function or quality of life.

The evidence for the use of the various available anti-inflammatory medications was mixed. Most of the evidence came from small studies, the majority of which suffered from a variety of methodological limitations that rendered them at risk of bias. The positive conclusion reported by the authors of the systematic review (Fischer 2010) seemed to be based largely on the favourable results seen in non-randomised studies. Based on the RCTs reviewed here, there was insufficient evidence from which to draw strong conclusions regarding any of these therapies.

GRADE quality judgement

There was very low quality evidence (evidence from RCT: high, downgrade once for single study and twice for small sample size) that topical DMSO did not effectively reduce pain in CRPS compared with placebo.

There was very low quality evidence (evidence from RCT: downgrade once for single study, twice for sample size and once for low methodological quality) that topical DMSO was more effective than placebo in improving patients' subjective rating of improvement.

There was low quality evidence (evidence from RCT: high, downgrade once for single study and once for sample size) that topical

DMSO did not improve composite CRPS scores compared with N-acetylcysteine.

There was very low quality evidence (evidence from RCT: downgrade once for single study, twice for sample size and once for lack of blinding) that topical DMSO more effectively improved CRPS composite scores than IVRB guanethidine.

There was very low quality evidence (evidence from RCT, downgrade once for single study, twice for small sample) that intravenous mannitol was not more effective than placebo.

Bisphosphonates

Two non-Cochrane reviews (Brunner 2009; Chauvineau 2005) specifically investigated the evidence for the efficacy of bisphosphonates in CRPS-I. The following evidence was taken from both reviews because the earlier review (Chauvineau 2005) included a comparative RCT that was excluded by Brunner 2009 as it only considered trials of bisphosphonates compared with placebo.

Bisphosphonates versus placebo

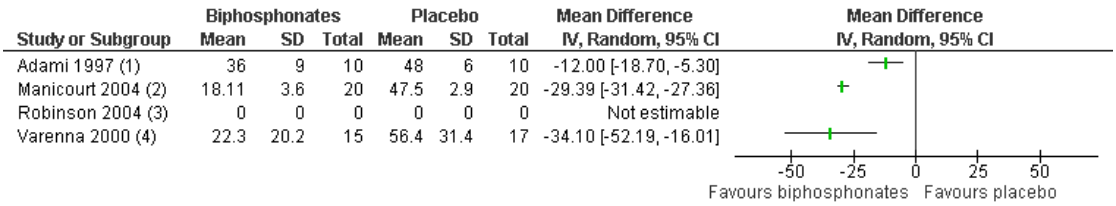
The reviews identified four trials which compared various bisphosphonates with placebo. All trials were small with sample sizes ranged from 20 to 39 participants. Brunner 2009 assessed the trials as being of 'moderate quality', and inspection of the quality assessment results revealed that all four trials did not address at least two of the 22 quality criteria at all and of the remaining criteria at least four more were 'less than appropriately' addressed for all four trials, though a number of the quality criteria reflected external rather than internal validity.

Two trials compared alendronate with placebo. One of these (Adami 1997, n = 20) delivered alendronate intravenously (7.5 mg for three days) and one (Manicourt 2004, n = 39) orally (40 mg/day for eight weeks). One trial (Robinson 2004, n = 27) compared intravenous (IV) pamidronate (60 mg single infusion) with placebo and one trial (Varenna 2000, n = 32) compared IV clondronate (300 mg/day for 10 days) with placebo. Of these trials, three (Adami 1997; Manicourt 2004; Varenna 2000) specifically recruited patients with clinical signs of regional osteopenia or osteoporosis. Robinson 2004 did not specifically assess the presence of bone changes in included participants.

Pain

Of these four trials, Brunner 2009 pooled data on pain (0 to 100 VAS) from two (Manicourt 2004; Robinson 2004) (oral alendronate and IV pamidronate versus placebo, combined n = 66). The remaining two trials were excluded from the pooled analysis on the basis of excessive methodological heterogeneity. They reported a weighted average effect of -22.4 at four weeks and -21.6 at 12 weeks on a 0 to 100 pain VAS scale. No precision estimates or measures of statistical significance or heterogeneity were reported and little information was provided regarding the statistical methods used to pool data except that data were pooled using variance weights. As such this estimate should be interpreted with caution. Of the trials not included in the meta-analysis no information regarding pain relief was provided by Brunner 2009. Data obtained from the authors of Adami 1997 demonstrated a between group mean difference in pain intensity in favour of alendronate over placebo (0 to 100 VAS) of -12 (95% CI -18.7 to -5.5) at the end of the two week blind treatment period, representing a reduction from the baseline pain score in the control group of 17% (95% CI 7 to 26). Data obtained following a request to the authors of Manicourt 2004 demonstrated a between group difference of -29.39 (95% CI -31.42 to -27.36) at the end of the eight week treatment period. This represented a reduction in pain of 59% (95% CI 54 to 63) of the baseline pain scores in the control group. Varenna 2000 reported a mean difference at 40 days after treatment of -34.10 (95% CI -52.1 to -16.019) on a 0 to 100mm VAS scale. Expressed as a percentage of the baseline mean pain score in the control group this equated to a 54.6% (95% CI 25.6 to 83.5) reduction in pain intensity, which met the criteria for a substantial clinically important difference, although the estimate was imprecise and the lower confidence limit was below the threshold of a moderately important difference. We were unable to extract the necessary data for the study of Robinson 2004. Pooling of the available data was considered inappropriate due to the very high statistical heterogeneity (I^2 > 90%). The individual study data are presented in Figure 2. This heterogeneity may plausibly have arisen from differences in the specific bisphosphonate used or the method of delivery. Importantly, all trials for which data were available demonstrated an effect that meets the IMMPACT recommendations threshold for a minimum clinically important difference and two of these meet the threshold for a substantial clinically important difference.

Figure 2. Effect sizes for RCTs of bisphosphonates versus placebo (immediate post-treatment period).



(1) IV alendronate
(2) oral Alendronate
(3) IV Pamidronate (data not available)
(4) IV Clodronate

Adverse events

In the trial of IV pamidronate (Robinson 2004) five patients in the treatment group and two in the control group developed influenza type symptoms and two patients in the control group developed an infusion site reaction. In one trial of IV alendronate (Adami 1997) three patients in the placebo control group developed a fever; in one trial of IV clondronate (Varenna 2000) three patients from the placebo control group developed asymptomatic hypocalcaemia. In one trial of oral alendronate (Manicourt 2004) one participant in the control group withdrew due to gastrointestinal side effects.

Other outcomes

None of the trials reported quality of life outcomes.Two studies of alendronate (IV and oral) (Adami 1997; Manicourt 2004) reported a significant improvement in joint mobility, measured in different ways; and one study (IV pamidronate) reported an improvement in physical function using the Short Form (SF)-36 after one and three months. No information regarding the size of these effects was reported in the review.

Brunner 2009 concluded that the evidence from trials investigating the effects of bisphosphonates in CRPS-I was scarce, that pooled analysis suggested a favourable effect on pain, and that for other clinically relevant outcomes all four studies showed trends towards favourable effects. However, they stated that there was insufficient evidence to recommend their use in practice.

GRADE quality judgement

There was low quality evidence that bisphosphonates may be effective for treating pain in CRPS-I (evidence from a number of RCTs: high, downgrade twice on sample size across studies, once for suboptimal scoring on multiple quality criteria and inadequate data reporting, upgrade once for consistent effect across studies). It was possible that these effects might be specific to CRPS that is accompanied by clinical signs of osteopenia or osteoporosis.

Bisphoshonates versus alternative interventions

Chauvineau 2005 identified one additional comparative trial rated as 'average quality' on a three-item quality assessment tool (Cohen 1998, n = 14) of bisphosphonates (IV pamidronate 60 mg, single dose) compared with intranasal calcitonin (200 IU/day for 15 days). Outcomes included pain, grip strength and range of motion, and participants were followed over six months. No difference was observed between the two groups for any outcome. Adverse events were not reported.

GRADE quality judgement

There was very low quality evidence that IV pamidronate was not superior to calcitonin nasal spray (evidence from one RCT: high, downgrade once for single trial and twice for sample size and once for methodological limitations).

Calcitonin

Two non-Cochrane reviews that investigated calcitonin for CRPS were reviewed (Perez 2001; Tran 2010) since the earlier review included two non-English language comparative trials that were not included in the later review.

Calcitonin versus placebo or no treatment

Two trials were identified that compared nasal calcitonin with placebo. Of these, one trial (Bickerstaff 1991, n = 38) observed no difference for any outcome and one trial (Gobelet 1992, n = 66) observed greater improvement in static and dynamic pain scores and range of motion at the end of an eight week treatment phase. One trial (Gobelet 1986, n = 24) compared daily subcutaneous calcitonin combined with physical therapy with physical therapy

alone and demonstrated no difference in pain, range of motion or fitness to work. Using a weighted methodological quality assessment, expressed as a percentage (higher scores equating to higher quality), Perez 2001 scored one trial (Gobelet 1986) at 45%, one at 75% (Gobelet 1992) and one (Bickerstaff 1991) at 43%. Using a more limited quality tool that assessed just two criteria for blinded assessment and sample size justification, Tran 2010 found that all three studies failed to present a sample size justification and only one study (Gobelet 1992) met the criteria for blinded assessment.

In their review, Perez 2001 pooled data on pain relief from trials of calcitonin versus placebo up to 2001 (data from Bickerstaff 1991; Gobelet 1986; Gobelet 1992). Using a random effects-model they found an effect size (modified Glass Δ , adjusted to account for sample size) of 0.444 (SD 0.362, P = 0.005) with no significant heterogeneity. This review concluded that calcitonin seemed effective in reducing pain but the more recent review by Tran 2010, which did not include a meta-analysis or non-English language studies, concluded that since most trials failed to detect a benefit calcitonin has not been proven to reliably decrease pain or swelling or increase range of motion.

Calcitonin versus alternative interventions

One trial (Sahin 2006, n = 35) compared nasal calcitonin with a course of oral paracetamol (acetaminophen), both in conjunction with physical therapy for three weeks, and demonstrated no between group differences in pain, range of motion or any other outcome measures. Tran 2010 noted that this trial did not provide a sample size justification but did blind the assessors. Two trials (Friez 1982, n = 55; Cherot 1983, n = 95) of very low quality (quality score 29% and 15%, respectively) compared calcitonin with griseofulvin or ß-blockers and found comparable results. As stated above, the review by Chauvineau 2005 identified one additional comparative trial rated as of 'average quality' on a three-item quality assessment tool (Cohen 1998, n = 14) of intranasal calcitonin (200 IU/day for 15 days) compared with bisphosphonates (IV pamidronate 60 mg, single dose). Outcomes included pain, grip strength and range of motion and participants were followed over six months. No difference was observed between the two groups for any outcome. Adverse events were not reported.

Adverse events

Neither review that considered calcitonin reported the incidence or nature of adverse events. It was not clear whether this reflected a lack of events or a lack of reporting.

GRADE quality judgement

There was low quality evidence (evidence from a meta-analysis of controlled trials: high, downgrade once for methodological limitations and once on sample size, pooled n = 128) that calcitonin delivered in a variety of ways was more effective at reducing CRPS-related pain than placebo.

There was very low quality evidence (evidence from an RCT: high, downgrade once for single study and twice for sample size) that nasal calcitonin was not superior to oral paracetamol.

There was very low quality evidence (evidence from an RCT: high, downgrade once for single trial, twice for sample size and twice for very low quality) that calcitonin was as effective as griseofulvin or ß-blockers for the treatment of CRPS.

There was very low quality evidence (evidence from an RCT: high, downgrade once for methodological limitations and twice for small sample size) that intranasal calcitonin was as effective as a single dose of IV pamidronate across multiple outcomes.

Gabapentin

Gabapentin versus placebo

One Cochrane review (Moore 2011) investigated gabapentin for chronic neuropathic pain and fibromyalgia and included one cross-over trial (van de Vusse 2004, n = 58) that specifically investigated gabapentin versus placebo for the treatment of pain in CRPS-I. Participants were randomised to receive either a maximum of 1800 mg/day gabapentin orally or placebo with their usual analgesics unchanged. The study achieved 5/5 on the Jadad methodology scale but was assessed as being at high risk of bias due to incomplete outcome data (analysis was only performed on completers, with a 21% withdrawal rate) and sample size and at unclear risk of bias based on the duration of follow up (only three weeks) and on outcomes (the criteria for judging a participant as 'much improved' were not clearly defined).

The study did not demonstrate a significant effect on pain. A responder analysis for the outcome pain 'very much improved' found a relative risk (RR) of 4.00 (95% CI 0.90 to 17.83, P = 0.07).

Adverse events

Moore 2011 presented data on adverse events from all studies of gabapentin for chronic neuropathic pain and fibromyalgia (including but not exclusive to CRPS). In 11 studies (n = 2356) that reported the proportion of participants who experienced at least one adverse event, the RR was 1.3 (95% CI 1.2 to 1.4) and the number needed to treat to harm (NNH) was 6.6 (95% CI 5.3 to 9). For serious adverse events (14 studies, n = 2702) the RR was 1.3 (95% CI 0.9 to 2).

Data were also provided on the following specific adverse events when gabapentin was used across a wide range of chronic neuropathic pain conditions: somnolence (16 studies, n = 2800) RR 3.2 (95% CI 2.5 to 4.2), NNH 9.2 (95% CI 7.7 to 12); dizziness (16 studies, n = 3150) RR 3.2 (95% CI 2.5 to 4.2), NNH 7 (95% CI 6.1 to 8.4); peripheral oedema (nine studies, n = 2402)

RR 3.4 (95% CI 2.1 to 5.3), NNH 19 (95% CI 14 to 29); and ataxia and gait disturbance (five studies, n = 544) RR 4.5 (95% CI 1.9 to 11), NNH 13 (95% CI 9 to 24). In the included trial in CRPS patients (van de Vusse 2004) dizziness, somnolence and lethargy were more commonly reported with gabapentin than with placebo. A higher number of reports of headache, nausea, feeling drunk and disturbed gait were also found in the gabapentin group but these did not reach statistical significance in this small sample.

GRADE quality judgement

There was very low quality evidence that gabapentin was not effective for the treatment of CRPS-I (evidence from one RCT: high, downgrade once for single trial, twice for sample size and once for incomplete outcome data).

There was high quality evidence (from multiple RCTs) that participants taking gabapentin experienced a variety of adverse events more frequently than those taking placebo, but that the incidence of serious adverse events were not more frequent.

NMDA receptor antagonists

One included non-Cochrane review (Collins 2010) specifically investigated the efficacy of N-methyl-d-aspartate (NMDA) receptor antagonists for the treatment of neuropathic pain. They included three trials specific to CRPS.

NMDA receptor antagonists versus placebo

One cross-over trial (Finch 2009, n = 20) investigated a topical 10% ketamine cream to a placebo cream in a mixed population of CRPS-I and CRPS-II patients. However, while the reviewers included the study by Finch 2009 that study did not include pain intensity as a clinical outcome, rather they assessed the effects of topical ketamine on allodynia. As such that study was not considered further in this overview. Two parallel trials (Schwartzman 2009, n = 19; Sigtermans 2009, n = 60) studied IV ketamine versus placebo. Applying an adapted version of the Delphi list Collins 2010 assessed both trials as being of good methodological quality (using a cut-off for good quality of fulfilling $\geq$ 6/11 criteria) though data for each specific quality item were not presented in their review.

Schwartzman 2009 compared IV ketamine at a maximum dosage of 0.35 mg/kg/h over four hours each working day for 10 days in a mixed group of patients with CRPS-I and CRPS-II. Sigtermans 2009 compared IV ketamine (S+ enantiomer) at a mean (SD) dose of 22.2 (2) mg/h continuously for 4.2 days in patients with CRPS-I. While both studies reported positive results on pain, Collins 2010 performed a meta-analysis of these two studies (n = 79) which revealed significant heterogeneity (I^2 = 55%) and did not indicate a significant positive pooled effect of IV ketamine on pain relief in CRPS (inverse variance, random-effects model, standardised mean difference (SMD) -0.65, 95% CI -1.47 to 0.16, P = 0.11). However, this pooled effect size appeared inconsistent with the presented forest plot. In order to check this result we reanalysed this data from the same time points (see Figure 3). Using inverse variance and a random-effects model our analysis suggested a non-significant pooled effect size, more consistent with the Collins 2010 forest plot, though with much higher heterogeneity (SMD -3.07, 95% CI -7.85 to 1.72, P = 0.21, I^2 = 98%). The effect size observed by Sigtermans 2009 (our analysis) was much larger (SMD -5.52, 95% CI -6.66 to -4.38, P < 0.001) than that observed by Schwartzman 2009 (our analysis) (SMD -0.64, 95% CI -1.57 to 0.29, P = 0.18). Collins 2010 suggested that the heterogeneity in effect sizes may be explained by the use of the more potent S+ enantiomer in the trial by Sigtermans 2009, although the dosage schedule also differed substantially between the studies. However, both studies utilised the same numerical rating scale (NRS) with the same anchors. As such, these studies met the assumptions which would support a meta-analysis using the more meaningful mean difference as the pooled measure of effect. This analysis (inverse variance, random-effects model) (see Figure 4) suggested a pooled mean difference on a 0 to 10 NRS of -2.63 (95% CI -3.39 to -1.88) with a much reduced degree of heterogeneity (I^2 = 28%) and suggested a significant effect of ketamine on pain (P = 0.00001). Expressed as a proportion of the baseline levels of pain in the larger of the two studies (Sigtermans 2009) (7.0, SD 1.3) this equated to a 38% (95% CI 27 to 48) reduction in pain with ketamine, which would meet the IMMPACT criteria for a moderately important benefit. This suggested that the observed heterogeneity was in large part a statistical artefact due to the use of the standardised mean difference (SMD) as the summary effect measure and that the use of different enantiomers between studies had little bearing on outcome. Sigtermans 2009 and Schwartzman 2009 followed participants for 12 weeks post-treatment. Sigtermans 2009 reported that the difference in pain scores remained statistically significant at week 11 but was no longer significant at week 12. They did not present data for pain scores at this time point. Schwartzman 2009 reported that the difference in pain scores remained statistically significant at three to four week follow up but did not reach significance beyond that time.

Figure 3. Meta-analysis using SMD of pain VAS scores for studies of ketamine identified in the review by Collins 2011.

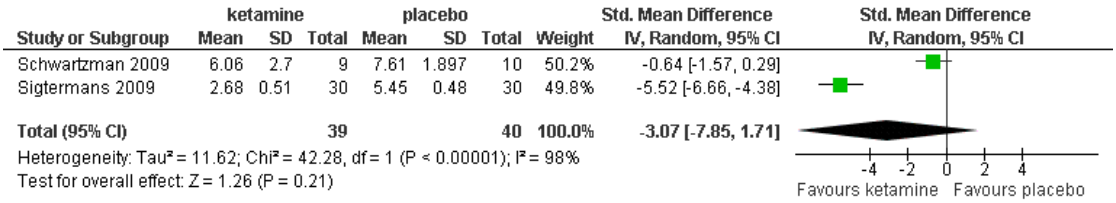
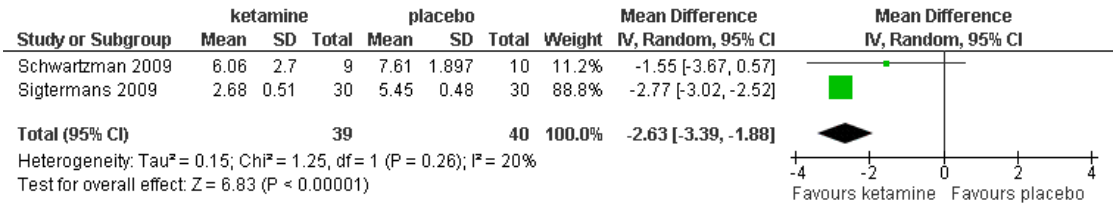


Figure 4. Meta-analysis using mean difference of pain VAS scores for studies of ketamine identified in the review by Collins 2011.



Collins conclude that based on the current evidence there was insufficient data from which to draw definite conclusions regarding neuropathic pain. However, this may have been in part based on the reporting of an incorrect effect size and the degree of caution expressed may in part reflect the choice of meta-analysis method.

Adverse events

Collins 2010 provided a list of reported adverse events but offered no quantitative analysis of adverse events. From ketamine studies in a variety of neuropathic pain conditions, including but not exclusive to CRPS, they list the following adverse events: sedation, dreams, hallucinations, dissociative reactions, nausea, headache, dizziness, fatigue, changes in mood, altered sight, feeling of unreality, dry mouth, light-headedness, paraesthesia, changed taste, dysarthria, euphoria, tinnitus, drunkenness, itching, muteness and hyperventilation. Schwartzman 2009 reported that 4/9 participants in the ketamine group reported nausea, headache, tiredness or dysphoria at some point during the trial compared with 2/10 in the placebo group. Sigtermans 2009 reported a statistically significant higher rate of the following side effects in the ketamine group: nausea 63% versus 17% in the placebo group, vomiting 47% versus 10% in the placebo group, psychomimetic effects 93% versus 17% in the placebo group, and headache 37% versus 33% in the placebo group. Neither trial reported serious adverse events though with such small numbers the risk of serious adverse events should not be ruled out.

For other NMDA antagonists for which there were no trials specifically on CRPS patients, a similar range of adverse events were listed, again without any quantitative assessment.

GRADE quality judgement

There was low quality evidence (evidence from RCTs: downgrade twice for sample size) that a course of IV ketamine may be effective for CRPS-related pain. The effects did not appear to be sustained beyond four to 11 weeks post-treatment.

Sarpogrelate hydrochloride

One non-Cochrane review (Tran 2010) identified one trial (Ogawa 1998, n = 37) which investigated the efficacy of the selective 5-HT_2 antagonist sarpogrelate hydrochloride in participants with a diagnosis of RSD (diagnostic criteria not specified). Tran 2010 assessed the study as unblinded and as not providing a sample size justification. Ogawa 1998 compared oral sarpogrelate hydrochloride (300 mg/day) plus conventional treatment (consisting of analgesics, antidepressants, antiepileptics, physical therapy and sedatives) to conventional treatment alone in 37 patients with RSD and 56 patients with postherpetic neuralgia, with a separate analysis of the data from the RSD group. Tran 2010 reported no difference in pain between the two groups in this non-placebo controlled trial,

although with sarpogrelate a greater proportion of participants reported improvement in burning pain sensation. Ogawa 1998 reported that in the RSD group pain intensity reduced significantly whereas it did not in the control group. However, results of a between-group comparison did not reach statistical significance (P = 0.136) and the size of effect, presented only in a graphical format, appeared trivial.

Adverse events

Tran 2010 did not report any information on adverse events for this drug. Ogawa 1998 reported that no severe side effects were observed but reported that across both diagnostic groups adverse reactions included diarrhoea, headache, palpitation, nausea, palmar oedema, dizziness, weight gain (each of which occurred only in one patient) and constipation (reported by two patients). The incidence of adverse reactions was 11.7% (7/60) compared with 3.8% (1/26) in the control group.

GRADE quality judgement

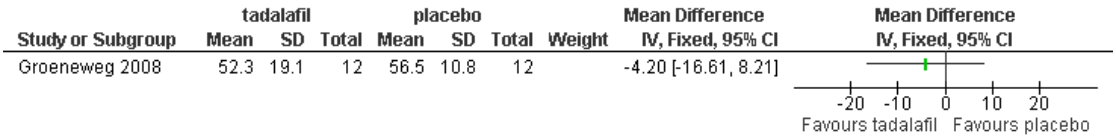
There was very low quality evidence (RCT evidence: not downgraded on lack of placebo or effective blinding as these biases might be expected to exaggerate an effect, downgrade once for single trial and twice for sample size) that sarpogrelate hydrochloride was not effective for reducing CRPS-related pain.

Tadalafil

One non-Cochrane review (Tran 2010) identified one trial (Groeneweg 2008) of the vasodilator tadalafil. The study was assessed by Tran 2010 as having a blinded assessment and a justification of the sample size.

Groeneweg 2008 compared oral tadalafil (10 mg/day for four weeks followed by 20 mg/day for eight weeks) with placebo in patients (n = 24) with chronic cold CRPS of the lower extremity (established using the diagnostic criteria described by Bruehl 1999). Both groups continued with physiotherapy. Pain was measured as a secondary outcome using a 0 to 100mm VAS. Groeneweg 2008 reported a significant reduction in pain at the end of treatment with the active group experiencing a 15% reduction in pain and the placebo group a 1% reduction. However, this result may have been influenced by baseline differences between the groups in mean pain ratings, and our own analysis of post-treatment pain scores (see Figure 5) suggested a smaller non-significant effect with a between-group difference in pain of 4.2/100 favouring the tadalafil group. We were not able to perform an analysis of change from baseline scores since the standard deviation (SD) of change scores was not available from the study reports. In light of the difference in mean pain scores at baseline the observed difference should be interpreted with caution. In any event the less conservative estimate of a 15% reduction in pain did not meet the IMMPACT criteria for a moderately important benefit, and no data on longer-term effects were available. Furthermore, no significant differences were observed across a number of functional scores.

Figure 5. Mean difference calculated for the trial of tadalafil versus placebo (Groeneweg 2008).



Adverse events

While the review by Tran 2010 did not report adverse events, the report by Groeneweg 2008 stated that there were no serious adverse events. Reports of a warm affected extremity and itching were present in most participants in the active group, and two participants of 12 in the active group reported experiencing whole body muscle pains.

GRADE quality judgement

There was very low quality evidence (RCT evidence: downgrade once for single trial, twice for small sample, and once for baseline differences) that tadalafil may have a small short-term effect on pain which was unlikely to be clinically significant, but no effect on function in chronic cold CRPS of the lower extremity.

Systemic local anaesthetic agents

In a Cochrane review of local anaesthetic agents to relieve neuropathic pain, Challapalli 2005 identified one trial (Wallace 2000) of IV lidocaine.

Intravenous lidocaine versus placebo

Wallace 2000 (n = 16) compared a single IV lidocaine infusion targeted to deliver a stepped increase in plasma concentrations of 1, 1.5, 2 or 3 µg/ml with IV diphenhydramine (70 to 80 mg) in a cross-over study with a one week washout period between interventions. Diphenhydramine was used as a placebo control in an attempt to preserve blinding since it shares a similar side effect profile to lidocaine. Challapalli 2005 awarded this study 3/5 on the Oxford quality scale.

While Wallace 2000 reported a statistically significant effect on spontaneous pain at the highest plasma concentration ($P < 0.05$) immediately post-intervention, the review by Challapalli 2005 reported no overall statistically significant effect on spontaneous pain but acknowledged a relationship between dose and degree of pain relief. From the original study report, no actual numeric data were provided for this comparison, including no specific data on the size of effect. Visual inspection of the presented graph suggested that the observed effect was very small, and substantially smaller than the IMMPACT recommendations for a moderately important benefit.

Adverse events

While actual numbers were not stated, Wallace 2000 reported that the mean lightheadedness score was higher in the lidocaine group than the placebo group ($P < 0.05$) but sedation and dry mouth scores were similar between groups.

GRADE quality judgement

There was very low quality evidence (RCT evidence: downgrade once for single trial, twice for sample size, once for lack of overall between group effects, once for a moderate score on the Jadad quality scale and twice for very short-term follow up) that high dose IV lidocaine infusion may have a small effect on pain compared to diphenhydramine. It was not clear whether this effect persisted beyond the immediate post-treatment period.

Interventional procedures

Clonidine (epidural)

One non-Cochrane review (Tran 2010) identified one trial of epidural clonidine (Rauck 1993). This small (n = 26) trial recruited patients with upper or lower limb CRPS that had not responded to previous sympathetic blocks. The trial was assessed as having adequately blinded assessors but did not provide a sample size justification. Patients received either 300 μg, 700 μg clonidine or saline on consecutive days via catheters placed at the C7 to T1 spinal levels for upper limb CRPS and at the L2 to L3 spinal levels for lower limb CRPS and were studied for six hours post-treatment with no apparent washout period. In the six hour period, pain was reported to be significantly improved versus placebo by a similar amount in both treatment groups. For the primary outcome of pain VAS, no numeric post-treatment scores were provided in the review or the original study report.

Adverse events

Sedation scores were found to be significantly higher in patients receiving the higher dose of clonidine (700 μg).

GRADE quality judgement

There was very low quality evidence that clonidine may provide immediate pain relief in CRPS that is refractory to sympathetic blockade (evidence from one RCT: high, downgrade once for single trial, twice for sample size, once for lack of washout period, once for insufficient outcome reporting and twice for very short-term follow up). It was not clear whether pain relief persisted for more than six hours post-treatment.

Intravenous regional blocks (Bier blocks)

Three included non-Cochrane reviews identified trials of intravenous regional blocks (IVRB) with a variety of agents. One review (Jadad 1995) specifically sought to systematically review the evidence for IVRBs and the other two (Forouzanfar 2002; Tran 2010) were general systematic reviews of a range of interventions including IVRBs.

Intravenous regional block atropine

Tran 2010 identified one study (Glynn 1993) of IVRB using atropine.

Glynn 1993 (n = 30) compared IVRB with atropine (0.6 mg in normal saline) to a normal saline placebo control in patients with sympathetically maintained pain (diagnosed by a positive response to a guanethidine IVRB) using a cross-over design. Three participants withdrew from the study and were excluded from the analysis. Pain was measured using a VAS for one week following the intervention. Tran 2010 judged the trial as adequately blinded. The sample size was not justified adequately. At one week no differences were observed in pain or mood. Tran 2010 concluded that the evidence did not support the use of IVRB with atropine.

Adverse events

Tran 2010 did not report any evidence relating to adverse events for IVRB with atropine.

GRADE quality judgement

There was very low quality evidence (evidence from an RCT: downgrade one for a single study, twice for a small sample size) that IVRB with atropine was not effective for sympathetically maintained pain.

Intravenous regional block bretylium

Jadad 1995 identified one study (Hord 1992, n = 12) that compared IVRB with bretylium to a lidocaine control. In a cross-over study Hord 1992 gave each patient with RSD (diagnostic criteria not clearly defined) two treatments of bretylium (1.5 mg/kg) + lidocaine (200 to 300 mg) and two treatments of lidocaine (200 to 300 mg) alone. The outcome was the duration post-IVRB that patients experienced ≥ 30% pain relief. The study reported that following the bretylium IVRB patients experienced a significantly longer period of ≥ 30% pain relief (active group mean (SD) duration of relief 20.0 (17.5) days versus control group mean 2.7 (3.7) days). Jadad 1995 identified the following methodological limitations with this study: the diagnostic criteria were poorly defined, and there was a high proportion of dropouts (5/12, of which two contributed some data) with no intention-to-treat analysis. They concluded that there was some evidence that bretylium IVRB blocks may be effective but that there was a substantial risk of a false positive.

Adverse events

Jadad 1995 did not report any evidence relating to adverse events for IVRB bretylium. Hord 1992 reported that one patient developed orthostatic hypotension and one demonstrated a reduction in heart rate of greater than 25%, which they attributed to resolution of pre-block anxiety.

GRADE quality judgement

There was very low quality evidence (trial evidence: downgrade once for single trial, twice for sample size, once for methodological limitations) that IVRB bretylium with lidocaine may have been more effective than lidocaine alone in providing a longer duration of pain relief (possibly around two weeks longer).

Intravenous regional block droperidol

Jadad 1995 identified one very small study (Kettler 1988, n = 6) of IVRB using droperidol (2.5 mg), due to its properties as a known α-adrenergic receptor antagonist and subsequent potential for altering sympathetic activity, plus heparin (500 to 1000 U) versus IVRB with heparin (500 to 1000 U) in normal saline in patients with RSD (three affecting the upper and three affecting the lower extremities). Jadad 1995 criticised the study for its high proportion of withdrawals and lack of intention-to-treat analysis. Only one patient in the droperidol group reported a reduction in pain compared with three in the placebo group. However, the trial was terminated early due to the number of patients reporting side effects and the lack of clear pain relief with droperidol over placebo.

Adverse events

Jadad 1995 did not present data on adverse events. In their study report Kettler 1988 described complications in three of six patients receiving droperidol. These included dysphoria and nausea (two patients), akithesia (two patients) and hypotension (one patient). One patient refused to complete the study as the akathisia, dysphoria and nausea were too distressing.

Jadad 1995 concluded that there was no RCT evidence to support the use of IVRB with droperidol but drew attention to the substantial risk of false negatives.

GRADE quality judgement

There was very low quality evidence (trial-based evidence: downgrade twice for very small sample size, once for single study and once for high withdrawal rate) that IVRB using droperidol was not an effective treatment for RSD-related pain. The procedure appeared to be associated with frequent adverse effects.

Intravenous regional block guanethidine

The review by Jadad 1995 identified four studies evaluating guanethidine IVRBs for reflex sympathetic dystrophy as well as presenting the results of their own RCT. Blanchard 1990 (n = 21) and Jadad 1995 (n = 9) compared guanethidine IVRB with placebo. Bonelli 1983 (n = 19) compared guanethidine with a stellate ganglion block with bupivacaine, and Rocco 1989 (n = 12) and Dhar 1992 (n = 15) both compared guanethidine with lignocaine. Tran 2010 identified two additional, more recent studies. Livingstone 2002 (n = 56) compared guanethidine with placebo in CRPS-I using the International Association for the Study of Pain (IASP) diagnostic criteria and Ramamurthy 1995 (n = 57) compared one, two or four guanethidine IVRBs in patients with non-chronic (< 3 months from onset) CRPS. Of these studies, five (Blanchard 1990; Dhar 1992; Jadad 1995; Livingstone 2002; Rocco 1989) used a cross-over design. Five of these studies (Blanchard 1990; Dhar 1992; Jadad 1995; Livingstone 2002; Rocco 1989) were double blinded and one (Bonelli 1983) was open label. In their review, Jadad 1995 identified a number of methodological weaknesses: Blanchard 1990 did not clearly define their diagnostic criteria for RSD, Blanchard 1990 and Rocco 1989 did not achieve cross-over of all participants, and Dhar 1992 provided no description of the technique. Tran 2010 assessed the study by Livingstone 2002 as including an adequate justification of sample size and adequate blinding of assessors, and the study by Ramamurthy 1995 as having adequate blinding of assessors but no sample size justification.

Using a variety of pain intensity-related outcome measures and dosing schedules none of these studies demonstrated a significant effect on pain compared with placebo, and Ramamurthy 1995 found no difference between groups receiving varying numbers of guanethidine blocks. Jadad 1995 and Tran 2010 both concluded that the available evidence did not support the efficacy of guanethidine for CRPS and RSD.

Adverse events

Jadad 1995 did not report the incidence of adverse events from their included studies but in their own study they stopped the trial early as two participants experienced severe episodes of postural hypotension, one of whom also developed bradycardia and chest pain, despite neither having a prior history of cardiovascular disease. From the review by Tran 2010, Livingstone 2002 found that when compared with placebo, participants receiving guanethidine were more likely at 15 week follow up to experience persistent alterations in hand colour ($P = 0.015$) and sensitivity to changes in ambient temperature ($P = 0.003$), and at 30 weeks more participants receiving guanethidine reported altered hand temperature ($P < 0.001$) and digital swelling ($P < 0.04$).

GRADE quality judgement

Using the GRADE approach there was moderate quality evidence (multiple RCTs: all negative, downgrade twice for small sample sizes and upgrade once for consistently negative results) that guanethidine blocks were not effective in reducing pain in CRPS.

Intravenous regional block ketanserin

Two reviews (Forouzanfar 2002; Jadad 1995) together identified two cross-over studies of ketanserin IVRB (a 5-HT_2 receptor antagonist) (Bounameaux 1984; Hanna 1989). However while Hanna 1989 (n = 16 with peripheral burning pain, of which nine presented with 'signs of RSD') delivered ketanserin (10 mg, two treatments of ketanserin and two of placebo) via an IVRB, Bounameaux 1984 (n = 9) delivered the same dose but via a standard IV delivery with no tourniquet. Both studies used cross-over designs and compared ketanserin with a saline placebo. Using a 15-point methodology quality scale that produces a score out of 100, Forouzanfar 2002 judged both of these studies to be of low quality (score < 50/100). Jadad 1995 criticised the study by Hanna 1989 for poorly defined diagnostic criteria and an inadequate washout period. Similarly Bounameaux 1984 did not provide clear diagnostic inclusion criteria.

Bounameaux 1984 did not demonstrate an effect of ketanserin on an incompletely defined subjective symptoms score. Hanna 1989 reported a significant effect of ketanserin on mean weekly pain intensity only in the participants with signs of RSD. It did not appear that this was based on a between-groups test versus the placebo group. In addition, the carry-over of observed reductions in pain in the group that received ketanserin first persisted into the placebo testing phase, making such an assessment difficult. No numeric data were provided in the reviews of Jadad 1995 or Forouzanfar 2002, or the original study report, regarding the size of the effect.

Jadad 1995 concluded that there was some evidence for IVRB using ketanserin but that there was a substantial risk of false positives.

Adverse events

Neither review (Forouzanfar 2002; Jadad 1995) reported adverse events for ketanserin. Bounameaux 1984 reported that five patients complained of transient dizziness following ketanserin delivery. Hanna 1989 reported that following tourniquet release, drowsiness, shakiness and faintness were more frequent after ketanserin than placebo but that all side effects were mild and transient. Their data also suggested an increase in the incidence of palpitations and visual disturbances.

GRADE quality judgement

There was very low quality evidence (evidence from trials: downgrade once for conflicting evidence, twice for small sample and twice for serious methodological limitations, lack of data on effect size or between-groups analysis) that ketanserin might be effective at reducing pain in RSD.

Local sympathetic blockade

One Cochrane review (Cepeda 2005) specifically investigated the efficacy of local anaesthetic sympathetic blockade for CRPS and one more recent non-Cochrane review (Tran 2010) of all interventions for CRPS identified a further study of local sympathetic blockade using botulinum toxin A. This study was considered individually since botulinum toxin is not simply a local anaesthetic and would be expected to induce longer-lasting effects on the sympathetic nervous system.

Local anaesthetic sympathetic blockade

Cepeda 2005 identified two cross-over studies of local anaesthetic sympathetic blockade in CRPS. Price 1998 (n = 7) compared stellate ganglion block (four patients, bupivacaine 0.125%) or lumbar sympathetic block (three patients, 15 ml lidocaine 1%) with normal saline in patients with CRPS of the upper or lower extremities based on the IASP diagnostic criteria. Verdugo 1995 (n = 16) compared a stellate ganglion block with bupivacaine (0.125%) or normal saline in patients with CRPS of the upper extremity. Both studies investigated the proportion of participants who experienced 50% pain relief, and Price 1998 also measured the duration of pain relief and the mean between-group difference in pain relief on a VAS. Cepeda 2005 assessed the risk of bias across

four items: randomisation, concealed allocation, double blinding and information on dropouts. Other than concealed allocation for the Verdugo 1995 study, both trials met these criteria although it was noted that the study by Verdugo 1995 was published as a conference proceeding and the final results of the study have yet to be published in full.

For immediate pain relief Price 1998 observed no difference between anaesthetic block and placebo. Under both conditions six out of seven patients reported 50% pain relief. Verdugo 1995 found that 12 out of 16 patients receiving bupivacaine had 50% pain relief compared with eight out of 16 receiving placebo. Cepeda 2005 pooled these results using a Mantel-Haenszel random-effects model. The reported RR for 50% pain relief 30 minutes to two hours post-block was non-significant at 1.17 (95% CI 0.80 to 1.72).

For longer-term pain relief Verdugo 1995 found that 48 hours after blockade five out of 16 patients achieved 50% pain relief versus eight out of 16 receiving placebo. Price 1998 found that the duration of pain relief was longer with local anaesthetic block (three days) than with placebo (19.9 hours) despite finding similar proportions of responders between groups in terms of short-term pain relief.

Adverse events

Despite specifically seeking evidence on the incidence of adverse events Cepeda 2005 found that neither study reported side effects or complications.

Cepeda 2005 concluded that no conclusions could be drawn from the scarce data available, and no conclusions could be drawn regarding the safety of the procedure.

GRADE quality judgement

There was low quality evidence (trial evidence: downgraded twice for sample size) that local anaesthetic sympathetic blockade was not effective at reducing pain in CRPS.

Botulinum toxin A sympathetic blockade

Tran 2010 identified one study (Carroll 2009) that used botulinum toxin A to prevent release of acetylcholine in order to block sympathetic nerves.

In a cross-over study Carroll 2009 (n = 9, of whom seven completed the study, two were excluded from the analysis) compared sympathetic block with botulinum toxin A (75 U) plus bupivacaine (10 ml of 0.5%) with just bupivacaine (10 ml of 0.5%) in patients with CRPS of the lower extremity, established using the older IASP diagnostic criteria (Merskey 1994). The primary outcome was the duration that pain (measured using a VAS) remained below baseline levels. Tran 2010 assessed the study as adequately blinding assessment but not providing a justification of the sample size.

Carroll 2009 reported a significantly longer duration of analgesia in the botulinum toxin group: median time to analgesic failure 71 days (95% CI 12 to 253) compared with bupivacaine alone (< 10 days, 95% CI 0 to 12, P < 0.02). However, while Carroll 2009 claimed that pain significantly reduced in the botulinum toxin group they did not provide numeric data on pain scores for both groups.

Adverse events

Tran 2010 did not report information on adverse events. Carroll 2009 reported that one patient experienced two days of nausea and emesis that commenced five hours following botulinum toxin injection and resolved spontaneously.

Tran 2010 concluded that while this study suggested that botulinum toxin sympathetic block could increase the duration of analgesia, this requires further investigation.

GRADE quality judgement

There was very low quality evidence (trial evidence: downgraded once for single study, twice for small sample and once for incomplete outcome data) that sympathetic block using botulinum toxin A with local anaesthetic may have effectively increased the duration of analgesia in comparison to local anaesthetic alone by around two months. It was unclear what degree of pain relief might be achieved by this intervention.

Sympathectomy

One Cochrane review (Straube 2010) specifically reviewed the evidence for surgical or chemical sympathectomy in neuropathic pain and CRPS. They identified no studies comparing sympathectomy with placebo or sham interventions and only one study (Manjunath 2008) comparing two different approaches to sympathectomy.

Manjunath 2008 compared the effect on pain relief of percutaneous radiofrequency lumbar sympathectomy with neurolytic lumbar sympathectomy with phenol in 20 participants with CRPS-I of the lower extremity. Participants had chronic CRPS-I that was refractory to multidisciplinary treatment and unresponsive to medications for more than six months. They had also responded to a diagnostic block with 1% lidocaine on three occasions. Straube 2010 assessed the study as scoring 5/5 on the Oxford Quality Score, 13/16 on the Oxford Pain Validity Scale and not at high risk of bias.

Manjunath 2008 reported no significant between group difference one day after treatment or at four month follow up, although both groups reported reductions in pain.

Straube 2010 concluded that based on very limited evidence radiofrequency sympathectomy and neurolytic sympathectomy with

phenol were equally efficacious but that the practice of sympathectomy was based on very little high quality evidence. As such this technique should only be used cautiously in clinical practice in carefully selected patients.

Adverse events

All participants complained of injection site soreness lasting between five and seven days. One participant developed post-sympathectomy neuralgia in the phenol neurolysis group. Two participants in the radiofrequency group reported paraesthesia during needle positioning. Straube 2010 stated that the incidence of serious adverse events was not reported.

GRADE quality judgement

There was no evidence from controlled trials that sympathectomy was effective for treating pain in CRPS compared with placebo or no treatment.

There was very low quality evidence (evidence from RCT (high): downgrade once for single study and twice for sample size) that there was no difference in efficacy between radiofrequency and phenol neurolytic sympathectomy.

Neurostimulation methods

Non-invasive brain stimulation (repetitive transcranial magnetic stimulation)

In a Cochrane review of non-invasive brain stimulation techniques for chronic pain, O'Connell 2010 identified one study (Pleger 2004) of repetitive transcranial magnetic stimulation (rTMS) for CRPS.

In a cross-over trial Pleger 2004 (n = 10) compared the effect on pain intensity (VAS) of a single dose of rTMS applied to the motor cortex (stimulation parameters: frequency 10 Hz, coil orientation not specified, intensity (% of resting motor threshold) 110%, number of trains 10, duration of trains 1.2 sec, inter-train interval 10 sec, total number pulses 120) with sham stimulation in 10 participants with upper or lower extremity CRPS-I using the IASP criteria (Merskey 1994). Using the Cochrane risk of bias tool O'Connell 2010 assessed the study as being at unclear risk of bias with regard to assessor and participant blinding.

While Pleger 2004 reported a statistically significant between-group difference they did not present data from the sham condition. These data were provided to the reviewers on request. Including this study in a wider meta-analysis (generic inverse variance, random-effects model) they estimated a non-significant standardised mean difference of -0.14 (95% CI -0.57 to 0.29, P = 0.52). The raw mean difference on a 0 to 10 VAS was 0.38. The size of this study raised the possibility of a false negative.

Adverse events

While Pleger 2004 did not report any adverse events, among a wider group of studies of rTMS for chronic pain O'Connell 2010 found only minor transient adverse events (headache, nausea, dizziness or tinnitus) that occurred following both active and sham stimulation. One study of rTMS found a higher incidence of headache and neck pain after active stimulation (six out of 14) compared with sham (two out of 14). In general, many studies did not report the incidence and nature of adverse events.

GRADE quality judgement

There was very low quality evidence (trial evidence: downgraded once for single study, twice for very small sample size, once for conflicting conclusions between the revIew and original study and twice for short duration of follow up) that a single dose of high frequency rTMS did not effectively reduce pain in CRPS-I.

Spinal cord stimulation

One Cochrane review (Mailis-Gagnon 2004) specifically reviewed the evidence for spinal cord stimulation (SCS) in the treatment of chronic pain and identified three papers (Kemler 2000; Kemler 2001; Kemler 2002) relating to one study of SCS for RSD. A later Health Technology Assessments review (Simpson 2009) additionally identified two reports (Kemler 2004; Kemler 2006) with two year and five year results from the same study.

In this study 54 participants with RSD of the upper or lower extremity (established using the IASP criteria) were randomised to receive SCS via surgically implanted electrodes (frequency 85 Hz, bandwidth 210 msec) plus physical therapy (a standardised programme of graded exercises for strength, mobility and function, twice weekly for six months) or the same physical therapy without SCS. Pain intensity was the primary outcome and quality of life, function, self rated depression and the patients global perceived quality of life were all measured. In the SCS group participants received a test stimulation via a temporary electrode for seven days. Participants who experienced at least 50% pain relief for at least four days of this period received a permanent implant; those who did not received physical therapy only. Of 36 participants randomised to the SCS group 12 did not experience benefit in the test period and received only control treatment, but were included in the stimulation group in an intention-to-treat analysis. No sham SCS condition was used. Mailis-Gagnon 2004 assessed this study as scoring 3/5 on the Oxford Quality Scale as the caregiver and assessor were not blinded.

Pain

At one month (n = 54) significant differences were seen between the two groups in favour of the SCS + physiotherapy group. The

mean between-group difference in pain intensity at one month (0 to 10 VAS) was -2.70 (95% CI -3.77 to -1.63), at three months it was -2.50 (95% CI -3.94 to -1.06) and at six months it was -3.40 (95% CI -4.82 to -1.98). No responder analysis was given but, expressed as a percentage of the baseline pain level in the control group (6.7), this equated to a 51% (95% CI 30 to 71) reduction in pain with SCS + physical therapy compared to physical therapy alone. This met the IMMPACT recommendations for a substantially important benefit.

At two year (n = 51) and five year (n = 44) follow up between group differences in pain were not presented. However at two years the SCS group reported a mean (SD) change in pain from baseline of -2.1 (2.8) compared to a control group change of 0 (1.5) (P = 0.001). At five year follow up the change from baseline in the SCS group was -1.7 (SD not reported) compared to -1 in the control group (P = 0.25).

Health-related quality of life

No significant difference was observed in health-related quality of life at six months or two year follow up in an intention-to-treat analysis. A per protocol analysis at six months and two years demonstrated a significant effect on the pain component of the Nottingham Health Profile in both the upper (P = 0.02) and lower extremities (P = 0.008).

Function

No significant effect of SCS was observed in hand or foot function compared with the control group at six months and two year follow up.

Patients' perceptions of improvement

Significantly more patients considered themselves 'much improved' on a seven-point Global Perceived Effect scale in the SCS group at six months (P < 0.01) and at two years (P < 0.001).

Adverse events

Using data from all SCS studies Simpson 2009 described a range of adverse events including electrode migration, lead fracture, dural puncture and infection, and paraesthesia. Across all trials (n = 403) device removal was necessary in 1%, device-related complications ranged from 0% to 38% or with the exclusion of trials of short duration 5% to 38%. In the study by Kemler 2004 in CRPS at six months, of 24 participants given SCS there had been 13 device-related complications (some patients experienced more than one event), including two cases of dural puncture. Of these, five required surgery to resolve the problem and one was removed and replaced due to infection. At 24 months there had been 76 device-related complications of which nine required surgery.

Mailis-Gagnon 2004 concluded that there was limited evidence in favour of SCS for CRPS-I. Simpson 2009 concluded that the evidence suggested that SCS was effective for CRPS-I.

GRADE quality judgement

There was very low quality evidence (trial evidence: downgrade once for single study, twice for sample size, and once for lack of a sham or placebo control) that SCS + physiotherapy was effective at reducing pain in CRPS-I in comparison to physiotherapy alone for up to two years.

There was very low quality evidence (trial evidence: downgrade once for single study, twice for sample size, once for lack of a sham or placebo control, and once as the effect was not found in an intention-to-treat analysis) that SCS may improve health-related quality of life. There was very low quality evidence (trial evidence: downgrade once for single study, twice for sample size) that SCS was not effective at improving function in CRPS. There was very low quality evidence (trial evidence: downgrade once for single study, twice for sample size and once for lack of a sham or placebo control) that SCS was effective at improving patients' own perceptions of overall improvement for up to two years. Adverse events appeared frequent and the need for further surgery was not a rare occurrence.

Physiotherapy and occupational therapy

Three non-Cochrane reviews (Daly 2009; Forouzanfar 2002; Rothgangel 2011) identified seven reports (Durmus 2004; Moseley 2004; Moseley 2005; Oerlemans 1999; Oerlemans 1999a) of five trials of physical and occupational therapy type interventions.

General physical and occupational therapy

Daly 2009 identified three reports of one three-armed trial (Oerlemans 1999; Oerlemans 1999a; Oerlemans 2000) (n = 135) which compared physiotherapy (PT) with the specific objectives stated as "increase pain control, optimise coping, extinguish the source of pain and improve skills" plus a fixed protocol of medical treatment to occupational therapy (OT) with the specific objectives stated as "reduce inflammation, normalise sensation, improve function and activities of daily living" plus the same medical treatment protocol in patients with RSD. Using a quality checklist that returned a score out of 16 Daly 2009 assessed the study as 'good quality' (11/16). The third control group received a social work (SW) intervention which consisted of passive attention and advice. It was not clear which specific modalities were employed in either of the active therapy groups but the number and duration of treatment session differed depending on the severity and response to treatment. Relevant outcomes included pain, impairment and

disability. PT demonstrated statistically significant between-group improvements in pain and impairment at 12 months compared to OT or SW. However, these differences were small for both pain (PT versus OT: 0 to 100 VAS mean difference 4.5, 95% CI -10.1 to 19.1; PT versus SW: 5.2, 95% CI -3.3 to -7.1) and impairment (0 to 50 scale PT versus OT: mean difference 1.6, 95% CI 1 to 2.2; PT versus SW: 5.1, 95% CI 4.6 to 5.6). We were unable to extract data from the immediate post-treatment period or the three or six month follow up from either the original study reports or the review by Daly 2009, and we have not been able to obtain these data from the study authors. However, estimating the effect size from the presented graphs in the original study reports suggested no significant difference between PT and OT at any time point for pain or impairment, but that compared with the passive attention control PT and OT were superior at reducing pain at two, four and six months and PT, but not OT, was superior at improving impairment. The largest improvement in pain was seen in PT versus SW at six month follow up and was estimated to be a reduction of -19.50 (95% CI -32.05 to -6.95), which represented a reduction of 26% (95% CI 9 to 43) from baseline. This would meet the IMMPACT threshold for a minimum clinically important difference but not that of a moderate difference. This estimate should be treated with caution since it was based on the imputation of data represented only in a low resolution graphical format. The estimated data for these comparisons are presented in Figure 6; Figure 7; Figure 8; Figure 9.

Figure 6. Physiotherapy (PT) versus social work (SW). Outcome: pain (0-100 VAS). Data extracted by hand from graphical format (Oerlemans 1999a).

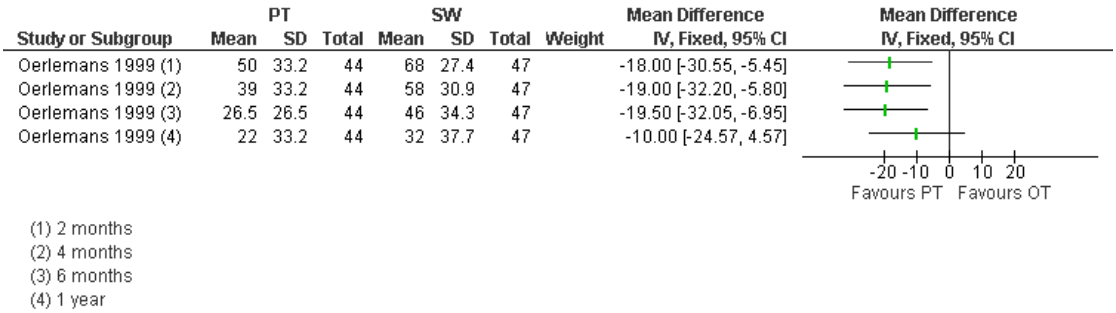


Figure 7. Occupational therapy (OT) versus social work (SW). Outcome: pain (0-100 VAS). Data extracted by hand from graphical format (Oerlemans 1999a).

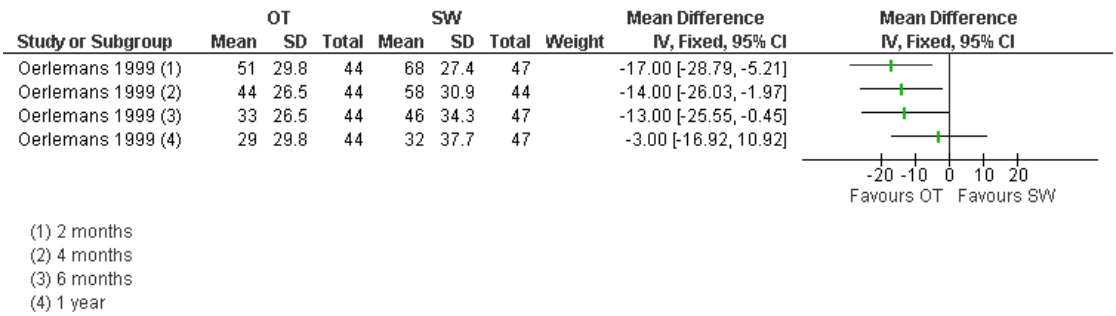
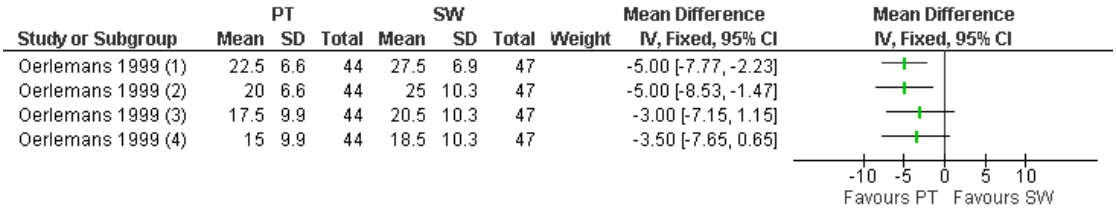
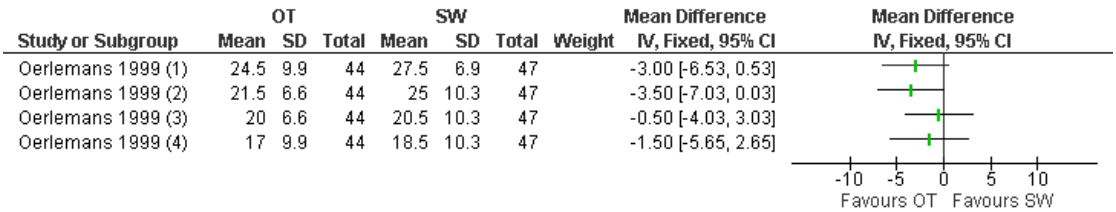


Figure 8. Physiotherapy (PT) versus social work (SW). Outcome: impairment (0-50 scale). Data extracted by hand from graphical format (Oerlemans 1999).



(1) 2 months
(2) 4 months
(3) 6 months
(4) 1 year

Figure 9. Occupational therapy (OT) versus social work (SW). Outcome: impairment (0-50 scale). Data extracted by hand from graphical format (Oerlemans 1999).



(1) 2 months
(2) 4 months
(3) 6 months
(4) 1 year

Forouzanfar 2002 identified one trial (Uher 2000) of exercise (three times a week for six weeks) combined with manual lymph drainage massage with exercise alone in 35 patients with CRPS-I. They demonstrated no differences between groups in a study which Forouzanfar 2002 gave a methodological quality score (using a 15-item checklist that returned a score out of 100) of 55/100.

Daly 2009 concluded that there was good quality level II evidence that pain management PT combined with medical management was more effective than OT or SW combined with medical management in patients with upper limb CRPS-I, but that the clinical relevance of this finding was questionable.

Adverse events

No evidence on adverse events was reported by Daly 2009.

GRADE quality judgement

There was low quality evidence (trial level: downgrade once for sample size and once for single study) that PT in addition to medical management was more effective than OT or SW in addition to medical management for improving pain and disability but that this difference was not clinically important.

There was very low quality evidence (evidence from RCT: downgrade once for sample size, once for single study and once as the data were estimated from a graphical format) that PT and OT were significantly more effective than a passive attention control in reducing pain for up to six months, and that PT, but not OT, was effective at improving impairment for up to four months compared with a passive attention-based SW control.

There was very low quality evidence (trial level: downgrade twice for single study, twice for sample size and once for methodological limitations) that manual lymph drainage did not offer additional

clinical benefit to exercises.

Pulsed electromagnetic field treatment

Daly 2009 identified one study (Durmus 2004, n = 40) which compared pulsed electromagnetic field (EMF) treatment (100 Gauss, 50 Hz, x 5 weekly for six weeks) plus calcitonin and a stretching exercise routine to placebo EMF plus calcitonin and stretching in patients with CRPS-I (IASP diagnostic criteria) following Colles fracture. Using a quality checklist that returned a score out of 16 Daly 2009 assessed the study as 'good quality' (12/16).

At the end of treatment Durmus 2004 found no between-group difference in pain at rest (VAS), pain on activity, or range of motion.

Daly 2009 concluded that there was good quality level II evidence (evidence obtained from at least one properly designed RCT, Australian National Health and Medical Research Council hierarchy of evidence) that EMF treatment offered no added benefit to calcitonin and exercise in upper limb CRPS-I patients.

Adverse events

No evidence on adverse events was presented by Daly 2009 or Durmus 2004.

GRADE quality judgement

There was very low quality evidence (trial evidence: downgrade once for single trial, twice for sample size) that EMF treatment offered no added benefit to calcitonin and exercise in upper limb CRPS-I patients.

Graded motor imagery and mirror therapy

In a review of mirror therapy for a range of conditions Rothgangel 2011 identified two studies (Moseley 2004; Moseley 2006) of graded motor imagery (GMI), which incorporated mirror therapy, and two studies (Cacchio 2009; Cacchio 2009a) of mirror therapy alone in participants with post-stroke CRPS. Daly 2009 included one additional study of graded motor imagery (Moseley 2005). Moseley 2006 included participants with CRPS as well as phantom limb pain post-amputation and phantom pain post-brachial plexus avulsion injury. Separate numerical data on the CRPS patients was provided by the author on request.

Graded motor imagery

Pain

Moseley 2004 (n = 15) compared a six week graded motor imagery (GMI) programme (consisting of two weeks of practising a task involving the recognition of limb laterality followed by two weeks of motor imagery followed by two weeks of mirror-box therapy, to be practised by participants every waking hour) with usual physiotherapy care (at least one session a week with additional home training) in patients with CRPS-I (IASP criteria). Both groups continued with their usual medical care. Using an 11-point quality scale with four additional quality and clinical relevance items, Rothgangel 2011 assessed this study as scoring 5.5/11, and 3/4 on the additional items. Points were not scored due to lack of reporting of concealment of allocation, baseline comparability, acceptable compliance levels, and due to a lack of blinded care provider, correction for attention, patient blinding and reporting of side effects. Using a quality checklist that returned a score out of 16 Daly 2009 assessed the study as 'good quality' (12/16). Moseley 2006 compared the same GMI regime to usual care in 37 participants with CRPS-I. Rothgangel 2011 gave this study a quality score of 8/11 and 3/4 on the additional criteria and Daly 2009 assessed the study as 'very good quality' (13/16).

Both studies demonstrated significant differences between groups at the end of six week treatment and at three month follow up on pain intensity. Pooling of results (from CRPS patients only, see Figure 10) using a fixed-effect model gave an effect size of -14.45 (95% CI -23.02 to -5.57, P = 0.001) on a 0 to 100 VAS with no significant heterogeneity. Expressed as a percentage of the mean baseline pain levels in the control group of the larger study (n = 58) this equated to a 25% (95% CI 9 to 39) reduction in pain intensity at six weeks. Pooling data from the longer-term follow up (three months for Moseley 2004 and six months for Moseley 2006, see Figure 11) produced an effect size of -21.64 (95% CI -30.02 to -13.27). This equated to a 37% (95% CI 22 to 51) reduction in pain intensity at three to six months. While the immediate post-treatment effect was below the threshold for a moderately clinically important difference it exceeded the IMMPACT threshold for a minimally important benefit (15%) and the latter effect met the threshold for a moderately important benefit.

Figure 10. Meta-analysis of GMI programmes versus usual care for pain. Outcome 0-100 VAS. Immediate post-treatment results.

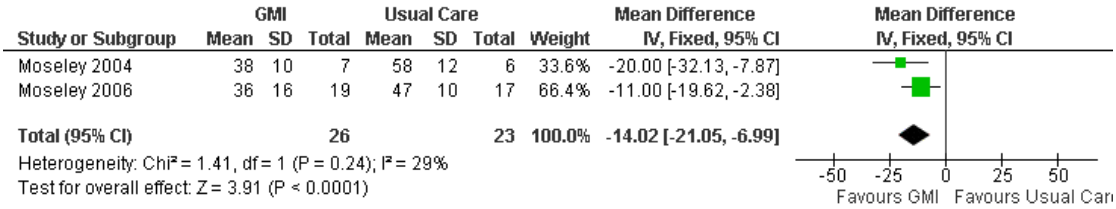
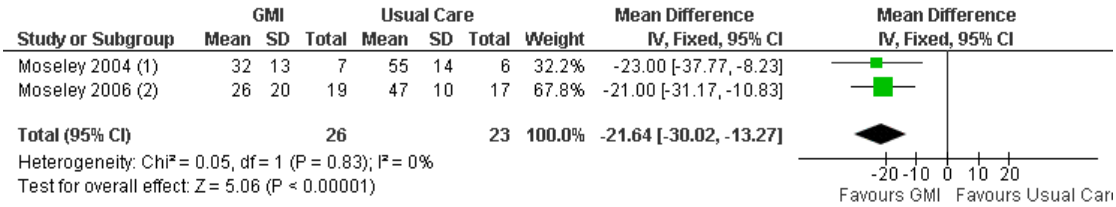


Figure 11. Meta-analysis of GMI programmes versus usual care for pain. Outcome 0-100 VAS. Results at follow up (3 or 6 months).



(1) 3 month
(2) 6 month

Daly 2009 identified a separate trial (Moseley 2005, n = 20) that compared GMI with the three components delivered in the same (correct) order with unordered GMI, with the components delivered in a way at odds with the hypothesised mechanism of action, in a similar group of CRPS-I patients. At the end of the six week treatment period there was a significant but small difference in pain intensity (0 to 100 scale) in favour of ordered GMI of 10 (95% CI -3 to 20) and of 18 (95% CI 5 to 25) at 12 weeks follow up. Daly 2009 assessed the study as 'good quality' (12/16).

Disability

Both GMI trials measured function or disability using a patient-specific task-related functional scale in which patients were asked to select five activities or tasks that they regularly performed prior to their injury but now found difficult to perform because of pain. Using an 11-point numerical rating scale (NRS) they were asked "How well can you perform that task now?" and the average of the five scales was taken as the score. A higher score indicated better functional recovery.

Pooling of the data on function (from CRPS patients only, obtained following request to the author), using the inverse variance method and a fixed-effect model, returned a mean difference of 1.90 (95% CI 1.96 to 2.54) at the end of treatment (see Figure 12) and 2.69 (95% CI 1.80 to 3.58) at follow up (see Figure 13), without statistically significant heterogeneity. This represented a large improvement in function from the baseline score in the control group of the larger trial (Moseley 2006) of 0.5.

Figure 12. Meta-analysis of GMI programmes versus usual care for function. Outcome 0-11 patient specific functional scale. Immediate post-treatment results.

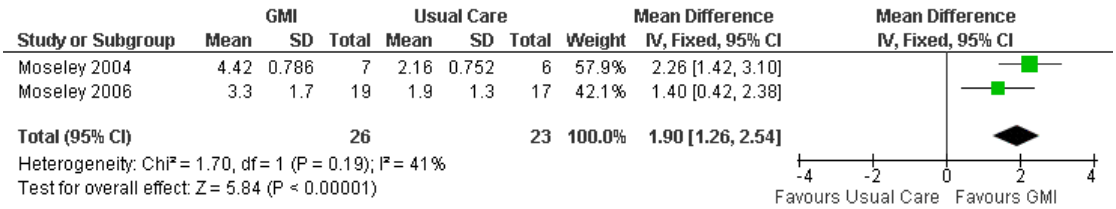
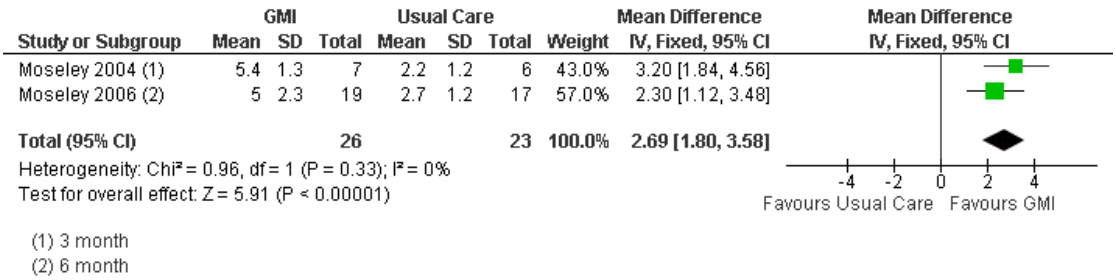


Figure 13. Meta-analysis of GMI programmes versus usual care for function. Outcome 0-11 patient-specific functional scale. Results at follow up (3 or 6 months).



Mirror therapy

Two trials of mirror therapy were identified in patients with post-stroke CRPS-I (IASP criteria). Cacchio 2009 (n = 48) compared mirror therapy (exercising the unaffected arm whilst attending to its reflection in place of the concealed affected arm; multiple movements of the shoulder, elbow, wrist and hand) for 30 minutes/day for two weeks then 60 minutes/day for two further weeks compared to the same movements without the mirror component (the mirror was covered to conceal the reflection). Both groups continued usual care. In a separate study Cacchio 2009a (n = 24) followed a similar mirror therapy exercise plan but for 30 minutes daily for four weeks and compared this to either covered mirror therapy or mental imagery training.

Rothgangel 2011 scored the methodological quality of Cacchio 2009 as 7/11 with 2/4 on their additional criteria. Specifically, the study was given an unclear rating for the method of randomisation, concealment of allocation, patient blinding and for the detail offered regarding the intervention. The score (Cacchio 2009a) was 3.5/11 with 1/4 on the additional criteria (Cacchio 2009a).

Both studies reported a significant improvement in pain with mirror therapy. From the original study report Cacchio 2009 reported a mean between-group difference following treatment in pain at rest (0 to 10 VAS) of -2.9 (95% CI -4.23 to -1.57) and in pain on movement of -3.10 (95% CI -4.28 to -1.92). At six month follow up the difference was still present, -3.4 (95% CI -4.71 to -2.09) for pain at rest and -3.8 (95% CI -4.96 to -2.64) for pain on movement. While no responder analysis was carried out in relation to the control group baseline score for pain at rest this equated to a 39% (95% CI 20 to 56) reduction in pain at the end of treatment that was sustained at six month follow up. Cacchio 2009a reported that seven out of eight patients in the mirror therapy group reported reduced pain (median change in 0 to 100 VAS of -51 mm, range -70 to -18) compared with one of eight patients in the covered mirror therapy group and two of eight patients in the mental imagery group; the median change was not reported for either the covered mirror or mental imagery groups. At the end of the treatment period pain scores were significantly lower in the mirror therapy group compared to the other two groups. However, no further between-group data were reported.

With regards to disability, Cacchio 2009 also reported a significant mean between-group difference in functional limitation (Wolf motor function (WMFT) test 0 to 5 functional ability subscale,

where lower scores indicate less functional limitation) of -1.9 (95% CI -2.36 to -1.44) at the end of treatment and of -2.3 (95% CI -2.88 to -1.72) at six month follow up. Cacchio 2009a reported significant improvements but did not present any extractable data for that outcome.

Considering the evidence in a range of pathologies Rothgangel 2011 concluded that firm conclusions could not be drawn regarding the efficacy of mirror therapy. Daly 2009 concluded that there was good quality evidence (level 2) that graded motor imagery plus medical management was more effective than standard physiotherapy plus medical management for upper or lower limb CRPS-I, but their conclusions were based on evidence that included a study comprising a mixed neuropathic population including conditions not considered in this overview.

Adverse events

Rothgangel 2011 noted a lack of attention to potential adverse events in the mirror therapy literature and Daly 2009 similarly found that no studies reported adverse events.

GRADE quality judgement

There was low quality evidence (evidence from two RCTs: downgrade twice for small sample, once for methodological limitations, upgrade once for consistently found effect sustained at longer-term follow up) that graded motor imagery plus medical management was more effective at reducing pain and improving function than conventional physiotherapy plus medical management in the treatment of CRPS-I and that the effect size may be of moderate clinical significance.

There was very low quality evidence (evidence from RCT: high, downgrade once for single study and twice for sample size) that ordered GMI was more effective at reducing CRPS-I related pain than unordered GMI although this effect appeared to be small and lacked clinical significance.

There was low quality evidence (evidence from a number of RCTs: downgrade twice for small sample, once for methodological limitations, upgrade once for consistently found effect sustained over longer-term follow up) that mirror therapy reduced pain and improved upper limb function in post-stroke CRPS compared with covered mirror therapy and that the effect may have moderate clinical significance.

Alternative therapies

Acupuncture

Three reviews identified studies of acupuncture for CRPS. One review specifically sought to identify studies of acupuncture for post-stoke shoulder-hand syndrome (Lu 2009), one review included acupuncture studies in a general review of physiotherapy interventions for CRPS-I (Smith 2005) and one review included studies of acupuncture in a review of all treatments for CRPS-I (Forouzanfar 2002).

Lu 2009 identified three studies of acupuncture for shoulder-hand syndrome after stroke (Chang 2005; Jin 2007; Liu 2006). While all three studies were described as RCTs the randomised nature of the studies was not mentioned or described in the methodology sections. Using the Oxford Quality Scale all three studies achieved scores of 1/5. Two trials (Chang 2005, n = 80; Liu 2006, n = 100) compared acupuncture and rehabilitation (positioning the damaged limb and exercises) to the same rehabilitation without acupuncture. One study (Jin 2007, n = 72) compared electro-acupuncture plus rehabilitation therapies (details not specified) to lidocaine, triamcinolone acetonide and vitamin B12. All three studies reported significant benefits in the acupuncture group. Chang 2005 reported significant improvements in function (Fugl-Meyer score), shoulder pain and shoulder movement. Jin 2007 reported a significantly higher 'cure' rate in the electro-acupuncture group, as did Liu 2006 in the acupuncture group. While all three studies demonstrated improvement with acupuncture Lu 2009 concluded that the poor quality of the studies and small sample size indicated that a positive conclusion regarding the efficacy of acupuncture for shoulder-hand syndrome required further confirmation.

Smith 2005 identified two trials of acupuncture for CRPS-I in adults. Ernst 1995 compared traditional acupuncture (five sessions/week for three weeks) to sham acupuncture (needles inserted in non-acupuncture 'point' locations) in 14 patients with chronic CRPS-I of the upper or lower extremities. Both groups also received a home exercise programme of limb elevation, exercises and cryotherapy. Kho 1995 compared classical acupuncture (five sessions/week for three weeks) with sham acupuncture (not described) in 28 patients with RSD of the upper or lower extremity. Smith reported that both studies reported greater short-term pain relief (VAS) with acupuncture versus sham but did not measure long-term results. Forouzanfar 2002 did not include the study by Ernst 1995 in their review but report that Kho 1995 found positive but non-significant results with acupuncture. From the original report by Ernst 1995 pain (VAS) reduced to a mean (standard error) of 17/100 (9.3) of baseline level in the acupuncture group compared with 28.6/100 (7.2) in the sham group. No formal statistical analysis was presented or discussed due to 'insufficient sample size'. While offering some broad methodological critique Smith 2005 did not present a systematic quality assessment of included studies. They concluded that acupuncture may help in the treatment of CRPS-I but that recurrent limitations in the literature (not exclusive to included acupuncture studies) meant that it was not possible to determine the effectiveness of individual treatments.

Forouzanfar 2002 identified two further studies of acupuncture. Korpan 1999 (n = 14) compared acupuncture five times a week for three weeks to sham (not described) in patients with CRPS-I

and did not demonstrate any improvement. Fialka 1993 compared acupuncture (five times/week for three weeks) to sham (type of sham not reported by Forouzanfar 2002) in 14 patients with RSD. At the end of treatment no significant between-group difference was observed in mean pain reduction (VAS). Forouzanfar 2002 used a 15-item methodological quality checklist that returned a score out of 100. They assessed Korpan 1999 as scoring 41.5, Kho 1995 as scoring 26.5 and Fialka as scoring 38/100. While the specific scoring for each study on each criterion was not presented, all of these scores can be considered to reflect significant methodological limitations.

Adverse events

Neither Lu 2009 nor Smith 2005 reported the incidence or nature of any adverse events following acupuncture.

GRADE quality judgement

There was very low quality evidence (RCT evidence: high, downgrade twice for multiple methodological limitations and twice for sample size) that acupuncture might be effective at offering short-term pain relief in post-stroke shoulder pain when added to rehabilitation therapy, compared to rehabilitation therapy alone, and that electro-acupuncture plus rehabilitation therapies (details not specified) might be more effective than lidocaine, triamcinolone acetonide and vitamin B12.

There was very low quality evidence (evidence from RCTs: high, downgrade twice for multiple methodological limitations and twice for sample size) that acupuncture was not superior to sham acupuncture in the treatment of CRPS.

Qigong therapy

Smith 2005 and Forouzanfar 2002 identified one study (Wu 1999) of Qigong therapy. Wu 1999 (n = 26) compared Qigong therapy, consisting of physical exercises performed to specific music and visual images (six sessions over a four week period), to 'sham' Qigong treatment consisting of participants being shown visual images of abstract art, listening to similar music to the Qigong group but not exercising. Forouzanfar 2002 assessed this study as scoring 59/100 on methodological quality. The assessor was not blinded to the treatment condition. According to Smith 2005, Wu 1999 found that 91% reported a reduction in pain compared to 36% in the sham group, although the size of this reduction was not reported by either review. Both groups reported a reduction in anxiety although this reduction was significantly greater in the sham group. Again the size of this effect was not reported. No difference between groups was seen in range of motion. Smith 2005 reported no formal methodological quality assessment for this study.

Adverse events

Neither Forouzanfar 2002 nor Smith 2005 reported the incidence or nature of any adverse events following Qigong.

GRADE quality judgement

There was very low quality evidence (trial evidence: high, downgrade once for single trial, twice for small sample and once for methodological limitations) that Qigong therapy was superior to sham therapy in reducing CRPS-related pain.

Relaxation training

Smith 2005 identified one study (Fialka 1996, n = 18) which compared autogenic relaxation training (10 session over 10 weeks) in addition to a home programme of limb elevation, ice and therapeutic exercises to the same home programme without autogenic training in patients with upper limb CRPS. Forouzanfar 2002 gave a quality score of 38/100. They found no between-group differences in pain or range of motion. Smith 2005 reported no formal methodological quality assessment for this study.

GRADE quality judgement

There was very low quality evidence (trial evidence: high, downgrade once for single trial, twice for small sample size and once for methodological limitations) that relaxation therapy did not reduce pain when added to limb elevation, ice and therapeutic exercises.

DISCUSSION

Summary of main results

This overview demonstrates that while a broad range of therapeutic approaches have been proposed for the treatment of CRPS pain and disability there is a critical lack of high quality evidence evaluating the effectiveness of most of these therapies. Very few large, controlled trials have been undertaken for this condition.

High quality evidence

There is no high quality evidence for or against the effectiveness of any intervention for CRPS.

Moderate quality evidence

There is moderate quality evidence that intravenous regional blockade with guanethidine is not effective and that the procedure appears to be associated with a risk of significant adverse events.

Low quality evidence

There is low quality evidence that:

- ketamine, bisphosphonates and calcitonin may effectively reduce pain when compared with placebo at least in the short term;
- graded motor imagery (GMI) programmes may reduce pain and improve function more than conventional physiotherapy care and that these improvements are maintained at three to six months;
- mirror therapy may reduce pain and improve function more than a sham condition in post-stroke CRPS;
- topical DMSO does not improve composite CRPS scores more than N-acetylcysteine;
- local anaesthetic sympathetic blockade is not effective;
- physiotherapy or occupational therapy versus a social work passive attention control are associated with small positive effects at one year follow up that are unlikely to be clinically important.

Very low quality evidence

There is very low quality evidence that:

- compared with placebo, oral corticosteroids reduce pain;
- compared with placebo, epidural clonidine, intravenous regional block (IVRB) ketanserin and IVRB bretylium may be effective;
- sympathetic blockade with botulinum toxin A may deliver a longer duration of pain relief than local anaesthetic sympathetic blockade;
- topical DMSO improves patients' self ratings of improvement more than placebo;
- topical DMSO achieves greater improvements in composite CRPS scores than IVRB with guanethidine;
- topical DMSO does not reduce pain more than placebo;
- IV mannitol, gabapentin, sarpogrlate hydrochloride, IV lidocaine or tadalafil, IVRB atropine, IVRB dropiredol, repetitive transcranial magnetic stimulation (rTMS), pulsed electromagnetic field (EMF), relaxation therapy and manual lymphatic drainage are not effective;
- spinal cord stimulation in addition to physical therapy is more effective at reducing pain than physical therapy alone;
- physiotherapy and occupational therapy improve pain more than a passive attention social work control for up to six months and that physiotherapy but not occupation therapy improves impairment for up to four months compared to the same control;
- Qigong therapy may be effective versus sham Qigong therapy;
- acupuncture may offer short-term improvement in pain when added to rehabilitation compared with rehabilitation alone in post-stroke CRPS and that electro-acupuncture plus rehabilitation therapies (details not specified) might be more effective than lidocaine, triamcinolone acetonide and vitamin B12;
- acupuncture is not superior to sham in CRPS.

No evidence

There is no evidence from controlled trials from which to draw conclusions on the efficacy of surgical sympathectomy.

Overall completeness and applicability of evidence

The inclusion of both Cochrane and non-Cochrane reviews ensures that this overview represents a comprehensive summary of all existing eligible systematic reviews published prior to the search dates. Taking published systematic reviews as the sole evidence source and not including original trials that have not been identified by the included reviews increases the potential effect of publication lag and increases the chances that some trial evidence has not been considered in this overview. However, the inclusion of a recent broad systematic review of all available interventions (Tran 2010) mitigates this issue to some degree. We can only draw conclusions regarding treatments for which we found evidence. For some commonly used forms of analgesia, for example opioids, the included reviews identified no trials. As such we have not considered these treatments further in this overview.

Some studies and reviews predate the most recent diagnostic guidelines for CRPS and some did not consistently apply established diagnostic criteria for CRPS. This increases the risk that studies may have included participants who would not be classified as suffering from CRPS under current diagnostic criteria and represents a source of likely clinical heterogeneity within the included evidence. Some included reviews and studies do not clearly distinguish between CRPS-I or CRPS-II. Critically in all of the included studies we identified no trials specific to CRPS-II. If CRPS-II is considered to be a distinct clinical phenomena which might require a specific therapeutic approach then we must conclude that there is currently no quality evidence relating to any intervention with which to guide this process. With the exception of spinal cord stimulation there is very little data on long term (> one year) outcomes for any intervention. This represents an important limitation of the evidence base given the chronic nature of the condition.

Most of the included reviews and studies considered pain or composite RSD and CRPS scores as the primary outcome, and some measured function. The reporting of adverse events in reviews and original studies was not consistent and only a few studies measured quality of life, patient satisfaction or emotional well being. Due to inconsistency in reporting it was not possible to consistently report measures of effect size or the numbers needed to treat or harm. As a consequence, in many cases the clinical importance

of statistically positive effects remains unclear. Similarly any statements regarding evidence for efficacy should be considered in light of the best evidence of safety. Adverse events reporting was often incomplete and it was beyond the scope of this overview to systematically search for evidence on the safety of the included intervention where it was not presented in the included reviews or trials. In addition, given the small numbers of participants involved it is very difficult to estimate the risk of serious complications, yet a number of the interventions plausibly have the potential for causing such complications. It is possible to estimate the upper 95% confidence interval for serious harms using the rule of three (Eypasch 1995). For example, while both trials of intravenous ketamine (Schwartzman 2009; Sigtermans 2009) did not report any serious adverse events we can estimate that with a combined n of 79 we can be 95% confident that the risk of a serious complication is at most 4 in 100 patients. Such a level of risk would not be insubstantial.

We have not considered data relating to CRPS in children and the results of this overview should not be extrapolated to that patient group. We also have not included studies of interventions to prevent the onset of CRPS.

Quality of the evidence

At the review level, the quality of the non-Cochrane reviews measured using the AMSTAR tool was significantly lower in non-Cochrane reviews and the standard of reporting was varied. The fact that most non-Cochrane reviews do not publish protocols puts them at a disadvantage on the first criterion of the AMSTAR tool ("Was an 'a priori' design provided?") but accepting this the quality of the included non-Cochrane reviews remained lower. We have attempted to manage this issue by consulting the original included studies, where necessary.

The included reviews used a range of different methodological quality and risk of bias assessment tools. At the level of original studies the evidence base is characterised by small trials, with very few high quality studies that might be considered at low risk of bias. Given that we relied primarily on the quality and bias judgements of the included reviews, and did not systematically apply a standard risk of bias tool to each original study, it is possible that important sources of potential bias may have been missed.

The prevalence of small studies increases the risk of publication bias. While there was insufficient data for any intervention to investigate this formally it is likely that small study effects, wherein there is a propensity for negative studies to not reach full publication, might lead to an overly positive picture for some interventions, particularly in a field with such a limited evidence base (Moore 2010; Nüesch 2010). Using the GRADE criteria there is no high quality evidence for the effectiveness of any intervention for CRPS. There is moderate quality evidence that IVRB with guanethidine is not effective, but the bulk of the remaining literature consists of low or very low quality evidence. That the highest quality rating given to evidence in favour of any intervention is 'low' speaks to the parlous state of the evidence in CRPS. Given that the play of chance can have a substantial impact upon the results of trials where the numbers of participants in each arm is lower than 200 (Moore 2010), even where we have pooled data from a number of studies those estimates should be treated with due caution. Where we have concluded that there is 'low' quality evidence of effectiveness for an intervention, we would suggest that this evidence should be considered to be preliminary rather than conclusive and that there remains a need for further, larger clinical trials.

While 'very low' is the lowest judgement that can be made in the GRADE system, where some evidence exists, such a judgement indicates that there are numerous sources of potential bias that might explain the observed effects. Indeed for many interventions there were limitations that would have resulted in a lower judgement were that possible. It is our view that a judgement of 'very low' should be interpreted as meaning 'no credible evidence' for that intervention.

Beyond these limitations, clinical heterogeneity may also explain some of the disappointing results of trials of CRPS. Three broad pathophysiological pathways for CRPS have been identified, namely aberrant inflammatory mechanisms, vasomotor dysfunction and maladaptive neuroplastic changes (Marinus 2011). It is proposed that inter-individual differences in the extent to which these mechanisms are involved may account for this clinical heterogeneity (Marinus 2011). However, the condition remains incompletely understood. Improved targeting of treatments with regard to the underlying pathophysiological mechanisms of pain has long been recognised as a possible means for improving the effectiveness of pain treatments (Woolf 2004), but to date there is no widely accepted and validated system by which this might be achieved in CRPS. Such a system will require an improved understanding of the mechanisms of CRPS.

Potential biases in the overview process

While we have attempted to identify all eligible reviews using a comprehensive search strategy, it remains possible that we may have missed some key literature. We only included non-Cochrane reviews where the same intervention was not covered by an existing Cochrane review that was equally or more up to date. It is possible that this process may have impacted on our conclusions regarding some treatments, although the superior AMSTAR scores seen with the included Cochrane reviews suggests that they may represent a more reliable source of evidence.

It should be noted that the AMSTAR assessment effectively assesses the quality of reporting rather than directly measuring the quality of review conduct. In some cases non-Cochrane reviews may be disadvantaged by the limitations on full and thorough reporting imposed by a journal's publishing requirements.

The use of the GRADE criteria introduces an element of subjective judgement. It was also found to be more difficult when we were primarily assessing the included reviews rather than the original studies, all of which assessed and reported study quality in different ways. We have tried to be consistent in our judgements across the different interventions but it should be recognised that these judgements are open to interpretation. The decision to downgrade twice based on a sample size of less than 50 participants per arm may appear to some to be overly punitive. However this is based on the observation that studies of this size are potentially more biased than those with 50 to 200 participants, which themselves are at risk of bias (Moore 2010).

In the re-analysis of the data on NMDA receptor antagonists we did not plan a priori to convert the published analysis by Collins 2010 to the mean difference. However, we maintain that this analysis is more appropriate for the included data and none of the authors of this review have any specific professional or financial interest in the efficacy of ketamine or other NMDA antagonists for CRPS or any other condition.

Agreements and disagreements with other studies or reviews

In their recent clinical guidelines for the treatment of CRPS, involving a broad review of the evidence based on searches conducted in 2003, Perez 2010 recommend using the WHO analgesic ladder with the exception of strong opioids for managing CRPS-related pain. For neuropathic pain they recommend anticonvulsants and tricyclic antidepressants and for inflammatory symptoms free radical scavengers. Unlike this overview these guidelines draw on evidence from non-randomised studies and also on evidence from studies of neuropathic pain generally as well as CRPS-specific studies. Similarly, the recent UK guidelines (Goebel 2011) also recommend neuropathic pain medications.

On the basis of this overview there is no direct evidence from randomised trials to support the use of the WHO analgesic ladder, anticonvulsants or antidepressants for CRPS-I or II. It is the goal of clinical guidelines to offer recommendations for management, and in the absence of such evidence it seems reasonable to suggest a conventional, established approach to pain management. However, the validation of such recommendations through clinical trials should be a priority. The evidence identified in this overview relating to the efficacy of topical free radical scavengers for pain is conflicting, with the two higher quality trials demonstrating no effect and very low quality evidence that intravenous administration of the free radical scavenger mannitol is not effective. Guidelines recommend rehabilitation through physiotherapy or occupational therapy (Goebel 2011; Perez 2010). The evidence of clinically important differences at four and six month follow up resulting from these therapies was assessed as very low quality. Low quality evidence suggests that the long-term effects are very small and not clinically important. As such, there is insufficient evidence to date to confidently conclude that these therapies are effective.

Two systematic reviews of all interventions for CRPS-I (Forouzanfar 2002) and CRPS (Tran 2010), both of which only included randomised controlled trials (RCTs), have also concluded that there is limited evidence for the effectiveness of any intervention. Tran 2010 concludes that bisphosphonates have been proven to reliably reduce pain and are the only intervention to offer clear benefits for patients with CRPS. Given the small number of trials and various methodological limitations of the existing evidence we have graded the evidence that bisphosphonates are superior to placebo as low quality. As such we would suggest that the efficacy of bisphosphonates is not proven with confidence though may be promising and warrants further investigation. Tran 2010 concluded that apparent improvements seen with DMSO, corticosteroids, epidural clonidine, intrathecal baclofen, spinal cord stimulation and graded motor imagery (GMI) programmes need to be confirmed in further trials and we would concur with this recommendation. While there is low or very low quality evidence in favour of a variety of treatment approaches it should be emphasized that the small samples and mixed quality of much of the literature might alone explain some of the observed positive effects. Tran 2010 also conclude that the available evidence does not support the use of IVRB guanethidine, reserpine, droperidol, ketanserin, atropine or lidocaine with methylprednisolone and that the limited evidence in support of tadalafil, sarpogrelate and gabapentin suggest that they be used with caution. We would broadly concur with these conclusions.

In their review of bisphosphonate therapy Brunner 2009 concluded that while evidence is scarce, the few trials identified all suggest a positive effect. We would agree with this finding and have rated the evidence in favour of the efficacy of these drugs as low. Despite methodological and reporting shortcomings, all existing trials demonstrate a positive effect and two of the three trials from which we were able to estimate the size of effect suggested a substantially important benefit. That three of these trials specifically investigated bisphosphonates in patients with signs of osteopenic or osteoporotic changes in the affected extremity raises the possibility that the efficacy of these drugs might be restricted to a subgroup of patients with such changes, though there is not sufficient data available to confirm or refute this. Again the quality of the included data requires that these results be interpreted cautiously.

The reviews of Forouzanfar 2002 and Tran 2010, and the clinical guidelines of Perez 2001, predate the included review of NMDA receptor antagonists (Collins 2010) and as such do not draw conclusions for this therapy. Collins 2010 concluded that there is insufficient data from which to draw definite conclusions regarding the use of these drugs for neuropathic pain. Our reanalysis would suggest that ketamine may be effective for reducing pain in CRPS. While this evidence, arising from two small trials (combined n = 79), is by no means conclusive it does suggest that ketamine, and

perhaps other NMDA antagonists, might represent a promising therapy and target for future studies. However, given the known side effects of ketamine further rigorous studies of the benefits and risks of these drugs are clearly required.

A further systematic review (Cossins 2013) has been published after the date of our searches. This review sought to update the review of Forouzanfar 2002 using the same methodology to add new trials published between 2000 and 2012. It identified four small positive trials not identified by this overview. Of these one small trial (Goebel 2011, n = 13, two groups) demonstrated an effect of intravenous immunoglobulin versus placebo on pain; one small trial (Gustin 2010, n = 20, two groups) reported that a course of morphine and memantine was more effective for treating pain than morphine and placebo; one small trial (Frade 2005, n = 30, three groups) reported that the addition of a combined parecoxib, lignocaine and clonidine IVRB was superior to IV parecoxib with lignocaine and clonidine, or IVRB with lignocaine and clonidine alone and one additional small trial of rTMS (Picarelli 2010, n = 23, two groups) suggesting that rTMS was superior to sham rTMS when added to 'best medical treatment'. This review also identified 5 small negative studies not included in this overview, which did not demonstrate the efficacy of intrathecal glycine versus placebo (Munts 2009, n=19, two groups), intrathecal methylprednisolone versus placebo (Munts 2010, n=21, two groups), IVRB with ketorolac versus lidocaine (Eckmann 2011, n=10 cross-over study), occlusal splints verus no splints (Fischer 2008, n=20, two groups) and manual lymphatic drainage in addition to conventional therapy versus conventional therapy alone (Duman 2009, n=35, two groups). The broad conclusions of Cossins 2013 are in agreement with our own. However, due to the use of different criteria for grading the quality of evidence their review concludes that there is strong evidence to support the efficacy of bisphosphonates, rTMS and GMI. We would suggest that, for the reasons presented in this review, our judgements of low quality evidence for these treatments more accurately reflect the nature of the existing data. The review by Cossins 2013 is likely to meet our inclusion criteria when we update this overview but its inclusion is not likely to have substantively altered our main conclusions.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient high quality evidence on which to base comprehensive clinical guidance on the management of CRPS. However, there is moderate quality evidence that IVRB guanethidine is not effective. There is low or very low quality evidence relating to the efficacy of a range of therapies in CRPS although all of this evidence, both positive and negative, should be interpreted with caution and does not reliably aid clinical decision making. Until further larger trials are undertaken an evidence-based approach to managing CRPS will remain difficult.

Implications for research

There is a clear need for further research for most existing treatment for CRPS as reasonably confident conclusions can only be drawn for the ineffectiveness of IVRB guanethidine. There are many challenges to addressing this problem. Given the relatively low incidence of CRPS it is difficult to recruit adequate numbers into clinical trials. It seems likely that the best chance of solving this is though multicentre, international collaborative research projects which might recruit from much larger clinical populations. Future trials should use established diagnostic criteria and clearly report the type of CRPS under investigation. Trials should also consider the recent IMMPACT recommendations (Dworkin 2008; Dworkin 2009; Dworkin 2010; Dworkin 2012; Turk 2008; Turk 2008a) for the design of trials in chronic pain to ensure that outcomes, thresholds for clinical importance, assay sensitivity and study design are optimal. Furthermore, future trials should adhere to the CONSORT guidance and future systematic reviews should comply with the PRISMA statement on standards of reporting.

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REFERENCES

References to included reviews

Brunner F, Schmid A, Kissling R, Held U, Bachmann L M. Biphosphonates for the therapy of complex regional pain syndrome I - systematic review. *European Journal of Pain* 2009;**13**(1):17–21.

Cepeda MS, Carr D B, Lau J. Local anesthetic sympathetic blockade for complex regional pain syndrome. [Review]. *Cochrane Database of Systematic Reviews* 2005, Issue 4.

Challapalli V, Tremont-Lukats I, McNicol ED, Lau J, Carr DB. Systemic administration of local anesthetic agents to relieve neuropathic pain. [Review]. *Cochrane Database of Systematic Reviews* 2005, Issue 4.

Chauvineau V, Codine P, Herisson C, Pellas F, Pelissier J. What is the place of biphosphonates in the treatment of complex regional pain syndrome I?. *Annales de Readaptation et de Medecine Physique [Annals of Physical Medicine and Readaptation]* 2005;**48**(3):150–7.

Collins S, Sigtermans M J, Dahan A, Zuurmond WW, Perez RS. NMDA receptor antagonists for the treatment of neuropathic pain. *Pain Medicine* 2010;**11**(11):1726–42.

Daly AE Bialocerkowski A. Does evidence support physiotherapy management of adult Complex Regional Pain Syndrome Type One? A systematic review. European Journal of Pain 2009; Vol. 13, issue 4:339–53.

Fischer SGL, Zuurmond WWA, Birklein F, Loer SA, Perez RSGM. Anti-inflammatory treatment of Complex Regional Pain Syndrome. *Pain* 2010;**151**(2):251–6.

Forouzanfar T, Koke AJ, van Kleef M, Weber WE. Treatment of complex regional pain syndrome type I. European Journal of Pain 2002; Vol. 6, issue 2:105–22.

Jadad AR, Carroll D, Glynn CJ, McQuay HJ. Intravenous regional sympathetic blockade for pain relief in reflex sympathetic dystrophy: a systematic review and a randomized, double-blind crossover study. *Journal of Pain and Symptom Management* 1995;**10**(1):13–20.

Lu Y-M Fu L-X Mu J Xu H-J Qi Y. Acupuncture for post stroke shoulder hand syndrome: A systematic review. Chinese Journal of Evidence-Based Medicine 2009; Vol. 9, issue 9:976–8.

Mailis-Gagnon A, Furlan AD, Sandoval JA, Taylor R. Spinal cord stimulation for chronic pain. *Cochrane Database of Systematic Reviews* 2004, Issue 3.

Moore RA, Wiffen PJ, Derry S, McQuay HJ. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 3.

O'Connell NE, Wand BM, Marston L, Spencer S, DeSouza LH. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database of Systematic Reviews* 2010, Issue 9.

Perez RS, Kwakkel G, Zuurmond WW, de Lange JJ. Treatment of reflex sympathetic dystrophy (CRPS type 1): a research synthesis of 21 randomized clinical trials. *Journal of Pain and Symptom Management* 2001;**21**(6):511–26.

Rothgangel AS, Braun SM, Beurskens AJ, Seitz RJ, Wade DT. The clinical aspects of mirror therapy in rehabilitation: a systematic review of the literature. *International Journal of Rehabilitation Research* 2011;**34**(1):1–13.

Simpson E, Duenas A, Holmes M, Papaioannou D, Chilcott J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. *Health Technology Assessment* 2009;**13**(17):1–179.

Smith TO. How effective is physiotherapy in the treatment of complex regional pain syndrome type I? A review of the literature. *Musculoskeletal Care* 2005;**3**(4):181–200.

Straube S, Derry S, Moore RA, McQuay HJ. Cervico-thoracic or lumbar sympathectomy for neuropathic pain and complex regional pain syndrome. *Cochrane Database of Systematic Reviews* 2010, Issue 7.

Tran DQH, Duong S, Bertini P, Finlayson R. Treatment of complex regional pain syndrome: A review of the evidence. Canadian Journal of Anesthesia 2010; Vol. 57, issue 2: 149–66.

References to excluded reviews

Albazaz R, Wong YT, Homer-Vanniasinkam S. Complex regional pain syndrome: a review. *Annals of Vascular Surgery* 2008;**22**(2):297–306.

Athie-Garcia JM, Espinoza JA. Reflex sympathetic dystrophy. Case report and literature review [Distrofia simpatica refleja en el postoperatorio inmediato. Reporte de un caso y revision de la literature]. *Revista Mexicana Anestesiologia* 1992;**15**:30–2.

Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *European Journal of Neurology* 2010;**17**(9):1113–23.

Baidya DK, Agarwal A, Khanna P, Arora MK. Pregabalin in acute and chronic pain. Journal of Anaesthesiology Clinical Pharmacology 2011; Vol. 27, issue 3:307–14.

Bal R, Legree L, Diwan S. Nonopioid analgesic pipeline: Pharmacology, safety, tolerability, and potential advantages over established agents. Techniques in Regional Anesthesia and Pain Management 2010; Vol. 14, issue 2:75–85.

Beckerman H, de Bie RA, Bouter LM, de Cuyper HJ, Oostendorp RAB. De effectiviteit van lasertherapie bij aandoeningen van het bewegingsapparaat en de huid. *Nederlands Tijdschrift voor Fysiotherapie [Dutch Journal of Physical Therapy]* 1990;**100**(12):306–16.

Bekkering GE, Soares-Weiser K, Reid K, Kessels AG, Dahan A, Treede RD, et al. Can morphine still be considered to be the standard for treating chronic pain? A systematic review including pair-wise and network meta-analyses. Current Medical Research and Opinion 2011; Vol. 27, issue 7: 1477–91.

Bernstein RM. Injections and surgical therapy in chronic pain. Clinical Journal of Pain 2001; Vol. 17, issue 4: S94–S104.

Bittar RG, Kar-Purkayastha I, Owen SL, Bear RE, Green A, Wang S, et al. Deep brain stimulation for pain relief: A meta-analysis. Journal of Clinical Neuroscience 2005; Vol.

12, issue 5:515–9.
Blonk MI, Koder BG, van den Bemt PMLA Huygen FJPM. Use of oral ketamine in chronic pain management: A review. European Journal of Pain 2010; Vol. 14, issue 5: 466–72.
Blum K, Chen AL, Chen TJ, Prihoda TJ, Schoolfield J, Dinubile N, et al. The H-Wave(R) device is an effective and safe non-pharmacological analgesic for chronic pain: a meta-analysis. *Advances in Therapy* 2008;**25**(7):644–57.
Bronfort G, Haas M, Evans R, Leininger B, Triano J. Effectiveness of manual therapies: the UK evidence report. *Chiropractic & Osteopathy* 2010;**18**:3.
Campbell FA, Tramer MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *BMJ* 2001;**323**(7303):13–6.
Cao H, Han M, Li X, Dong S, Shang Y, Wang Q, et al. Clinical research evidence of cupping therapy in China: a systematic literature review. *BMC Complementary and Alternative Medicine* 2010;**10**:70.
Cepeda MS Lau J Carr D. Defining the therapeutic role of local anesthetic sympathetic blockade in complex regional pain syndrome: A narrative and systematic review. Clinical Journal of Pain 2002; Vol. 18, issue 4:216–33.
Claydon L, Fris C, Lucas R, Scott N, Silk L. The effects of exercise on pain relief in neuropathic pain conditions: A systematic review. European Journal of Pain. Supplements Vol. 4:129.
Covarrubias-Gomez A. The role of cannabinoids to manage pain. Revista Mexicana de Anestesiologia [Mexican Review of Anesthesiology] 2008; Vol. 31, issue 3:191–200.
del Pozo E. The effectiveness of levetiracetam in the treatment of neuropathic pain. Revista de neurologia [Review of Neurology] 2011; Vol. 53, issue 2:65–72.
Derry S, Lloyd R, Moore RA, McQuay HJ. Topical capsaicin for chronic neuropathic pain in adults.. *Cochrane Database of Systematic Reviews* 2009, Issue 4.
Duhmke RM, Cornblath DD, Hollingshead JR. Tramadol for neuropathic pain. *Cochrane Database of Systematic Reviews* 2004, Issue 2.
Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: Evidence-based recommendations. Pain 2007; Vol. 132, issue 3:237–51.
Eccles NK. A critical review of randomized controlled trials of static magnets for pain relief. *Journal of Alternative and Complementary Medicine* 2005;**11**(3):495–509.
Eisenberg E, McNicol ED, Carr DB. Opioids for neuropathic pain. *Cochrane Database of Systematic Reviews* 2006, Issue 3.
Ellis RF, Hing W. Neural mobilization: A systematic review of randomized controlled trials with an analysis of therapeutic efficacy. Journal of Manual and Manipulative Therapy 2008; Vol. 16, issue 1:8–22.
Ezendam D, Bongers RM, Jannink MJ. Systematic review of the effectiveness of mirror therapy in upper extremity function. *Disability and Rehabilitation* 2009;**31**(26): 2135–49.
Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain* 2005;**118**(3):289–305.
Finnerup NB, Otto M, Jensen TS, Sindrup SH. An evidence-based algorithm for the treatment of neuropathic pain. *Medgenmed [Medscape General Medicine]* 2007;**9**(2): 36.
Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain 2010; Vol. 150, issue 3:573–81.
Flórez S, León M, Torres M, Reyes F, Serpa JC, Ríos AM. Pharmacological management of neuropathic pain [Manejo farmacológico del dolor neuropático]. *Revista Columbia de Anestesiologia [Columbian Anesthesiology Journal]* 2009;**37** (4):358–74.
Fulop AM, Dhimmer S, Deluca JR, Johanson DD, Lenz RV, Patel KB, et al. A meta-analysis of the efficacy of laser phototherapy on pain relief. Clinical Journal of Pain 2010; Vol. 26, issue 8:729–36.
Geertzen JHB. Development of guidelines for the diagnostics and multidisciplinary treatment of Complex Regional Pain Syndrome Type I. *Journal of Neuropathic Pain & Symptom Palliation* 2006;**2**(3):73–7.
Geurts ACH, Visschers BAJ, van Limbeek J, Ribbers GM. Systematic review of aetiology and treatment of post-stroke hand oedema and shoulder-hand syndrome. *Scandinavian Journal of Rehabilitation Medicine* 2000;**32**(1):4–10.
Gill D, Derry S, Wiffen PJ, Moore RA. Valproic acid and sodium valproate for neuropathic pain and fibromyalgia in adults (Review). *Cochrane Database of Systematic Reviews* 2011, Issue 10.
Gonzalez-Escalada JR, Rodriguez MJ, Camba MA, Portoles A, Lopez R. Recommendations for the treatment of neuropathic pain. Revista de la Sociedad Espanola del Dolor [Spanish Journal of Pain] 2009; Vol. 16, issue 8:445–67.
Goodyear-Smith F, Halliwell J. Anticonvulsants for neuropathic pain: Gaps in the evidence. Clinical Journal of Pain 2009; Vol. 25, issue 6:528–36.
Gottschild S, Kroling P. Vibratory massage: A review of physiological effects and therapeutical efficacy. Physikalische Medizin Rehabilitationsmedizin Kurortmedizin [Journal of Physical and Rehabilitation Medicine] 2003; Vol. 13, issue 2:85–95.
Granot R, Day RO, Cohen ML, Murnion B, Garrick R. Targeted pharmacotherapy of evoked phenomena in neuropathic pain: a review of the current evidence. Pain Medicine 2007; Vol. 8, issue 1:48–64.
Harden RN. Pharmacotherapy of complex regional pain syndrome. *American Journal of Physical Medicine & Rehabilitation* 2005;**84**(3):S17–28.
Harden RN. Interdisciplinary management/functional restoration. *Journal of Neuropathic Pain & Symptom Palliation* 2006;**2**(3):57–68.
Haroutiunian S, Drennan DA, Lipman AG. Topical NSAID therapy for musculoskeletal pain. *Pain Medicine*

2010;**11**(4):535–49.
Hassantash SA, Afrakhteh M, Maier RV. Causalgia: a meta-analysis of the literature. *Archives of Surgery* 2003;**138**(11): 1226–31.
Hocking G, Cousins MJ. Ketamine in chronic pain management: an evidence-based review. *Anesthesia and Analgesia* 2003;**97**(6):1730–9.
Johnson MI, Bjordal J. Transcutaneous electrical nerve stimulation for the management of painful conditions: Focus on neuropathic pain. Expert Review of Neurotherapeutics 2011; Vol. 11, issue 5:735–53.
Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain* 1997;**73**(2):123–39.
Koltzenburg M. Painful neuropathies. Current Opinion in Neurology 1998; Vol. 11, issue 5:515–21.
Kouroukli I. Neuropathic pain management: Efficacy, safety, complications of interventional techniques: Radiofrequency techniques. European Journal of Pain Supplements 2010; Vol. 4:10.
Leite LC, Mondin L. Compex regional pain syndrome [Sindrome de dor regional complexa]. *Revista científica da Associação Médica de Caxias [Journal of the Medical Association of Caxias]* 2000;**9**(2):50–3.
Linde K, Vickers A, Hondras M, ter Riet G, Thormählen J, Berman B, et al. Systematic reviews of complementary therapies - an annotated bibliography. Part 1: Acupuncture. *BMC Complementary and Alternative Medicine* 2001;**1**(3).
Lord SM, Bogduk N. Radiofrequency procedures in chronic pain. *Best Practice & Research. Clinical Anaesthesiology* 2002; **16**(4):597–617.
Manchikanti L, Vallejo R, Manchikanti KN, Benyamin RM, Datta S, Christo PJ. Effectiveness of long-term opioid therapy for chronic non-cancer pain. *Pain Physician* 2011; **14**:E133–56.
Martinez JE, Goldenberg J, Pollak DF, Atra E. Reflex sympathetic dystrophy: a literature review. *Revista Brasileira Reumatologia [Brazilian Journal of Rheumatology]* 1993;**33** (2):61–4.
McHardy A, Hoskins W, Pollard H, Onley R, Windsham R. Chiropractic treatment of upper extremity conditions: A systematic review. *Journal of Manipulative and Physiological Therapeutics* 2008;**31**(2):146–59.
McQuay HJ, Moore RA, Eccleston C, Morley S, Williams AC. Systematic review of outpatient services for chronic pain control. *Health Technology Assessment* 1997;**1**(6): 1–135.
Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3.
Motsch J, Kamler M. alpha2-adrenergic agonists. Use in chronic pain - A meta-analysis. Schmerz [Pain] 1997; Vol. 11, issue 5:339–44.
Moulin DE, Clark AJ, Gilron I, Ware MA, Watson CP, Sessle BJ, et al. Pharmacological management of chronic neuropathic pain - consensus statement and guidelines from the Canadian Pain Society. *Pain Research & Management* 2007;**12**(1):13–21.
Namaka M, Gramlich CR, Ruhlen D, Melanson M, Sutton I, Major J. A treatment algorithm for neuropathic pain. *Clinical Therapeutics* 2004;**26**(7):951–79.
Namaka M, Leong C, Grossberndt A, Klowak M, Turcotte D, Esfahani F, et al. A treatment algorithm for neuropathic pain: an update. *Consultant Pharmacist* 2009;**24**(12): 885–902.
Neira LV, Neira MS, Guzman-Sarzon RM, Perez RC. Algodystrophy: A clinical therapeutic study [Algodistrofia: Estudio clinical y terapeutico]. *Diagnostico [Diagnosis]* 1988;**22**:29–43.
Nilsagard Y, Hammer A, Lovgren A, Frick L. Physiotherapy treatment of shoulder pain after stroke -- prevention and intervention. *Nordisk Fysioterapi [Nordic Physiotherapy]* 2004;**8**(4):174–82.
Nnoaham KE, Kumbang J. Transcutaneous electrical nerve stimulation (TENS) for chronic pain. *Cochrane Database of Systematic Reviews* 2008, Issue 3.
Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database of Systematic Reviews* 2010, Issue 1.
North R. Spinal cord stimulation for neuropathic pain. European Journal of Pain Supplements 2010; Vol. 4:10–11.
Pappagallo M. Capsaicin (TRPV1 agonist) therapy for pain relief: Farewell or revival?. Clinical Journal of Pain 2008; Vol. 24, issue 2:142–54.
Patel VB, Manchikanti L, Singh V, Schultz DM, Hayek SM, Smith HS. Systematic review of intrathecal infusion systems for long-term management of chronic non-cancer pain. *Pain Physician* 2009;**12**:345–60.
Perez RS, Zollinger PE, Dijkstra PU, Thomassen-Hilgersom IL, Zuurmond WW, Rosenbrand KCJ, et al. Evidence based guidelines for complex regional pain syndrome type 1. *BMC Neurology* 2010;**10**.
Pittler MH, Brown EM, Ernst E. Static magnets for reducing pain: Systematic review and meta-analysis of randomized trials. Canadian Medical Association Journal 2007; Vol. 177, issue 7:736–42.
Pittler MH, Ernst E. Complementary therapies for neuropathic and neuralgic pain: systematic review. *Clinical Journal of Pain* 2008;**24**(8):731–3.
Plested M, Budhia S, Gabriel Z. Pregabalin, the lidocaine plaster and duloxetine in patients with refractory neuropathic pain: a systematic review. BMC Neurology 2010; Vol. 10:116.
Prescrire. Complex Regional pain syndrome type 1. Some treatments assessed versus placebo, limited efficacy. *Prescrire International* 2009;**18**(104):267–71.
Rauck RL, Wallace MS, Burton AW, Kapural L, North JM. Intrathecal ziconotide for neuropathic pain: a review. *Pain Practice* 2009;**9**(5):327–37.
Rehberg B. Evidence-based integrative pain medicine. European Journal of Integrative Medicine 2010; Vol. 2,

issue 3:109–13.
Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. *Cochrane Database of Systematic Reviews* 2010, Issue 11.
Saarto T, Wiffen PJ. Antidepressants for neuropathic pain: A Cochrane review. *Journal of Neurology, Neurosurgery and Psychiatry* 2010;**81**(12):1372–3.
Schestatsky P. Definition, diagnosis and treatment of neuropathic pain [Definicao, diagnostico e tratamento da dor neuropatica]. *Publicação Científica do Hospital de Clínicas de Porto Alegre e Faculdade de Medicina da Universidade Federal do Rio Grande do Sul [Scientific Publication of the Hospital de Clinicas de Porto Alegre and Faculty of Medicine, Federal University of Rio Grande do Sul]* 2008;**28**(3):177–87.
Seidel S, Aigner M, Ossege M, Pernicka E, Wildner B, Sycha T. Antipsychotics for acute and chronic pain in adults. *Cochrane Database of Systematic Reviews* 2008, Issue 4.
So PS, Jiang Y, Qin Y. Touch therapies for pain relief in adults. *Cochrane Database of Systematic Reviews* 2008, Issue 4.
Trescot A, Glaser SE, Hansen H, Benyamin R, Patel S, Manchikanti L. Effectiveness of opioids in the treatment of chronic non-cancer pain. *Pain Physician* 2008;**11**: S181–S200.
Van den Berg P, Bierma-Zeinstra S, Koes B. Complex regional pain syndrome. A systematic review of its clinical manifestations and prognosis. Huisarts en Wetenschap [Family Practice] 2002; Vol. 45, issue 3:114–8.
Vergne-Salle P, Mejjad O, Javier RM, Maheu E, Fallut M, Glowinski J, Bertin P. Antiepileptic drugs to treat pain in rheumatic conditions. Recommendations based on evidence-based review of the literature and expert opinion. Joint, Bone, Spine 2009; Vol. 76, issue 1:75–85.
Vlassakov KV, Narang S, Kissin I. Local anesthetic blockade of peripheral nerves for treatment of neuralgias: systematic analysis. *Anesthesia and Analgesia* 2011;**112**(6):1487–93.
Watson C P, Gilron I, Sawynok J. A qualitative systematic review of head-to-head randomized controlled trials of oral analgesics in neuropathic pain. Pain Research and Management 2010; Vol. 15, issue 3:147–57.
Wetering EJVD, Lemmens KMM, Nieboer AP, Huijsman R. Cognitive and behavioral interventions for the management of chronic neuropathic pain in adults - A systematic review. European Journal of Pain 2010; Vol. 14, issue 7:670–81.
Wiedemann B. Ketamine for treatment of chronic pain: Meta-analysis. Schmerz 1997; Vol. 11, issue 4:276–81.
Wiffen PJ Rees J. Lamotrigine for acute and chronic pain. *Cochrane Database of Systematic Reviews* 2009, Issue 4.
Wiffen PJ, Derry S, Moore RA, McQuay HJ. Carbamazepine for acute and chronic pain in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 1.
Williams JA, Day M, Heavner J. Ziconotide: An update and review. Expert Opinion on Pharmacotherapy 2008; Vol. 9, issue 9:1575–83.
Zaccara G, Gangemi P, Perucca P, Specchio L. The adverse event profile of pregabalin: a systematic review and meta-analysis of randomized controlled trials. *Epilepsia* 2011;**52** (4):826–36.

Additional references

Adami 1997
Adami S, Fossaluzza V, Gatti D, Fracassi E, Braga V. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. *Annals of the Rheumatic Diseases* 1997;**56**(3): 201–4.

Albrecht 2006
Albrecht PJ, Hines S, Eisenberg E, Pud D, Finlay DR, Davar G, et al. Pathologic alterations of cutaneous innervation and vasculature in affected limbs from patients with complex regional pain syndrome. *Pain* 2006;**120**:244–66.

Ali 2000
Ali Z, Raja SN, Wesselmann U, Fuchs PN, Meyer RA, Campbell JN. Intradermal injection of norepinephrine evokes pain in patients with sympathetically maintained pain. *Pain* 2000;**88**(2):161–8.

Balshem 2011
Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* 2011; **64**(4):401–6.

Becker 2011
Becker LA, Oxman AD. Chapter 22: Overviews of reviews. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0*. The Cochrane Collaboration. Available from www.cochrane-handbook.org, 2011.

Bickerstaff 1991
Bickerstaff DR, Kanis JA. The use of nasal calcitonin in the treatment of post-traumatic algodystrophy. *British Journal of Rheumatology* 1991;**30**(4):291–4.

Birklein 2000
Birklein F, Weber M, Neundörfer B. Increased skin lactate in complex regional pain syndrome: evidence for tissue hypoxia?. *Neurology* 2000;**55**(8):1213–5.

Birklein 2001
Birklein F, Schmelz M, Schifter S, Weber M. The important role of neuropeptides in complex regional pain syndrome. *Neurology* 2001;**57**:2179–84.

Blanchard 1990
Blanchard J, Ramamurthy S, Walsh N, Hoffman J, Schoenfeld L. Intravenous regional sympatholysis: A double-blind comparison of guanethidine, reserpine, and normal saline. *Journal of Pain and Symptom Management* 1990;**5**(6):357–61.

BMJ Clinical Evidence
BMJ Clinical Evidence. Default search strategies used for BMJ Clinical Evidence. http://clinicalevidence.bmj.com/ceweb/about/search˙filters.jsp (accessed 13 April 2011).

Bonelli 1983
Bonelli S, Conoscente F, Movilia PG. Regional intravenous guanethidine vs. stellate ganglion block in reflex sympathetic dystrophies: a randomized trial. *Pain* 1983;**16**(3):297–307.

Bounameaux 1984
Bounameaux HM, Hellemans H, Verhaeghe R. Ketanserin in chronic sympathetic dystrophy. An acute controlled trial. *Clinical Rheumatology* 1984;**3**(4):556–7.

Braus 1994
Braus DF, Krauss JK, Strobel J. The shoulder-hand syndrome after stroke: A prospective clinical trial. *Annals of Neurology* 1994;**36**(5):728–33.

Bruehl 1999
Bruehl S, Harden RN, Galer BS, Saltz S, Bertram M, Backonja M, et al. External validation of IASP diagnostic criteria for Complex Regional Pain Syndrome and proposed research diagnostic criteria. International Association for the Study of Pain. *Pain* 1999;**81**(1-2):147–54.

Bruehl 2006
Bruehl S. Psychological interventions. In: Harden RN editor(s). *Complex regional pain syndrome: treatment guidelines*. Reflex Sympathetic Dystrophy Syndrome Association, 2006.

Bruehl 2010
Bruehl S. An update on the pathophysiology of complex regional pain syndrome. *Anesthesiology* 2010;**113**(3): 713–25.

Burton 2006
Burton AW. Interventional therapies. In: Harden NR editor (s). *Complex Regional Pain Syndrome: Treatment Guidelines*. Reflex Sympathetic Dystrophy Syndrome Association, 2006.

Cacchio 2009
Cacchio A, De Blasis E, De Blasis V, Santilli V, Spacca G. Mirror therapy in complex regional pain syndrome type 1 of the upper limb in stroke patients. *Neurorehabilitation and Neural Repair* 2009;**23**(8):792–9.

Cacchio 2009a
Cacchio A, De Blasis E, Necozione S, Di Orio F, Santilli V. Mirror therapy for chronic complex regional pain syndrome type 1 and stroke. *New England Journal of Medicine* 2009; **361**(6):634–6.

Carroll 2009
Carroll I, Clark JD, Mackey S. Sympathetic block with botulinum toxin to treat complex regional pain syndrome. *Annals of Neurology* 2009;**65**(3):348–51.

Chang 2005
Chang N, Liu S. Combining acupuncture and rehabilitation therapies on shoulder hand syndrome: analysis on the effectiveness. *Journal of the Fourth Military Medical University* 2005;**26**(24):2295–7.

Cherot 1983
Cherot A, Amor B. [Etude randomisée sur 95 casde trios traiements: calsyn 100, visken, grisé fulvineet phentonium]. *Revue du Rhumatisme et des Maladies Osteo- Articulaires [Journal of Rheumatic and Osteo-Articular Diseases]* 1983;**50**: 95–7.

Christensen 1982
Christensen K, Jensen EM, Noer I. The reflex dystrophy syndrome response to treatment with systemic corticosteroids. *Acta Chirurgica Scandinavica* 1982;**148**(8): 653–5.

Cohen 1998
Cohen P, Uebelhart D. Indications of Pamidronate disodique(Aredia*) in the treatment of post traumatic or post surgical of the distal upper limb algodystrophies [Indications du Pamidronate disodique(Aredia*) dans le traitement des algodystrophies post–traumatiques ou post–chirurgicales de l'extrémité distale du membre supérieur]. In: Simon L, Pélissier J, Hérisson C editor(s). *Progrès en MPR*. Paris: Masson, 1998:510–4.

Cossins 2013
Cossins L, Okell RW, Cameron H, Simpson B, Poole HM, Goebel A. Treatment of complex regional pain syndrome in adults: A systematic review of randomized controlled trials published from June 2000 to February 2012. *European Journal of Pain* 2013;**17**(2):158–73.

de Mos 2007
de Mos M, de Bruijn AGJ, Huygen FJPM, Dieleman JP, Stricker BHC, Sturkenboom MCJM. The incidence of complex regional pain syndrome: a population-based study. *Pain* 2007;**129**(1-2):12–20.

de Mos 2008
de Mos M, Huygen FJPM, Dieleman JP, Koopman JSHA, Stricker BHC, Sturkenboom MCJM. Medical history and the onset of complex regional pain syndrome (CRPS). *Pain* 2008;**139**(2):458–66.

de Mos 2009
de Mos, Sturkenboom MCJM, Huygen FJPM. Current understandings on complex regional pain syndrome. *Pain Practice* 2009;**9**(2):86–99.

Dhar 1992
Dhar S, McGlone F, Dean J, Klenerman L. The temporal significance of the placebo response in reflex sympathetic dystrophy. *Proceedings of the British Orthopaedic Research Society* 1992;**16**:16–17.

Drummond 2001
Drummond PD, Finch PM, Skipworth S, Blockey P. Pain increases during sympathetic arousal in patients with complex regional pain syndrome. *Neurology* 2001;**57**(7): 1296–303.

Drummond 2004
Drummond PD, Finch PM. Persistence of pain induced by startle and forehead cooling after sympathetic blockade in patients with complex regional pain syndrome. *Journal of Neurology, Neurosurgery, and Psychiatry* 2004;**75**(1):98–102.

Duman 2009
Duman I, Ozdemir A, Tan AK, Dincer K. The efficacy of manual lymphatic drainage therapy in the management of limb edema secondary to reflex sympathetic dystrophy. *Rheumatology International* 2009;**29**(7):759–63.

Durmus 2004
Durmus A, Cakmak A, Disci R, Muslumanoglu L. The efficiency of electromagnetic field treatment in Complex Regional Pain Sydrome Type I. *Disability and Rehabilitation* 2004;**26**(9):537–45.

Dworkin 2008
Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *Journal of Pain* 2008;**9**(2): 105–21.

Dworkin 2009
Dworkin RH, Turk DC, McDermott MP, Peirce-Sandner S, Burke LB, Cowan P, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain* 2009;**146**(3): 238–44.

Dworkin 2010
Dworkin RH, Turk DC, Peirce-Sandner S, Baron R, Bellamy N, Burke LB, et al. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. *Pain* 2010;**149**(2):177–93.

Dworkin 2012
Dworkin RH, Turk DC, Peirce-Sandner S, Burke LB, Farrar JT, Gilron I, et al. Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. *Pain* 2012;**153**(6):1148–58.

Eckmann 2011
Eckmann MS, Ramamurthy S, Griffin JG. Intravenous regional ketorolac and lidocaine in the treatment of complex regional pain syndrome of the lower extremity: A randomized, double-blinded, crossover study. *Clinical Journal of Pain* 2011;**27**(3):203–6.

Ernst 1995
Ernst E, Resch KL, Fialka V, Ritter-Dittrich D, Alcamioglu Y, Chen O, et al. Traditional acupuncture for reflex sympathetic dystrophy: A randomised, sham-controlled, double-blind trial. *Acupuncture in Medicine* 1995;**13**(2): 78–80.

Eypasch 1995
Eypasch E, Lefering R, Kum CK, Troidl H. Probability of adverse events that have not yet occurred: a statistical reminder. *BMJ* 1995;**311**:619–20.

Fialka 1993
Fialka V, Resch KL, Ritter-Dietrich D, Alacamlioglu Y, Chen O, Leitha T, et al. Acupuncture for reflex sympathetic dystrophy. *Archives of Internal Medicine* 1993;**153**:661.

Fialka 1996
Fialka V, Korpan M, Saradeth T, Paternostro-Slugo T, Hexel O, Frischenschlager O, et al. Autogenic training for reflex sympathetic dystrophy: A pilot study. *Complementary Therapies in Medicine* 1996;**4**:103–5.

Finch 2009
Finch PM, Knudsen L, Drummond PD. Reduction of allodynia in patients with complex regional pain syndrome: A double-blind placebo-controlled trial of topical ketamine. Pain 2009; Vol. 146:18–25.

Fischer 2008
Fischer MJ, Reiners A, Kohnen R, Bernateck M, Gutenbrunner C, Fink M, et al. Do occlusal splints have an effect on complex regional pain syndrome? a randomized, controlled proof-of-concept trial. *Clinical Journal of Pain* 2008;**24**(9):776–83.

Frade 2005
Frade LC, Lauretti GR, Lima IC, Pereira NL. The antinociceptive effect of local or systemic parecoxib combined with lidocaine/clonidine intravenous regional analgesia for complex regional pain syndrome type I in the arm. *Anesthesia and Analgesia* 2005;**101**(3):807–11.

Friez 1982
Friez L, Pere G, Breuillard PH, Meigan S. Comparison of treatment with griseofulvin, betablockers and calcitonin in 55 cases of post traumatic algoneurodystrophy [Comparaison du traiement par la griseofulvine, les betabloquants et la calcitonine dans 55 cas d' algoneurodystrophie post–traumatique]. *Revue du Rhumatisme et des Maladies Osteo-Articulaires [Journal of Rheumatic and Osteo-Articular Diseases]* 1982;**49**:857-60.

Geertzen 1994
Geertzen JHB, De Bruijn H, De Bruijn-Kofman AT, Arendzen JH. Reflex sympathetic dystrophy: Early treatment and psychological aspects. *Archives of Physical Medicine and Rehabilitation* 1994;**75**(4):442–6.

Geha 2008
Geha PY, Baliki MN, Harden RN, Bauer WR, Parrish TB, Apkarian AV. The brain in chronic CRPS pain: abnormal gray-white matter interactions in emotional and autonomic regions. *Neuron* 2008;**60**(4):570–81.

Glynn 1993
Glynn CJ, Stannard S, Collins PA, Casale R. The role of peripheral sudomotor blockade in the treatment of patients with sympathetically maintained pain. *Pain* 1993;**53**(1): 39–42.

Gobelet 1986
Gobelet C, Meier J-L, Schaffner W. Calcitonin and reflex sympathetic dystrophy syndrome. *Clinical Rheumatology* 1986;**5**(3):382–8.

Gobelet 1992
Gobelet C, Waldburger M, Meier JL. The effect of adding calcitonin to physical treatment on reflex sympathetic dystrophy. *Pain* 1992;**48**(2):171–5.

Goebel 2010
Goebel A, Baranowski A, Maurer K, Ghiai A, McCabe C, Ambler G. Intravenous immunoglobulin treatment of the complex regional pain syndrome: a randomized trial. *Annals of Internal Medicine* 2010;**152**(3):152–8.

Goebel 2011
Goebel A, Barker CH, Turner-Stokes L, et al. Complex regional pain syndrome in adults: UK guidelines for diagnosis, referral and management in primary and secondary care. Royal College of Physicians. London 2011.

Goris 1987
Goris RJ, Dongen LM, Winters HA. Are toxic oxygen radicals involved in the pathogenesis of reflex sympathetic dystrophy?. *Free Radical Research Communications* 1987;**3** (1-5):13–8.

Groeneweg 2008
Groeneweg G, Huygen FJPM, Niehof SP, Wesseldijk F, Bussmann JBJ, Schasfoort FC, et al. Effect of tadalafil on blood flow, pain, and function in chronic coldComplex Regional Pain Syndrome: a randomized controlled trial. BMC Musculoskeletal Disorders 2008; Vol. 9:143.

Gustin 2010
Gustin SM, Schwarz A, Birbaumer N, Sines N, Schmidt AC, Veit R, et al. NMDA-receptor antagonist and morphine decrease CRPS-pain and cerebral pain representation. *Pain* 2010;**151**(1):69–76.

Hanna 1989
Hanna MH, Peat SJ. Ketanserin in reflex sympathetic dystrophy. A double-blind placebo controlled cross-over trial. *Pain* 1989;**38**(2):145–50.

Harden 2006a
Harden RN, Bruehl S. Introduction and diagnostic considerations. In: Harden RN editor(s). *Complex regional pain syndrome: treatment guidelines*. Reflex Sympathetic Dystrophy Syndrome Association, 2006.

Harden 2006b
Harden RN. Pharmacotherapy. In: Harden RN editor(s). *Complex regional pain syndrome: treatment guidelines*. Reflex Sympathetic Dystrophy Syndrome Association, 2006.

Harden 2006c
Harden RN, Swan M, Costa BR, Barthel J, King AL. Interdisciplinary management. In: Harden RN editor(s). *Complex regional pain syndrome: treatment guidelines*. Reflex Sympathetic Dystrophy Syndrome Association, 2006.

Hord 1992
Hord AH, Rooks MD, Stephens BO, Rogers HG, Fleming LL. Intravenous regional bretylium and lidocaine for treatment of reflex sympathetic dystrophy: A randomized, double-blind study. *Anesthesia and Analgesia* 1992;**74**(6): 818–21.

Jin 2007
Jin Y, Wang J, Wang An. Acupuncture with rehabilitation therapies on shoulder hand syndrome: 40 observational cases. *Journal of Clinical Acupuncture and Moxibustion* 2007;**23**(1):14–5.

Kalita 2006
Kalita J, Vajpayee A, Misra UK. Comparison of prednisolone with piroxicam in complex regional pain syndrome following stroke: A randomized controlled trial. *QJM - Monthly Journal of the Association of Physicians* 2006;**99**(2): 89–95.

Kemler 2000
Kemler MA, Barendse GAM, Van Kleef M, De Vet HCW, Rijks CPM, Furnée CA, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *New England Journal of Medicine* 2000;**343**(9):618–24.

Kemler 2001
Kemler MA, Reulen JPH, Barendse GAM, Van Kleef M, De Vet HCW, Van Den Wildenberg FAJM. Impact of spinal cord stimulation on sensory characteristics in complex regional pain syndrome type I: A randomized trial. *Anesthesiology* 2001;**95**(1):72–80.

Kemler 2002
Kemler MA, Furnée CA. Economic evaluation of spinal cord stimulation for chronic reflex sympathetic dystrophy. *Neurology* 2002;**59**(8):1203–9.

Kemler 2004
Kemler MA, De Vet HCW, Barendse GAM, Van Den Wildenberg FAJM, Van Kleef M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: Two years' follow-up of the randomized controlled trial. *Annals of Neurology* 2004;**55**(1):13–8.

Kemler 2006
Kemler MA, De Vet HCW, Barendse GAM, Van Den Wildenberg FAJM, Van Kleef M. Spinal cord stimulation for chronic reflex sympathetic dystrophy - Five-year follow-up. *New England Journal of Medicine* 2006;**354**(22): 2394–6.

Kettler 1988
Kettler RE, Abram SE. Intravenous regional droperidol in the management of reflex sympathetic dystrophy: A double-blind, placebo-controlled, crossover study. *Anesthesiology* 1988;**69**(6):933–6.

Kho 1995
Kho KH. The impact of acupuncture on pain in patients with reflex sympathetic dystrophy. *The Pain Clinic* 1995;**8** (1):59–61.

Koban 2003
Koban M, Leis S, Schultze-mosgau S, Birklein F. Tissue hypoxia in complex regional pain syndrome. *Plastic and Reconstructive Surgery* 2003;**104**:149–57.

Korpan 1999
Korpan MI, Dezu Y, Scneider B, Leitha T, Fialka-Moser V. Acupuncture in the treatment of posttraumatic pain syndrome. *Acta Orthopaedica Belgica* 1999;**65**:197–201.

Lefaucheur 2008
Lefaucheur JP. Principles of therapeutic use of transcranial and epidural cortical stimulation. *Clinical Neurophysiology* 2008;**119**(10):179-84.

Lewis 2007
Lewis JS, Kersten P, Mccabe CS, McPherson KM, Blake DR. Body perception disturbance: a contribution to pain in complex regional pain syndrome (CRPS). *Pain* 2007;**133** (1-3):111–9.

Liu 2006
Liu D, Zhang X. Effect of acupuncture on reflex sympathetic dystrophy syndrome (RSDS). *Modern Journal of Integrated Chinese Traditional and Western Medicine* 2006;**15**(3): 326–7.

Livingstone 2002
Livingstone JA, Atkins RM. Intravenous regional guanethidine blockade in the treatment of post-traumatic

complex regional pain syndrome type 1 (algodystrophy) of the hand. *Journal of Bone and Joint Surgery - Series B* 2002; **84**(3):380–6.

Lotze 2007

Lotze M, Moseley GL. Role of distorted body image in pain. *Current Rheumatology Reports* 2007;**9**(6):488–96.

Lukovic 2006

Lukovic TZ, Ilic KP, Jevtic M, Toncev G. Corticosteroids and physical agents in treatment of complex regional pain syndrome type I. *Medicus* 2006;**7**(2):70–2.

Maihöfner 2004

Maihöfner C, Handwerker HO, Neundörfer B, Birklein F. Cortical reorganization during recovery from complex regional pain syndrome. *Neurology* 2004;**63**(4):693–701.

Manicourt 2004

Manicourt D-H, Brasseur J-P, Boutsen Y, Depreseux G, Devogelaer J-P. Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity. *Arthritis and Rheumatism* 2004;**50**(11): 3690–7.

Manjunath 2008

Manjunath PS, Jayalakshmi TS, Dureja GP, Prevost AT. Management of lower limb complex regional pain syndrome type 1: An evaluation of percutaneous radiofrequency thermal lumbar sympathectomy versus phenol lumbar sympathetic neurolysis - A pilot study. *Anesthesia and Analgesia* 2008;**106**(2):647–9.

Marinus 2011

Marinus J, Moseley GL, Birklein F, Baron R, Maihöfner C, Kingery WS, et al. Clinical features and pathophysiology of complex regional pain syndrome. *Lancet Neurology* 2011; **10**(7):637–48.

McCabe 2008

McCabe CS, Haigh RC, Blake DR. Mirror visual feedback for the treatment of complex regional pain syndrome (Type 1). *Current Pain and Headache Reports* 2008;**12**(2):103–7.

Merskey 1994

Merskey H, Bogduk N. Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms.. *Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms*. 2nd Edition. Seattle: IASP Press, 1994.

Moore 2008

Moore RA, Barden J, Derry S, McQuay HJ. Managing potential publication bias. In: McQuay HJ, Kalso E, Moore RA editor(s). *Systematic reviews in pain research: methodology refined*. Seattle: IASP Press, 2008:15–23.

Moore 2010

Moore RS, Eccleston C, Derry S, Wiffen P, Bell RF, Straube S, et al. "Evidence" in chronic pain - Establishing best practice in the reporting of systematic reviews. *Pain* 2010; **150**(3):386–9.

Moseley 2004

Moseley GL. Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial. *Pain* 2004;**108**:192–8.

Moseley 2005

Moseley GL. Is successful rehabilitation of complex regional pain syndrome due to sustained attention to the affected limb? A randomised clinical trial. *Pain* 2005;**114**(1-2): 54–61.

Moseley 2006

Moseley GL. Graded motor imagery for pathologic pain: A randomized controlled trial. *Neurology* 2006;**67**(12): 2129–34.

Moseley 2008

Moseley GL, Zalucki NM, Wiech K. Tactile discrimination, but not tactile stimulation alone, reduces chronic limb pain. *Pain* 2008;**137**:600–8.

Munts 2009

Munts AG, van der Plas AA, Voormolen JH, Marinus J, Teepe-Twiss IM, Onkenhout W, et al. Intrathecal glycine for pain and dystonia in complex regional pain syndrome. *Pain* 2009;**146**(1-2):199–204.

Munts 2010

Munts AG, van der Plas AA, Ferrari MD, Teepe-Twiss IM, Marinus J, van Hilten JJ. Efficacy and safety of a single intrathecal methylprednisolone bolus in chronic complex regional pain syndrome. *European Journal of Pain* 2010;**14** (5):523–8.

Nelson 2006

Nelson DV, Stacey BR. Interventional therapies in the management of complex regional pain syndrome. *Clinical Journal of Pain* 2006;**22**(5):438–42.

Niehof 2006

Niehof SP, Huygen FJPM, van der Weerd RWP, Westra M, Zijlstra FJ. Thermography imaging during static and controlled thermoregulation in complex regional pain syndrome type 1: diagnostic value and involvement of the central sympathetic system. *Biomedical Engineering Online* 2006;**5**:30.

Nüesch 2010

Nüesch E, Trelle S, Reichenbach S, Rutjes AWS, Tschannen B, Altman DG, et al. Small study effects in meta-analyses of osteoarthritis trials: Meta-epidemiological study. *BMJ* 2010;**341**(7766):241.

Oaklander 2009

Oaklander AL, Fields HL. Is reflex sympathetic dystrophy/ complex regional pain syndrome type I a small-fiber neuropathy?. *Annals of Neurology* 2009;**65**(6):629–38.

Oerlemans 1999

Oerlemans HM, Goris RJA, De Boo T, Oostendorp RAB. Do physical therapy and occupational therapy reduce the impairment percentage in reflex sympathetic dystrophy? . *American Journal of Physical Medicine and Rehabilitation* 1999;**78**(6):533–9.

Oerlemans 1999a

Oerlemans HM, Oostendorp RAB, De Boo T, Goris RJA. Pain and reduced mobility in complex regional pain syndrome I: Outcome of a prospective randomised controlled clinical trial of adjuvant physical therapy versus occupational therapy. *Pain* 1999;**83**(1):77–83.

Oerlemans 2000
Oerlemans HM, Oostendorp RAB, De Boo T, Van Der Laan L, Severens JL, Goris RJA. Adjuvant physical therapy versus occupational therapy in patients with reflex sympathetic dystrophy/complex regional pain syndrome type i. Archives of Physical Medicine and Rehabilitation 2000; Vol. 81, issue 1:49–56.

Ogawa 1998
Ogawa S, Suzuki H, Shiotani Ml, Ooseto K, Masuda Y, Kawachi S, et al. A randomized clinical trial of sarpogrelate hydrochloride for neuropathic pain in patients with post-herpetic neuralgia and reflex sympathetic dystrophy. Pain Clinic 1998; Vol. 11, issue 2:125–32.

Perez 2003
Perez RSGM, Zuurmond WWA, Bezemer PD, Kuik DJ, Van Loenen AC, De Lange JJ, et al. The treatment of complex regional pain syndrome type I with free radical scavengers: A randomized controlled study. *Pain* 2003;**102** (3):297–307.

Perez 2008
Perez RS, Pragt E, Geurts J, Zuurmond WW, Patijn J, van Kleef M. Treatment of patients with complex regional pain syndrome type I with mannitol: A prospective, randomized, placebo-controlled, double-blinded study. *Journal of Pain* 2008;**9**(8):678–86.

Picarelli 2010
Picarelli H, Teixeira MJ, de Andrade DC, Myczkowski ML, Luvisotto TB, Yeng LT, et al. Repetitive transcranial magnetic stimulation is efficacious as an add-on to pharmacological therapy in complex regional pain syndrome (CRPS) type I. *Journal of Pain* 2010;**11**(11):1203–10.

Pleger 2004
Pleger B, Janssen F, Schwenkreis P, Völker B, Maier C, Tegenthoff M. Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. Pain 2004; Vol. 356:87–90.

Pleger 2005
Pleger B, Tegenthoff M, Ragert P, Förster A-F, Dinse HR, Schwenkreis P, et al. Sensorimotor returning in complex regional pain syndrome parallels pain reduction. *Annals of Neurology* 2005;**57**(3):425–9.

Pleger 2006
Pleger B, Ragert P, Schwenkreis P, Forster AF, Wilimzig C, Dinse H, et al. Patterns of cortical reorganization parallel impaired tactile discrimination and pain intensity in complex regional pain syndrome. *Neuroimage* 2006;**32**: 503–10.

Prager 2010
Prager JP. What does the mechanism of spinal cord stimulation tell us about complex regional pain syndrome?. *Pain Medicine* 2010;**11**(8):1278–83.

Price 1998
Price DD, Long S, Wilsey B, Rafii A. Analysis of peak magnitude and duration of analgesia produced by local anesthetics injected into sympathetic ganglia of complex regional pain syndrome patients. *Clinical Journal of Pain* 1998;**14**(3):216–26.

Ramamurthy 1995
Ramamurthy S, Hoffman J. Intravenous regional guanethidine in the treatment of reflex sympathetic dystrophy/causalgia: a randomized, double-blind study. *Anesthesia and Analgesia* 1995;**81**:718–23.

Rauck 1993
Rauck RL, Eisenach JC, Jackson K, Young LD, Southern J. Epidural clonidine treatment for refractory reflex sympathetic dystrophy. *Anesthesiology* 1993;**79**(6):1163–9.

Reinders 2002
Reinders MF, Geertzen JHB, Dijkstra PU. Complex regional pain syndrome type I: use of the international association for the study of pain diagnostic criteria defined in 1994. *Clinical Journal of Pain* 2002;**18**(4):207–15.

Robinson 2004
Robinson JN, Sandom J, Chapman PT. Efficacy of pamidronate in complex regional pain syndrome type I. *Pain Medicine* 2004;**5**(3):276–80.

Rocco 1989
Rocco AG, Kaul AF, Reisman RM, Gallo JP, Lief PA. A comparison of regional intravenous guanethidine and reserpine in reflex sympathetic dystrophy a controlled, randomized, double-blind crossover study. *Clinical Journal of Pain* 1989;**5**(3):205–9.

Sahin 2006
Sahin F, Yilmaz F, Kotevoglu N, Kuran B. Efficacy of salmon calcitonin in complex regional pain syndrome (type 1) in addition to physical therapy. *Clinical Rheumatology* 2006;**25**(2):143–8.

Sandroni 2003
Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. *Pain* 2003;**103**(1-2):199–207.

Schinkel 2006
Schinkel C, Gaertner A, Zaspel J, Zedler S, Faist E, Schuermann M. Inflammatory mediators are altered in the acute phase of posttraumatic complex regional pain syndrome. *Clinical Journal of Pain* 2006;**22**(3):235–9.

Schmelz 2001
Schmelz M, Weber M, Birklein F, Neundo B. Facilitated neurogenic inflammation in complex regional pain syndrome. *Pain* 2001;**91**:251–7.

Schwartzman 2009
Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: A double-blind placebo controlled study. Pain 2009; Vol. 147:107–15.

Schwenkreis 2003
Schwenkreis P, Janssen F, Rommel O, Pleger B, Volker B, Hosbach I, et al. Bilateral motor cortex disinhibition in

complex regional pain syndrome (CRPS) type I of the hand. *Neurology* 2003;**61**:515–9.

Shea 2007
Shea BJ, Grimshaw JM, Wells G, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* 2007;**7**:10.

Shipton 2009
Shipton EA. Complex regional pain syndrome: mechanisms, diagnosis, and management. *Current Anaesthesia and Critical Care* 2009;**20**:209–14.

Sigtermans 2009
Sigtermans MJ, van Hilten JJ, Bauer MCR, Arbous MS, Marinus J, Sarton EY, et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain 2009; Vol. 145:304–11.

Stanton-Hicks 2002
Stanton-Hicks MD, Burton AW, Bruehl SP, Carr DB, Harden RN, Hassenbusch SJ, et al. An updated interdisciplinary clinical pathway for CRPS: report of an expert panel. *Pain Practice* 2002;**2**(1):1–16.

Swart 2009
Swart CMA, Stins JF, Beek PJ. Cortical changes in complex regional pain syndrome (CRPS). *European Journal of Pain* 2009;**13**(9):902–7.

Tan 2005
Tan ECTH, Oyen WJG, Goris RJA. Leukocytes in complex regional pain syndrome type I. *Inflammation* 2005;**29**(4-6): 182–6.

Taskaynatan 2004
Taskaynatan AM, Ozgul A, Kenan Tan A, Dincer K, Alp Kalyon T. Bier block with methylprednisolone and lidocaine in CRPS type I: A randomized, double-blinded, placebo-controlled study. *Regional Anesthesia and Pain Medicine* 2004;**29**(5):408–12.

Turk 2008
Turk DC, Dworkin RH, McDermott MP, Bellamy N, Burke LB, Chandler JM, et al. Analyzing multiple endpoints in clinical trials of pain treatments: IMMPACT recommendations. *Pain* 2008;**139**(3):485–93.

Turk 2008a
Turk DC, Dworkin RH, Revicki D, Harding G, Burke LB, Cella D, et al. Identifying important outcome domains for chronic pain clinical trials: An IMMPACT survey of people with pain. *Pain* 2008;**137**(2):276–85.

Uher 2000
Uher EM, Vacariu G, Schneider B, Fialka V. Comparison of manual lymph drainage with physical therapy in complex regional pain syndrome type I. A comparative randomized controlled therapy study. *Wiener klinische Wochenschrift [The Central European Journal of Medicine]* 2000;**112**: 133–7.

van de Vusse 2004
van de Vusse AC, Stomp-van den Berg SGM, Kessels AHF, Weber WE. Randomised controlled trial of gabapentin in Complex Regional Pain Syndrome type 1. BMC Neurology 2004; Vol. 4:13.

Varenna 2000
Varenna M, Zucchi F, Ghiringhelli D, Binelli L, Bevilacqua M, Bettica P, et al. Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. A randomized, double blind, placebo controlled study. *Journal of Rheumatology* 2000;**27**(6):1477–83.

Verdugo 1995
Verdugo RJ, Moya MF, Cea JG, Salinas HA, Bilbeny CJ. Stellate ganglion block in reflex sympathetic dystrophy: a double-blind crossover study. Program & Abstracts of the 1st Scientific Meeting of the European Federation of IASP chapters. 1995.

Wallace 2000
Wallace MS, Ridgeway BM, Leung AY, Gerayli A, Yaksh TL. Concentration-effect relationship of intravenous lidocaine on the allodynia of complex regional pain syndrome types I and II. *Anesthesiology* 2000;**92**(1):75–83.

Woolf 2004
Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Annals of Internal Medicine* 2004;**140**(6):441–51.

Wu 1999
Wu W, Bandilla E, Ciccone DS, Yang J, Cheng S-C S, Carner N, et al. Effects of qigong on late-stage complex regional pain syndrome. *Alternative Therapies in Health and Medicine* 1999;**5**(1):45–54.

Zuurmond 1996
Zuurmond WWA, Langendijk PNJ, Bezemer PD, Brink HEJ, De Lange JJ, Van Loenen AC. Treatment of acute reflex sympathetic dystrophy with DMSO 50% in a fatty cream. *Acta Anaesthesiologica Scandinavica* 1996;**40**(3): 364–7.

* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. The Budapest clinical diagnostic criteria for CRPS

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in three of the four following categories • *Sensory*: reports of hyperaesthesia and/or allodynia • *Vasomotor*: reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry • *Sudomotor/oedema*: reports of oedema and/or sweating changes and/or sweating asymmetry • *Motor/trophic*: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign at time of evaluation in two or more of the following categories • *Sensory*: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement) • *Vasomotor*: evidence of temperature asymmetry and/or skin colour changes and/or asymmetry • *Sudomotor/oedema*: evidence of oedema and/or sweating changes and/or sweating asymmetry • *Motor/trophic*: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

Table 2. AMSTAR tool: Quality assessment criteria

Criteria	Specific requirements
1. Was an 'a priori' design provided?	The research question and inclusion criteria should be established before the conduct of the review
2. Was there duplicate study selection and data extraction?	There should be at least two independent data extractors and a consensus procedure for disagreements should be in place
3. Was a comprehensive literature search performed?	At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc
5. Was a list of studies (included and excluded) provided?	A list of included and excluded studies should be provided.

Table 2. AMSTAR tool: Quality assessment criteria (*Continued*)

6. Were the characteristics of the included studies provided?	In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported
7. Was the scientific quality of the included studies assessed and documented?	'A priori' methods of assessment should be provided (e.g. for effectiveness studies if the author(s) chose to include only randomised, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations
9. Were the methods used to combine the findings of studies appropriate?	For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?)
10. Was the likelihood of publication bias assessed?	An assessment of publication bias should include a combination of graphical aids (e.g. funnel plot, other available tests) and/or statistical tests (e.g. Egger regression test)
11. Was the conflict of interest stated?	Potential sources of support should be clearly acknowledged in both the systematic review and the included studies
Total Score	

Each criterion judged as 'Yes' (score one point), 'No' (score no point), 'Can't answer' (score no point) or 'not applicable' (score one point). Total score summed out of a maximum 11 points.

Table 3. Reasons for review or paper exclusion

Reason for exclusion	Papers excluded
Not a systematic review*	Athie-Garcia 1992; Baidya 2011; Ezendam 2009; Harden 2005; Harden 2006, Hassantash 2003; Johnson 2011; Koltzenburg 1998; Kouroukli 2010; Bal 2010; Leite 2000; Manchikanti 2011; Martinez 1993; Neira 1988; Nilsagard 2004*; North 2010; Schestasky 2008; Williams 2008

Table 3. Reasons for review or paper exclusion (*Continued*)

Insufficient CRPS exclusivity	Attal 2010; Beckerman 1990; Bekkering 2011; Bernstein 2001; Bittar 2005; Blonk 2010; Blum 2008; Bronfort 2010; Campbell 2001; Cao 2010; Covarrubias-Gomez 2008; del Pozo 2011; Derry 2009; Duhmke 2004; Dworkin 2007; Eccles 2005; Eisenberg 2006; Ellis 2008; Finnerup 2005; Finnerup 2007; Finnerup 2010; Florez 2010; Claydon 2010; Fulop 2010; Gill 2011; Haroutiunian 2010; Gottschild 2003; Linde 2001; Lord 2002; McHardy 2008; Moore 2009; Moulin 2007; Namaka 2004; Namaka 2009; Nnoaham 2008; Noble 2010; Pappagallo 2008; Patel 2009; Pittler 2007; Pittler 2008; Plested 2010; Rauck 2009; Rehberg 2010; Saarto 2010; So 2008; Seidel 2008; Trescott 2008; Vlassakov 2011; Watson 2010; Wetering 2010; Wiedemann 1997; Wiffen 2009; Saarto 2010a; Wiffen 2011; Zaccara 2011
No novel coverage in addition to existing Cochrane reviews or more recently published included reviews**	Albazaz 2008; Cepeda 2002; Geertzen 2006; Goodyear-Smith 2009; Kingery 1997; Perez 2010; Prescrire 2009; Vergne-Salle 2009; Van den Berg 2002
Duplicate to included review	McQuay 1997 (duplicate of included review by Jadad 1995)
Not measuring relevant outcomes to this overview	Granot 2007
No RCTs identified	Hocking 2003; Motsch 1997

*Nilsagaard - Norwegian translators judgement (sole reviewer). Also lack of detail in report meant data extraction not possible.
** Where reviews considered all interventions for CRPS or 2 reviews compared the same intervention each review was compared to the most recent. Where an older review identified no RCTs that had not already been identified in a more recent review and the data were adequately reported in the more recent review, the older review was excluded. Similarly where more than one review investigated the same intervention or class of interventions, the equivalent process was followed.

Table 4. List of reviews, interventions and trials that contributed to the overview

Intervention	Review	Unique trials contributed and sample size (n)
Pharmacotherapies		
Bisphosphonates	Brunner 2009	Adami 1997 (20) Manicourt 2004 (39) Robinson 2004 (27) Varenna 2000 (32)
	Chauvineau 2005	Cohen 1998 (14)
Calcitonin	Tran 2010	Bickerstaff 1991 (38) Gobelet 1986 (24) Gobelet 1992 (66) Sahin 2006 (35)

Table 4. List of reviews, interventions and trials that contributed to the overview (*Continued*)

	Perez 2001	Cherot 1983 (95) Friez 1982 (55)
Corticosteroids	Fischer 2010	Braus 1994 (36) Christensen 1982 (23) Kalita 2006 (60) Lukovic 2006 (60) Taskaynatan 2004 IVRB (22)
Epidural clonidine	Tran 2010	Rauck 1993 (26)
NMDA antagonists	Collins 2010	Schwartzman 2009 (19) Sigtermans 2009 (60)
Free radical scavengers	Fischer 2010	Geertzen 1994 (26) Goris 1987 (20) Perez 2003 (146) Perez 2008 (41) Zuurmond 1996 (30)
Gabapentin	Moore 2011(C)	van de Vusse 2004 (58)
Sarpogrelate hydrochloride	Tran 2010	Ogawa 1998 (30)
Systemic local anaesthetic agents	Challapalli 2005 (C)	Wallace 2000 (16)
Tadalafil	Tran 2010	Groeneweg 2008 (24)
Interventional and surgical procedures		
Epidural clonidine	Tran 2010	Rauck 1993 (26)
IVRB atropine	Tran 2010	Glynn 1993 (30)
IVRB bretylium	Jadad 1995	Hord 1992 (7)
IVRB dropiredol + heparin	Jadad 1995	Kettler 1988 (6)
IVRB guanethidine	Jadad 1995	Blanchard 1990 (21) Bonelli 1983 (19) Jadad 1995 (9) Rocco 1989 (10) Dhar 1992 (15)
	Tran 2010	Livingstone 2002 (56) Ramamurthy 1995 (57)

Table 4. List of reviews, interventions and trials that contributed to the overview (*Continued*)

IVRB ketanserin	Jadad 1995	Hanna 1989 (16)
	Forouzanfar 2002	Bounameaux 1984 (9)
Local anaesthetic sympathetic blockade	Cepeda 2005	Price 1998 (7) Verdugo 1995 (16)
	Tran 2010	Carroll 2009 (7)
Sympathectomy	Straube 2010 (C)	Manjunath 2008 (20)
Neurostimulation methods		
Spinal cord stimulation	Mailis-Gagnon 2004 (C)	Kemler 2000; Kemler 2001; Kemler 2002 (54)
	Simpson 2009	Kemler 2004; Kemler 2006
Repetetive transcranial magnetic stimulation (motor cortex)	O'Connell 2010	Pleger 2004 (10)
Physical and rehablitation interventions		
Manual lymph drainage	Forouzanfar 2002	Uher 2000 (35)
Mirror therapy and GMI	Rothgangel 2011	Cacchio 2009 (48) Cacchio 2009a (24) Moseley 2004 (15) Moseley 2006 (37)
Physiotherapy and occupational therapy	Daly 2009	Oerlemans 1999 (135)
Pulsed electromagnetic frequency therapy	Daly 2009	Durmus 2004 (40)
Alternative therapies		
Acupuncture and Qigong	Lu 2009	Chang 2005 (80) Jin 2007 (72) Liu 2006 (100)
	Smith 2005	Ernst 1995 (14) Fialka 1993 (14) Kho 1995 (28) Wu 1999 (26)
	Forouzanfar 2002	Korpan 1999 (14)

Table 4. List of reviews, interventions and trials that contributed to the overview (*Continued*)

Autogenic relaxation training	Smith 2005	Fialka 1996 (18)

Table 5. Characteristics of included reviews

Review	Date assessed as up to date*	Population	Interventions	Comparison Interventions	Outcomes for which data were reported**	Review Limitations†
Cochrane reviews						
Cepeda 2005	November 2003	CRPS (formal diagnostic criteria not required)	selective sympathetic blockade (excl. somatic nerve blocks, local anaesthetics or sympatholytic drugs)	placebo	short and long-term pain relief. Adverse events	
Challapalli 2005	May 2004	patients of any age with neuropathic pain	lidocaine or its analogues given orally or parenterally	placebo or other therapy	intensity of pain or its relief. Adverse effects	
Mailis-Gagnon 2004	September 2003	adult patients with chronic pain (duration >6 months)	spinal cord stimulation (surgically or percutaneously implanted)	no stated limitations	pain relief, functional status/ disability, well being, satisfaction with treatment, complications, quality of life	
Moore 2011	January 2011	adult patients with chronic neuropathic pain	gabapentin (any dose)	placebo, no intervention or any active comparator	pain intensity or relief. Patient global impression of change. Withdrawal due to lack of efficacy or adverse events, adverse events, function	
O'Connell 2010	November 2009	adult patient with chronic pain (duration > 3 months)	non-invasive brain stimulation techniques	sham stimulation controls	pain intensity/ severity, disability, quality of life, adverse events	

Table 5. Characteristics of included reviews (*Continued*)

Straube 2010	May 2010	any age, any duration, neuropathic pain	destructive surgical or chemical cervicothoracic or lumbar sympathectomy	placebo or other active treatment	pain relief lasting for a minimum of 4 weeks, adverse events and complications, occurrence or persistence of new or expanded pain	
non-Cochrane reviews						
Brunner 2009	April 2007	CRPS-I (diagnostic criteria not specified)	bisphosphonates	placebo	pain, function, quality of life, adverse events	details of meta-analysis insufficient
Chauvineau 2005	2003	CRPS-I (diagnostic criteria not specified)	bisphosphonates	placebo, calcitonin	Not specified	
Collins 2010	October 2009	acute or chronic neuropathic pain	NMDA receptor antagonists	placebo	pain, adverse events	
Daly 2009	September 2007	CRPS-I, with stated diagnostic criteria	physiotherapy (alone or delivered in combination with other therapies)	any comparison	pain, function	
Fischer 2010	December 2009	CRPS-I (diagnostic criteria not specified)	anti-inflammatory therapies	any comparison	pain, ROM, clinical improvement	positive conclusions influenced by non-randomised studies
Forouzanfar 2002	June 2000	RSD and CRPS-I	any treatment	any comparison	pain intensity	
Jadad 1995	May 1993	RSD (diagnostic criteria not specified)	intravenous regional sympathetic blockade	any comparison	pain intensity	
Lu 2009	Sept 2008	Post-stroke shoulder hand syndrome	acupuncture	sham or other intervention	pain, ROM, ability to conduct daily activities	information extracted via an interpreter

Table 5. Characteristics of included reviews (*Continued*)

Perez 2001	May 2000	RSD, CRPS-I (diagnostic criteria not specified)	medicinal treatments	any comparison	pain relief	
Rothgangel 2011	August 2010	all adult patients suffering from stroke, phantom limb pain or CRPS (diagnostic criteria not specified)	mirror therapy (more than 2 interventions) in isolation or combination with other types of treatment	any comparison	at least one important clinical outcome pain, motor function	includes studies that are not pure mirror therapy - therefore effects observed may not be due to mirror therapy component
Simpson 2009	August 2007	adults with chronic neuropathic or ischaemic pain with inadequate response to medical or surgical treatment	spinal cord stimulation (incl. implantable pulse generator systems (rechargeable and non-rechargable) and radiofrequency receiver systems	medical or surgical treatment that does not include spinal cord stimulation	pain, health-related quality of life, function, anxiety and depression, complications and adverse effects	
Smith 2005	November 2004	CRPS-I (diagnostic criteria not specified)	physiotherapy modalities (one or more)	any comparison	pain, function, patient subjective success, sickness impact profile, depression, anxiety	reporting of methodology limited
Tran 2010	April 2009	CRPS (diagnostic criteria not specified)	any intervention	any comparison	any clinical outcomes	only English language trials included

* For non-Cochrane reviews the final month/year that the search included

** of interest to this overview

† not clearly covered by AMSTAR assessment (see Table 6)

Table 6. Results of AMSTAR quality assessment

	AMSTAR Item											
Review ID	1	2	3	4	5	6	7	8	9	10	11	Score /11

Table 6. Results of AMSTAR quality assessment (*Continued*)

Cochrane reviews												
Cepeda 2005	Y	N	Y	Y	Y	Y	Y	Y	Y	NA	N	9
Challapalli 2005	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	N	10
Mailis-Gagnon 2004	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	N	10
Moore 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10
O'Conne 2010	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	N	10
Straube 2010	Y	Y	Y	N	Y	Y	Y	Y	NA	NA	N	9
non-Cochrane reviews												
Brunner 2009	Y	Y	N	N	N	Y	Y	Y	CA	N	N	5
Chauvineau 2005	CA	N	Y	N	N	Y	Y	Y	NA	N	N	5
Collins 2010	CA	N	N	N	N	Y	Y	Y	Y	N	N	4
Daly 2009	CA	N	Y	N	N	Y	Y	Y	NA	N	N	5
Fischer 2010	CA	N	N	N	N	Y	Y	Y	NA	NA	N	5
Forouzanfar 2002	CA	Y	Y	N	N	Y	Y	Y	NA	NA	N	7

Table 6. Results of AMSTAR quality assessment (*Continued*)

Jadad 1995	CA	N	N	N	N	Y	N	Y	NA	N	N	3
Lu 2009	CA	Y	Y	N	N	Y	Y	Y	NA	NA	N	5
Perez 2001	CA	N	N	N	N	Y	Y	Y	Y	NA	NA	4
Roth-gangel 2011	CA	Y	Y	N	Y	Y	Y	Y	NA	N	N	7
Simp-son 2009	CA	N	Y	Y	Y	Y	Y	Y	NA	NA	N	8
Smith 2005	CA	N	Y	N	N	Y	N	Y	NA	N	N	4
Tran 2010	CA	N	N	N	Y	Y	N	Y	NA	NA	N	5

Y = Yes - criteria met (score 1 point), n = No - criteria not met (score 0 points), CA = Can't answer (score 0 points)
NA = not applicable (score 1 point)

Table 7. Overview of reviews

Outcome	Intervention and comparison intervention	Contributing reviews	Relative effect?	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Pain						
Pharmacotherapy						
Anti-inflammatory treatments						
	Corticosteroids (Oral)	Fischer 2010				
	Oral prednisolone 5mg/day + diverse physical agents versus placebo + same		Outcome: 0-10 pain VAS no statistically significant difference	60 (1)	Very low	

Table 7. Overview of reviews (*Continued*)

	Topical free radical scavengers	Fischer 2010				
	DMSO 50% in fatty cream versus placebo fatty cream over 2 months		Outcome 0-10 pain VAS No significant difference	31 (1)	Very low	
	IVRB corticosteroids					
	IVRB methylprednisolone 40mg with lidocaine10ml 2% once a week versus 100ml saline x3 in total		Outcome pain VAS No significant difference	22 (1)	Very low	
	Intravenous free range scavengers	Fischer 2010				
	Mannitol 10% versus placebo every day for 5 days		Outcome pain VAS 0-100 No significant improvement	41 (1)	Very low	
Bisphosphonates						
		Brunner 2009; Chauvineau 2005				
	Bisphosphonates (IV, oral) versus placebo		Outcome pain VAS 0-100 Pooled estimates: 4 weeks -22.4 (95%CIs not available) 12 weeks -21.6 (95% CIs not available)	66 (2)	Low	Pooled estimates obtained using data from 2 out of 4 identified trials. Minimal detail given re: statistical approach to pooling. No precision estimates available. Remaining two trials also positive
Calcitonin						

Table 7. Overview of reviews (*Continued*)

	Calcitonin *(varied delivery and dosage) versus placebo	Perez 2001	Effect size (Glass Δ adjusted for sample size) 0.444, SD 0.362, P<0.002	118 (3)	Low	
	Nasal Calcitonin versus oral paracetamol	Tran 2010	Pain, no significant difference	35 (1)	Very low	
	Nasal calcitonin versus IV pamidronate	Chauvineau 2005	Pain, no significant difference	14 (1)	Very low	
Gabapentin						
	Gabapentin 1800mg/ day orally versus placebo	Moore 2011	Pain. No significant effect	58 (1)	Very low	
NMDA receptor antagonists						
	IV ketamine (variable dosage) versus placebo	Collins 2010	Pain 0-10 NRS mean difference post-treatment -2.63 (95% CI -3.39-1.88) I^2=21%, P=0.00001	79 (2)	Low	
Sarpogrelate hydrochloride						
	oral sarpogrelate hydrochloride (300mg/ day) plus conventional treatment versus conventional treatment alone for 3 months	Tran 2010	Pain 0-100 VAS No significant difference observed	30 (1)	Very low	
Systemic local anaesthetic agents						
	IV lidocaine infusion targeted to deliver a stepped increase	Challapalli 2005	Spontaneous pain 0-100 VAS high dose lidocaine may have a		Very low	

Table 7. Overview of reviews (*Continued*)

	in plasma concentrations of 1, 1.5, 2 or 3 µg/ml versus "placebo" IV diphenhydramine (70-80mg)		small short-term effect (immediately post-infusion)			
Tadalafil						
	Oral tadalafil (10mg/day for four weeks followed by 20mg/day for 8 weeks) versus placebo	Tran 2010	Pain 0-100 VAS Study report: 14% improvement versus placebo Our analysis: -4.20mm (95% CI -16.61 to 8.21) (not significant)	24 (1)	Very low	
Interventional procedures						
Epidural clonidine						
	Epidural clonidine versus placebo	Tran 2010	300 or 600μg clonidine reduced pain VAS greater than placebo (saline). 6 hours post-treatment No numeric data presented No long-term follow up	26 (1)	Very low	
Intravenous regional anaesthetic blocks (IVRB)						
	Atropine (0.6mg) versus placebo	Tran 2010	Pain VAS No effect	33 (1)	Very low	
	Bretylium (1.5mg/kg) + lidocaine (200-300mg) versus lidocaine (200-300mg)	Jadad 1995	Duration of ≥30% pain relief active group mean (SD) 20.0 (17.5) days		Very low	

Table 7. Overview of reviews (*Continued*)

			control group mean 2.7 (3.7) days			
	Dropiredol (2.5mg) + heparin (500-1000U) versus heparin (500-1000U)	Jadad 1995	Pain VAS No effect observed	6 (1)	Very low	
	Guanethidine (varied dose) versus placebo	Jadad 1995; Tran 2010	Pain (miscellaneous) No effect in any study	189 (6)	Moderate	
	Ketanserin (10mg) versus placebo	Jadad 1995	weekly pain VAS Demonstrated a significant effect (no effect size available)	9 (1)	Very low	
Local Sympathetic Blockade						
	Local anaesthetic sympathetic blockade (lidocaine or bupivacaine) versus placebo	Cepeda 2005	Short-term pain relief RR 1.17 (95% CI 0.80 to 1.72) (no significant effect)	23 (2)	Very low	
	Botulinum toxin A (75 units) plus bupivacaine (10ml of 0.5%) with just bupivacaine (10ml of 0.5%)	Tran 2010	Median time to analgesic failure 71 days (95% CI 12-253) with botulinum toxin versus bupivacaine compared to <10 days (95% CI 0-12) with bupivacaine alone P<0.02	7 (1)	Very low	
Sympathectomy						
		Straube 2010	Pain		No evidence	
Neurostimulation methods						

Table 7. Overview of reviews (*Continued*)

	High frequency repetitive transcranial magnetic stimulation (single session) versus sham stimulation	O'Connell 2010	Pain VAS SMD -0.14 (95% CI -0.57 to 0.29) P= 0.52	9 (1)	Very low	
	Spinal cord stimulation (SCS) + physical therapy versus physical therapy alone	Mailis-Gagnon 2004; Simpson 2009	Pain 0-10 VAS mean difference 6 months (-3.40 (95% CI -4.82 to -1.98)	54 (1)	Very low	
Physiotherapy/ Occupational Therapy						
	Physiotherapy (PT) versus occupational therapy (OT) versus social work (SW)	Daly 2009; Smith 2005	One year follow up: pain 0-100 VAS PT vs OT mean difference 4. 5 (95% CI -10.1 to 19.1) PT vs SW 5.2 (-3.3 to 7.1)	135 (1)	Low	
	Manual lymph drainage massage and exercise versus exercise alone	Forouzanfar 2002	Pain verbal rating scale No significant difference	35 (1)	Very low	
	Pulsed electromagnetic field plus calcitonin and exercise versus sham EMF plus calcitonin and exercise	Daly 2009	Pain VAS No significant difference	40 (1)	Very low	
	Graded motor imagery programme versus conventional physiotherapy	Daly 2009; Rothgangel 2011	Pain VAS 0-100 pooled mean difference: end of treatment: -14.45 (95% CI -23.02 to -5.57,	49 (2)	Low	

Table 7. Overview of reviews (*Continued*)

			P=0.001) at 3-6 month follow up: -21.64 (95% CI -30.02 to -13.27, P<0.001)			
	Mirror therapy versus covered mirror therapy. (post stoke CRPS)	Rothgangel 2011	Pain at rest 0-10 VAS Both studies report positive effects. Data extracted from one study mean difference -2.9 (95% CI -1.57 to -4.23) at end of treatment mean difference -3.4(95%CI -2.09 to -4.71) at 6 months	72 (2)	Low	
Alternative therapies						
	Acupuncture and rehab versus rehabilitation alone (post-stroke CRPS_	Lu 2009;	Various pain/outcome scores All conclude in favour of acupuncture	252 (3)	Very low	
	Acupuncture versus sham	Smith 2005	Pain VAS, no significant differences in any study	70 (4)	Very Low	
	Qigong therapy versus sham Qigong	Forouzanfar 2002; Smith 2005	% participants who reported a reduction in pain. 91% in Qigong group versus 36% in sham group	26 (1)	Very low	
	Relaxation therapy added to multimodal care ver-	Smith 2005	Pain - no significant difference	18 (1)	Very low	

Table 7. Overview of reviews (*Continued*)

	sus multi-modal care alone					
Composite clinical CRPS and RSD scores						
Anti-inflammatory treatments						
	Corticosteroids (oral)	Fischer 2010				
	Oral prednisolone 40mg/ day prednisolone versus piroxicam 20mg/day		Outcome: 0-14 composite CRPS score mean difference -5.10 (95% CI -6.55 to -3.65)	60 (1)	Very low	
	methylprednisolone 32mg/day versus placebo		Outcome: relevant improvement in composite shoulder-hand syndrome score (<4/14) No data given for between group comparisonS for drug versus placebo, Graphs appear not to demonstrate a difference	36 (1)	Very low	Unblinded study
	prednisolone 30mg/day versus placebo up to 12 weeks		Outcome: "75% clinical improvement" within 12 week period. Relative risk 4. 24 (95% CI 1.42 to 12.67) NNT 1	23 (1)		Unblinded study
	Topical free radical scavengers	Fischer 2010				
	DMSO 50% in fatty cream versus placebo fatty cream over 2 months		RSD score (0-5) A statistically significant improvement seen with DMSO ver-	31 (1)	Very low	

Table 7. Overview of reviews (*Continued*)

			sus placebo Inadequate data to determine effect size			
	DMSO 50% lotion applied x3 daily for 3 weeks versus regional IV Ismelin (guanethidine) blocks x2 weekly for 3 weeks		Composite score based on pain, oedema, discolouration, ROM (0-70 scale) Data not available "patients improved more" with DMSO cream	26 (1)	Very low	Unblinded study
	DMSO 50% cream x5 daily versus N-Acetylcysteine (NAC) 600mg x3 daily		ISS composite CRPS score (5-50) based on pain temperature, volume differences and function. No difference between the groups	146 (1)	Low	
5-HT_2 receptor antagonists						
	IV ketanserin (10mg) versus placebo	Forouzanfar 2002	Subjective pain score (not clearly defined). No effect observed	9 (1)	Very low	
Function/ Disability						
Neurostimulation methods						
	Spinal cord stimulation (SCS) + physical therapy versus physical therapy alone	Mailis-Gagnon 2004; Simpson 2009	Jebsens test. No difference at any time point	54 (1)	Very low	
Physiotherapy/ Occupational Therapy						
	Physiotherapy (PT) versus occupational ther-	Daly 2009; Smith 2005	1 year follow up: Impairment score (0-50	135 (1)	Low	

Table 7. Overview of reviews (*Continued*)

	apy (OT) versus social work (SW)		scale) PT vs OT mean difference 1.6 (95% CI 1 to 2. 2) PT vs SW mean difference 5.1 (95% CI 4.6 to 5.6)			
	Graded motor imagery versus usual care	Daly 2009; Rothgangel 2011	Patient-specific functional scale (0-11 NRS) , mean difference 1.90 (95% CI 1.26 to 2.54) at end of treatment, 2.69 (95% CI 1. 80 to 3.58) at 3 to 6 month follow up	49 (2)	Low	
Adverse Events	? Bisphosphonates	Brunner 2009				
Quality of life						
Neurostimulation methods	Spinal cord stimulation (SCS) + physical therapy versus physical therapy alone	Mailis-Gagnon 2004; Simpson 2009	Pain component of Nottingham Health Profile significant improvement with SCS	54 (1)	Very low	Effect not maintained in an intention-to-treat analysis
Anti-inflammatory treatments						
Topical free radical scavengers						
	Topical 50% DMSO in water versus placebo water x5 daily for 1 week	Fischer 2010	Outcome subjective evaluation of clinical improvement by patient Insufficient data	20 (1)	Very low	
Neurostimulation methods						

Table 7. Overview of reviews (*Continued*)

	Spinal cord stimulation (SCS) + physical therapy versus physical therapy alone	Mailis-Gagnon 2004; Simpson 2009	Global perceived effect More participants in SCS group considered themselves "much improved" at 6 months (P<0.01) and at two years (P<0.001)	54 (1)	Very low	

Unless specifically stated, otherwise comparisons refer to outcomes measured at the end of the intervention period.

APPENDICES

Appendix 1. Search strategy Ovid Medline

1 (review or review, tutorial or review, academic).pt.
2 (medline or medlars or embase or pubmed or cochrane).tw,sh.
3 (scisearch or psychinfo or psycinfo).tw,sh.
4 (psychlit or psyclit).tw,sh.
5 cinahl.tw,sh.
6 ((hand adj2 search*) or (manual* adj2 search*)).tw,sh.
7 (electronic database* or bibliographic database* or computeri?ed database* or online database*).tw,sh.
8 (pooling or pooled or mantel haenszel).tw,sh.
9 (peto or dersimonian or der simonian or fixed effect).tw,sh.
10 (retraction of publication or retracted publication).pt.
11 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12 1 and 11
13 meta-analysis.pt.
14 meta-analysis.sh.
15 (meta-analys* or meta analys* or metaanalys*).tw,sh.
16 (systematic* adj5 review*).tw,sh.
17 (systematic* adj5 overview*).tw,sh.
18 (quantitativ* adj5 review*).tw,sh.
19 (quantitativ* adj5 overview*).tw,sh.
20 (quantitativ* adj5 synthesis*).tw,sh.
21 (methodologic* adj5 review*).tw,sh.
22 (methodologic* adj5 overview*).tw,sh.
23 (integrative research review* or research integration).tw.
24 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25 12 or 24
26 exp Complex Regional Pain Syndromes/

27 exp Neuralgia/
28 regional pain syndrome*.mp.
29 CRPS.mp.
30 (reflex and (sympathetic or neurovascular) and dystrophy).mp.
31 (RSD or RND).mp.
32 ((sudeck's or sudecks) adj atrophy).mp.
33 algodystrophy.mp.
34 shoulder-hand syndrome*.mp.
35 causalgia.mp.
36 algoneurodystrophy.mp.
37 (neuropathic pain or neuralgia).mp.
38 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39 25 and 38
key:
mp = protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier
tw = textword
sh = subject heading
pt = publication type

Appendix 2. Search Stategy Ovid EMBASE

1 exp review/
2 (literature adj3 review*).ti,ab.
3 exp meta analysis/
4 exp "Systematic Review"/
5 or/1-4
6 (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab.
7 retracted article/
8 6 or 7
9 5 and 8
10 (systematic* adj2 (review* or overview)).ti,ab.
11 (meta?anal* or meta anal* or meta-anal* or metaanal* or metanal*).ti,ab.
12 9 or 10 or 11
13 exp neuralgia/
14 regional pain syndrome*.mp.
15 CRPS.mp.
16 (reflex and (sympathetic or neurovascular) and dystrophy).mp.
17 (RSD or RND).mp.
18 ((sudeck's or sudecks) adj atrophy).mp.
19 algodystrophy.mp.
20 shoulder-hand syndrome*.mp.
21 causalgia.mp.
22 algoneurodystrophy.mp.
23 (neuropathic pain or neuralgia).mp.
24 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25 12 and 24
key:
mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword
ti,ab=title,abstract

Appendix 3. Search strategy DARE/ CDSR

#1 MeSH descriptor Complex Regional Pain Syndromes explode all trees
#2 MeSH descriptor Neuralgia explode all trees
#3 regional pain syndrome*
#4 CRPS
#5 (reflex and (sympathetic or neurovascular) and dystrophy)
#6 RSD or RND
#7 (sudeck's or sudecks) next atrophy
#8 algodystrophy
#9 shoulder-hand syndrome*
#10 causalgia
#11 algoneurodystrophy
#12 (neuropathic pain or neuralgia)
#13 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)

Appendix 4. Search strategy CINAHL

Search modes - Boolean/Phrase
S1 MJ review
S2 TX literature N3 review
S3 MJ meta analysis
S4 MJ systematic review
S5 (S1 or S2 or S3 or S4)
S6 (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane)
S7 retracted article
S8 S6 or S7
S9 S5 and S8
S10 (systematic* N2 (review* or overview))
S11 TX (meta?anal* or meta anal* or meta-anal* or metaanal* or metanal*)
S12 S9 or S10 or
S13 MJ NEURALGIA
S14 TX regional pain syndrome*
S15 TX CRPS
S16 TX (reflex and (sympathetic or neurovascular) and dystrophy)
S17 TX (RSD or RND)
S18 TX ((sudeck's or sudecks) N8 atrophy)
S19 TX algodystrophy
S20 TX shoulder-hand syndrome*
S21 TX causalgia
S22 TX algoneurodystrophy
S23 TX (neuropathic pain or neuralgia)
S24 S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23
S25 S12 and S24

Appendix 5. Search strategy PEDro

All diagnostic terms from OVID EMBASE entered separately under domain “systematic reviews”

Appendix 6. Search strategy LILACS

COMPLEX REGIONAL PAIN SYNDROMES“ or ”NEURALGIA“ or ”CAUSALGIA“ or ”REFLEX SYMPATHETIC DYSTROPHY“ [Subject descriptor] or ”regional pain syndrome“ or neuralgia or sudecks or sudeck’s or algodystophy or ”shoulder hand syndrome“ or causalgia or algoneurodystrophy or ”neuropathic pain“ or CRPS or RSD or RND [Words] and ”REVIEW“ or ”META-ANALYSIS“

Appendix 7. Search results by source.

DATABASE	Date of Search	Range of search	RESULTS
MEDLINE	7/10/11	Medline 1948 to Sep week 4 2011	417
EMBASE	7/10/11	1980 to 2011 week 39	1070
CDSR	7/10/11	Issue 10 2011	331
DARE	7/10/11	Issue 4 2011	98
PEDro	10/10/11	1929 to date	21
LILACS	11/10/11	All years	103
NCDDR			defunct
CINAHL	10/10/11	1982 to date of search	152
		TOTAL	2192 (incl lilacs)
		DUPLICATES	600 (excl lilacs)
		FINAL TOTAL	1592 (incl.lilacs)
		Rejected at title/ abstract stage	1486
		Additional articles identified by authors or content experts	1
		Additional articles identified by hand searching references	1
		Total for full text checking	108
		Excluded at full text stage	88

(*Continued*)

	Unretrievable	1
	Final no. of included reviews	19

WHAT'S NEW

Last assessed as up-to-date: 1 March 2013.

Date	Event	Description
17 June 2015	Review declared as stable	This review will be assessed for further updating in 2016.

CONTRIBUTIONS OF AUTHORS

NOC: conceived and designed the protocol. Performed and collated the searches in collaboration with the Trials Search Co-ordinator, applied eligibility criteria, assessed reviews, extracted and analysed data and led the write up of the overview.

BM: contributed to protocol design, applied eligibility criteria, assessed papers, extracted and analysed data and informed the write up of the overview.

LM: has provided statistical advice and support and advised on the drafting of the manuscript. Also contributed to the protocol design.

JM: contributed to protocol design. Acted as third reviewer and informed the write up of the overview.

GLM: contributed to protocol design. Advised as a content expert on CRPS, reviewed the final list of reviews for possible omissions and informed the write up of the review.

DECLARATIONS OF INTEREST

GLM receives a salary from the National Health and Medical Research Council of Australia and University of South Australia.

One of our group (GLM) was the sole author on the two included trials of GMI (Moseley 2004; Moseley 2006) and has co-authored a recent textbook on its use in chronic pain, including CRPS. This author was not involved in the data extraction process related to GMI nor the writing of the results relating to this approach.

NOC, BMW and LM were all authors of one of the included reviews (O'Connell 2010). As such, to reduce bias a different author (JM) performed the primary AMSTAR assessment and data extraction on this review.

SOURCES OF SUPPORT

Internal sources

- Brunel University, UK.

Salary for NOC

- University of Notre Dame, Australia.

Salary for BW

- University College London, UK.

Salary for LM

- Neuroscience Research Australia, Australia.

Salary for JM

- University of South Australia, Australia.

Salary for GLM

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Disabled Persons; Analgesics [administration & dosage]; Calcitonin [therapeutic use]; Complex Regional Pain Syndromes [*therapy]; Diphosphonates [therapeutic use]; Guanethidine [therapeutic use]; Imagery (Psychotherapy) [methods]; Ketamine [administration & dosage]; Nerve Block [methods]; Pain Management [*methods]; Physical Therapy Modalities; Review Literature as Topic; Sympatholytics [therapeutic use]

MeSH check words

Adult; Humans