EJP
European Journal of Pain

REVIEW ARTICLE

Treatment of complex regional pain syndrome in adults: A systematic review of randomized controlled trials published from June 2000 to February 2012

L. Cossins[1]*, R.W. Okell[2]*, H. Cameron[3], B. Simpson[4], H.M. Poole[5], A. Goebel[6]

1 Pain Research Institute, Clinical Sciences Centre, University Hospital Aintree, Liverpool, UK
2 Department of Anaesthesia, Leighton Hospital, Crewe, UK
3 Rehabilitation & Assessment Directorate, Acute Services, NHS Greater Glasgow & Clyde, UK
4 Department of Neurosurgery, University Hospital of Wales, Cardiff, UK
5 School of Natural Sciences & Psychology, Liverpool John Moores University, UK
6 Pain Research Institute, Institute of Translational Medicine, University of Liverpool, UK

Correspondence
Andreas Goebel
E-mail: andreasgoebel@rocketmail.com

Funding sources
This work was supported by the Pain Relief Foundation, Liverpool.

Conflicts of interest
Dr. Goebel has received grant support and speaker honoraria from CSL-Behring, Talecris, Baxter and Biotest, companies that produce intravenous immunoglobulin. The other authors report no conflicts of interest.

*These authors contributed equally to this work.

Accepted for publication
12 August 2012

doi:10.1002/j.1532-2149.2012.00217.x

[Correction added after online publication 14 November: The timeline in title has been corrected to '. . . trials published from June 2000 to February 2012']

Abstract

Complex regional pain syndrome (CRPS) is a disabling pain condition with sensory, motor and autonomic manifestations. Uncertainty remains about how CRPS can be effectively managed. We conducted a systematic review of randomized controlled trials (RCTs) for treatment and prophylactic interventions for CRPS published during the period 2000–2012, building on previous work by another group reviewing the period 1966–2000. Bibliographic database searches identified 173 papers which were filtered by three reviewers. This process generated 29 trials suitable for further analysis, each of which was reviewed and scored by two independent reviewers for methodological quality using a 15-item checklist. A number of novel and potentially effective treatments were investigated. Analysing the results from both review periods in combination, there was a steep rise in the number of published RCTs per review decade. There is evidence for the efficacy of 10 treatments (3× strong – bisphosphonates, repetitive transcranial magnetic stimulation and graded motor imagery, 1× moderate and 6× limited evidence), and against the efficacy of 15 treatments (1× strong, 1× moderate and ×13 limited). The heterogeneity of trialled interventions and the pilot nature of many trials militate against drawing clear conclusions about the clinical usefulness of most interventions. This and the observed phenomenon of excellent responses in CRPS subgroups would support the case for a network- and multi-centre approach in the conduct of future clinical trials. Most published trials in CRPS are small with a short follow-up period, although several novel interventions investigated from 2000 to 2012 appear promising.

1. Introduction

Complex regional pain syndrome (CRPS) is the term given to a group of painful conditions, which has an incidence of 26/100.000 life years (de Mos et al., 2007). CRPS is associated with sensory, motor, autonomic, skin and bone abnormalities in a limb (Veldman et al., 1993; Stanton-Hicks et al., 1995; Baron, 2004; Bruehl, 2010; Goebel, 2011; Marinus et al., 2011). It usually arises after trauma to a limb, but without any relation to the severity of the trauma, and in 10% of cases, no or only very minor trauma is reported (Veldman et al., 1993; de Mos et al., 2009) The diagnosis of CRPS is based on clinical history, examination and exclusion of alternative causes. The recommended 'Budapest' diagnostic criteria (Harden

What's already known about this topic?

- Systematic review of randomized controlled trials for treatment and prophylactic interventions for complex regional pain syndrome published during the period 2000–2012, building on previous work by another group reviewing the period 1966–2000.

What does this study add?

- In this systematic review we have assessed randomized controlled trials (RCTs) published between 2000 and 2012; we also provide a combined overview of all RCTs (1966–2012), and present the level of evidence for the reviewed interventions.

et al., 2007) have a diagnostic specificity of 0.69 (see Table 1). Superseded criteria include the 'IASP criteria' with a specificity of 0.36 (Bruehl et al., 1999), and the 'Veldman' criteria which were developed in an orthopaedic context (Veldman et al., 1993).

A lack of understanding of the underlying pathophysiology for CRPS contributes to the difficulty in developing definitive treatments; a large number of treatments have been investigated (Rowbotham, 2006). This systematic review is a follow-up to an earlier review of randomized controlled trials (RCTs) of CRPS treatment published between 1966 and 2000 (Forouzanfar et al., 2002).[1] Additional systematic reviews since 2000 have looked at the available evidence for either all or specific treatment methods. Perez et al. (2010) reviewed trial literature (both RCTs and other designs) from 1980 to 2005. The authors did not summarize their review findings but provided treatment recommendations. Tran de et al. (2010) recently reviewed RCTs published from January 1950 to April 2009. In this narrative review, conducted without formal quality scoring, the authors excluded trials requiring specialist skills or equipment. They found that 'only bisphosphonates appear to offer clear treatment benefits'. Five specific treatments for CRPS have been reviewed separately: local anaesthetic blocks (Cepeda et al., 2005), spinal cord stimulation (SCS) (Taylor, 2006), bisphosphonates (Brunner et al., 2009), and chemical and surgical sympathectomy (Straube et al., 2010). In a review of physiotherapeutic methods used in the treatment of CRPS, Daly and Bialocerkowski (2009) concluded that existing CRPS clinical guidelines (Stanton-Hicks et al., 2002; Harden et al., 2006) on the use of specialized treatment methods are in general not sufficiently underpinned by trial evidence. However, they found good evidence for the use of graded motor imagery (GMI) (Moseley, 2004, 2005, 2006) based on three RCTs from one research group.

We considered it important to conduct a systematic review restricted to RCTs which included all suitable RCTs, and where trial quality would be formally assessed and scored as had been carried out in the earlier review (Forouzanfar et al., 2002).We assessed RCTs published between June 2000 and February 2012 using almost identical methodology as Forouzanfar et al.'s. We present our results for this review period and also provide a summary of findings from both review periods.

2. Methods

We reviewed RCTs published on either the treatment or prevention of CRPS from July 2000 to April 2010.[2] We subsequently reviewed RCTs published from April 2010 to February 2012. A previous review published in 2002 (Forouzanfar et al., 2002), which reviewed RCTs on the treatment and prevention of reflex sympathetic dystrophy and CRPS from 1966 to June 2000, provided the basis for the review methodology.

Medline (PubMed), SCOPUS, CINAHL, and AMED bibliographic databases and the Cochrane Central Register of Controlled Trials were searched electronically using combinations of the following indexed search terms: 'complex regional pain syndromes', 'causalgia', 'reflex sympathetic dystrophy', with 'therapy', 'drug therapy', 'rehabilitation', 'prevention and control', and limited to 'randomised controlled trials' and 'clinical trials'. All foreign language papers were included, and translated if necessary. Major European and American trial registries were searched for unpublished trials completed at least 2 years prior to the end date for this review.

We included trials that studied patients suffering from either CRPS I or CRPS II (without/with associated injury to a major nerve). Trials conducted in mixed populations of both CRPS and non-CRPS patients were included if the publication included a power analysis demonstrating the suitability of a separate statistical analysis for the CRPS group.

Three reviewers pre-filtered a third of identified studies each, according to their randomization

[1]Another comprehensive review had been published 5 years earlier (W.S. Kingery. Pain 1997 73(2); 123–129).

[2]We included publications which had been published online by the end date.

Table 1 Budapest clinical diagnostic criteria.

All of the following statements must be met:	
■ The patient has continuing pain which is disproportionate to any inciting event.	
■ The patient has at least one sign in two or more of the categories below.	
■ The patient reports at least one symptom in three or more of the categories below[a].	
■ No other diagnosis can better explain the signs and symptoms.	
Category	Sign/Symptom
1 'sensory'	Allodynia (pain to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement) and/or hyperalgesia (to pinprick)
2 'vasomotor'	Temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
3 'sudomotor/oedema'	Oedema and/or sweating changes and/or sweating asymmetry
4 'motor/trophic'	Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair/nail/skin)

[a]To fulfil Research Diagnostic Criteria, patients must report at least one symptom in all four categories of signs and symptoms.

method. In case of uncertainty, the reviewers conferred with each other. We included only RCTs conducted in adult CRPS. We included trials if they were described as randomized and the method of randomization was appropriate[3] (Jadad et al., 1996). Other than in the earlier review (see Table 2), if a trial was randomized, and the randomization method was described but was inappropriate, the study was excluded and the reason was noted. If the study was described as randomized, but the method of randomization was not described, the study was included and this lack of description was noted in the results (Jadad et al., 1996). Where necessary, we contacted authors for clarification.

Then three reviewers (A.G., R.O., L.C.) jointly investigated the included randomized trials with regard to their outcome measures. If pain intensity was measured either as a primary or secondary outcome using either a numerical rating scale (NRS), a visual analogue scale (VAS), a verbal rating scale (VRS) (Dworkin et al., 2005), or a neuropathic pain scale (NPS) (Galer and Jensen, 1997), or if prevention of CRPS was the outcome measure, the study was included. Studies that used only composite outcomes made up of various primary parameters, e.g., a 'CRPS score' (Kalita et al., 2006) without also giving pain intensity, were excluded (Fig. 1; Supporting Information Appendix S1 for a list of excluded trials).

We evaluated the filtered studies for their methodological quality by using a 15-item quality checklist (de Vet et al., 1997) (Supporting Information Appendix S4). Each item was weighted, with a maximum score of 100. High-quality trials had a score of 50 or greater. Three groups of two reviewers scored the identified papers and offered comments in some cases. Scores were agreed between reviewers and any disagreement was settled by a third reviewer. It should be noted that trials involving active participation, where blinding is not possible, can only achieve a lower maximum score of 90/100.

[3]Randomization was deemed appropriate if it allowed each patient to have the same chance of receiving each treatment whereby the investigators could not predict which treatment was assigned. Therefore, methods of allocation using date of birth, date of admission, hospital numbers or consecutive alternation were not appropriate.

2.1 CRPS subgroups

Where a study was conducted in a subgroup of patients, this restriction was noted. Some studies in post-operative settings were conducted predominantly with patients who had CRPS of recent onset, while other studies excluded this group. We indicated the study population as 'early' or 'long-standing'. Study populations were defined as long-standing CRPS if: (1) those with 6 months or less disease duration had been explicitly excluded; or (2) where no cut-off was provided, the participants' mean or median disease durations were longer than 19 and 14 months, respectively. These two cut-off values (19 and 14 months) were derived from the lowest mean and median disease duration in those studies, which had explicitly excluded patients with disease duration of 6 months or less.

2.2 Study classification as 'positive' or 'negative'

Studies were considered to have a positive outcome if the pain intensity was statistically significantly reduced, or the CRPS incidence was reduced by the intervention when compared with placebo, comparison treatment or no-treatment control groups.

2.3 Trials of two or more active interventions

If there was no additional placebo/control group, and no significant difference between active interventions, these trials were excluded.

Table 2 Differences in trial inclusion criteria between the 2002 review and the current review.

Criterion/Study	Included in Forouzanfar et al. 2002	Included in the current review
Study population		
Adults	Yes	Yes
Children	Not addressed	No
CRPS I	Yes	Yes
CRPS II	No	Yes
Randomization		
Randomized	Yes	Yes
Appropriate randomization method	Not addressed	Yes
Inappropriate randomization method	Not examined	No
Randomization, but method not stated	Not addressed	Yes
Study outcome		
Pain scale (NRS, VAS, VRS, NPS)	Yes	Yes
Composite scores only (NRS/VAS/VRS/NPS pain intensity not reported)	Yes	No
Non-pain outcome measures only	No	No
Protocol		
Treatment versus placebo/control[a]	Yes	Yes
Treatment 1 versus treatment 2, no control	Yes	No (unless there was a significant difference between the two treatment outcomes)

NRS, numeric rating scale; VAS, visual analogue scale; VRS, verbal rating scale; NPS, neuropathic pain scale.
[a]With either no intervention in control group or some congruent intervention in both the active and control groups.

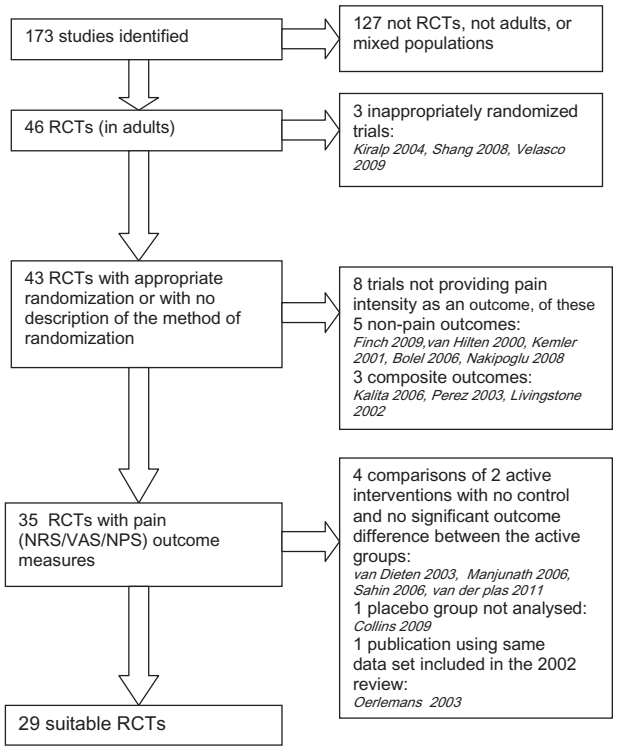

Figure 1 Flow diagram of the selection of suitable trials. RCT, randomised controlled trial; NRS, numeric rating scale; NPS, neuropathic pain scale; VAS, visual analogue scale. The 26 identified and 16 excluded RCTs are referenced in Supporting Information Appendix S1.

2.4 Levels of evidence

In line with the 2002 review, we used the van Tulder et al.'s (1997) method to determine the level of evidence for the efficacy of interventions, based on both trial methodological quality and outcomes (Table 3).

3. Results

173 potentially suitable studies were identified. Twelve of these were non-English language papers, ten of which had either an English abstract, or were written in languages understood by one of the reviewers, i.e., German, Dutch or French. One paper was written in Chinese and was translated by an external agency (Shang et al., 2008) and one paper was written in Spanish (Rodriguez et al., 2006) and was translated by a Spanish pain specialist.

Table 3 van Tulder classification of the levels of evidence of interventions assessed in randomized controlled trials underpinning four levels of effectiveness.

Level of effectiveness	Evidence required
Strong	Multiple high-quality trials
Moderate	One high-quality trial + one or more low-quality trials
Limited	One high-quality trial or multiple low-quality trials
No evidence	One low-quality trial or no relevant trials or contradictory outcomes

Of the 173 trials, 46 were described as randomized. Three of these were excluded, because their randomization method was inappropriate (Fig. 1). Of the remaining 43 studies, 8 were excluded because they did not provide NRS, VAS, VRS or NPS pain intensity measures, and 8 because they compared two or more active interventions with no significant outcome difference, without including a control/placebo group. One study, which did not analyse the results in the placebo group, was also excluded, and a further study was also excluded because a previous publication using the same data set was included in the 2002 review (Fig. 1). A search of international trial registries identified one large trial, completed in 2008, which had not been published (http://www.clinicaltrials.gov). The trial assessed treatment with oral lenalidomide, and was sponsored by Celgene Corporation, NJ, USA. Several requests for trial data were sent to Celgene but no response was forthcoming.

3.1 Methodological quality

In all cases, the two reviewers resolved any disagreements by consensus, without resorting to a third reviewer. Quality scores for the 29 trials are summarized in Supporting Information Appendix S5. Twenty-three trials (79%) were of high quality (score of 50 or greater). Trials were usually small; 24/29 trials had <25 patients in each treatment arm. In several cases, reviewers commented on study quality issues not captured by the scoring system. These comments are given in Table 4.

3.2 Diagnosis

All 29 studies required that patients had 'CRPS' as opposed to earlier diagnostic terms. Fourteen trials used the recently modified 'Budapest'[4] diagnostic criteria for CRPS (Bruehl et al., 1999; Manicourt et al., 2004; Moseley, 2004, 2005; Taskaynatan et al., 2004; Harden et al., 2007; Fischer et al., 2008; Groeneweg et al., 2008; Perez et al., 2008; Cacchio et al., 2009a,b; Duman et al., 2009; Groeneweg et al., 2009; Schwartzman et al., 2009; Sigtermans et al., 2009; Goebel et al., 2010). Twelve trials used the earlier 'IASP' (International Association for the Study of Pain) criteria (Supporting Information Appendix S2) (Merskey and Bogduk, 1994; Tran et al., 2000; Durmus et al., 2004; Pleger et al., 2004; Robinson et al., 2004; van de Vusse et al., 2004; Rodriguez et al., 2006; Carroll et al., 2009; Munts et al., 2009, 2010; Gustin et al., 2010; Picarelli et al., 2010; Eckmann et al., 2011) In one study (Kemler et al., 2000), although the older diagnostic term of 'Reflex Sympathetic Dystrophy' (Kozin et al., 1976) was used, patients fulfilled minimally modified IASP criteria for CRPS. The remaining two trials used other criteria, but nonetheless termed the investigated condition 'CRPS': one trial (Zollinger et al., 2007) used the Veldman criteria (Veldman et al., 1993) (Supporting Information Appendix S3) and one trial (Frade et al., 2005) used other criteria.

3.3 CRPS subgroups

We classified trials according to the disease duration of included patients. A 'long-standing CRPS' trial was either where patients with ≤ 6 months disease duration had been excluded, or where participants had >14 months median disease duration, or >19 months mean duration (Methods section). Twenty of 28 treatment studies included patients with longstanding CRPS and 8 studies included patients with early CRPS. Some trials included CRPS subgroups defined by other criteria than disease duration. The trials of oral tadalafil and topical transdermal isosorbide dinitrate treatment included only patients who had cold limbs (Groeneweg et al., 2008, 2009). Two mirror therapy trials (Cacchio et al., 2009a,b) included exclusively patients with post-stroke CRPS. One trial was limited to patients with CRPS-dystonia (Munts et al., 2009). Additional trials were conducted in groups following specific trauma, or were restricted to only upper or lower limbs. Details are given in Table 4.

3.4 Trial design

The 29 included trials evaluated 24 specific interventions[5] and 1 prophylactic measure. Six studies had a crossover, the remainder a parallel design. In some cases, the reviewers registered particular design concerns (Table 4).

3.5 Treatments

Trials assessed 22 treatments not investigated before, including (in order of publication) SCS, oral gabapentin, intravenous regional block (IVRB) ('Bier Block') with methylprednisolone, oral alendronate, intravenous pamidronate, repetitive transcranial magnetic stimulation (rTMS; two trials), electromagnetic field therapy, GMI (two trials), IVRB with parecoxib, intra-

[4]Earlier terms for the 'Budapest' criteria were the 'Bruehl' or 'Bruehl-Harden' criteria.

[5]In some cases, there was more than one trial per treatment: two trials of mirror therapy, two trials of low-dose ketamine, two trials of repetitive transcranial magnetic stimulation, two trials of graded motor imagery.

Table 4 List of included RCTs according to outcome, intervention and publication date.

Author	Diagnosis RSD/CRPS (IASP or Budapest/Bruehl or Veldman or other criteria)	Intervention	Group comparisons A – active P – placebo C – control[a] × – crossover	Pain outcomes VAS/NRS/VRS NPS	Outcome – positive/negative/ equal effect Effect size (ES)/Confidence intervals (CIs)	Comments	Total score (Method)	Disease duration (early – <6 months or <14 months median/<19 months mean, or long-standing)	Journal (year) (in order of publication)
Trials with positive outcomes in order of publication – treatment									
Drugs									
Robinson	CRPS (IASP)	IV pamidronate	A v P	VAS	Positive, ES/CI not stated	Included both patients with and without bony changes	57	Long-standing (mean 21.6 months; range 3 months to 6 years)	Pain Med (2004)
Manicourt	CRPS (Budapest)	Oral alendronate	A v P + open label	VAS	Positive, ES/CI not stated	Dose not available in some countries; in patients with bone abnormalities on X-ray and bone scintography	73	Early (mean 7.5 months)	Arthrit & Rheum (2004)
Frade	CRPS (Other)	Local versus systemic parecoxib (for details, see text), 1 block/week × 3 weeks	[b]A1 v. A2 v. C	VAS	Positive for IV regional parecoxib ES/CI not stated	Small groups, upper limb only; primary outcome not predefined	52	Long-standing (range 7–18 months)	Anesth Analg (2005)
Groenenweg	CRPS (Budapest)	Oral tadalafil	A v P	VAS	Positive for pain ES/CI not stated	Only patients with cold limbs	74	Long-standing (mean 3.5 years)	BMC Musculoskeletal (2008)
Sigtermans	CRPS (Budapest)	IV ketamine (low-dose continuous infusion for 4.5 days)	A v P	NRS	Positive ES/CI not stated	Negative for function	84	Long-standing (median 7.4 years)	Pain (2009)
Schwartzman	CRPS (Budapest)	IV ketamine infusion 4 h/day × 10 days (+ clonidine and midazolam in both groups)	A v P	NRS	Positive ES/CI not stated	Pain NRS measured 1.5 months after last treatment. Primary outcome not defined.	49	Long-standing (>6 months)	Pain (2009)
Carroll	CRPS (IASP)	Botulinum toxin + LSB with bupivacaine	[c]A1 v A2 (control) ×		Positive for extending duration of pain relief from LSB ES/CI not stated	Small, highly selected group: seven patients, lower limb; patients who previously had 50% pain relief >5 h duration with lumbar sympathetic block	49	Long-standing (>6 months)	Annals Neurol (2009)
Goebel	CRPS (Budapest)	IV immunoglobulins	A v P ×	NRS	Positive ES (95% CI) 1.55 (1.29–1.82) NRS units	Small numbers	84	Long-standing (>6 months; mean 19 months)	Ann Intern Med (2010)
Gustin	CRPS (IASP)	Morphine with memantine	[c]A1 v A2 (control)	VAS	Positive ES/CI not stated	Restricted to upper limb. Combination more effective than morphine alone from 1 to at least 8 weeks.	58	Long-standing (>6 months; mean 16 months; range 6–36 months)	Pain (2010)
Procedures									
Kemler	CRPS (IASP, but termed RSD)	Spinal cord stimulation	A v C (physiotherapy in both groups)	VAS	Positive ES/CI not stated	Slightly modified CRPS criteria. Ongoing effect on pain and quality of life, but no effect on function at 2 years. Effect on pain not significant from 3 years onward.	64.5	Long-standing (mean 37 months)	P NEngJMed (2000, 2006), Ann Neurol (2004), J Neurosurg (2008)

Table 4 (continued)

Author	Diagnosis RSD/CRPS (IASP or Budapest/Bruehl or Veldman or other criteria)	Intervention	Group comparisons A – active P – placebo C – control[a] × – crossover	Pain outcomes VAS/NRS/VRS NPS	Outcome – positive/negative/ equal effect Effect size (ES)/Confidence intervals (CIs)	Comments	Total score (Method)	Disease duration (early – <6 months or <14 months median/<19 months mean, or long-standing)	Journal (year) (in order of publication)
Pleger	CRPS (IASP)	Transcranial magnetic stimulation	A v P ×	VAS	Positive ES/CI not stated	Small group	63	Long-standing (>2 years; mean 35 months)	Neurosci Let (2004)
Picarelli	CRPS (IASP)	Transcranial magnetic stimulation	A v P	VAS	Positive ES/CI not stated	Upper limb. Greatest pain relief at day 10 of intervention, not persisting after 1 week or 3 months	50	Long-standing (>6 months; mean 81 months; range 10–180 months)	J Pain (2010)
Rehabilitation									
Moseley	CRPS (Budapest)	Graded motor imagery	A v C ×	NPS	Positive ES (95% CI) 20 (10.1–29.9) NPS points at 6 weeks	After uncomplicated wrist fracture	63.5	Long-standing (>6 months post fracture)	Pain 2004
Moseley	CRPS (Budapest)	Graded motor imagery	[d]A 1 v A2 v A3	NPS	Positive ES/CI not stated	After uncomplicated wrist fracture. The trial shows that the effect is dependent on the order of sub-interventions.	58	Long-standing (>6 months post fracture)	Pain (2005)
Cacchio[a]	CRPS (Budapest)	Mirror therapy (30 min × 2 weeks, then 1 h × 2 weeks + 4 weeks of rehab) 5 × 1 h control	A v P	VAS	Positive ES/CI not stated	Post stroke. Positive at 3 months, but not at 1 month.	59	Early (<6 months after stroke)	Neurorehab & Neural Repair (2009)
Cacchio[b]	CRPS (Budapest)	Mirror therapy versus mental imagery	[b]A 1 v A2 v C (sham mirror therapy)	VAS on movement	Positive for mirror therapy ES/CI not stated	Post stroke; upper limb only; letter publication: methods not well described	41	Long-standing (>6 months post stroke; median 14 months; range 7–21 months)	NEngJMed (2009)
Trials with positive outcomes – prevention									
Zollinger	Termed CRPS (Veldman)	200 mg/500 mg/1500 mg Vitamin C × 50 days	A v P	Presence of CRPS	Positive ES/CI not stated	Prevention study. Patients with wrist fracture. Non-IASP/non-Budapest criteria. Selection criteria unclear, as apparently 961 otherwise eligible patients were not invited.	64.5	N/A	Journal of Bone and Joint Surgery (Am) (2007)
Trials with negative outcomes									
Tran	CRPS (IASP)	Iohexol before LSB lignocaine	[c]A1 v A2 (control)	Percent pain relief	Negative ES/CI not stated	Enriched patient group: only those with prior response to either phentolamine or LSB included. Lower limb only[e].	33	Long-standing (mostly >10 months)	Anaesth Analg (2000)
van de Vusse	CRPS (IASP)	Gabapentin (increasing dose from 600 mg/day to 600 mg twice/day to 600 mg three times/day over 5 days for a total of 21 days)	A v P ×	VAS; NPS	Negative for pain; positive for sensory deficit ES/CI not stated	Low-dose 1800 mg	67	Long-standing (mean 44 months – analysed group)	BMC Neurol (2004)

Table 4 (continued)

Author	Diagnosis RSD/CRPS (IASP or Budapest/Bruehl or Veldman or other criteria)	Intervention	Group comparisons A – active P – placebo C – control[a] × – crossover	Pain outcomes VAS/NRS/VRS NPS	Outcome – positive/negative/ equal effect Effect size (ES)/Confidence intervals (CIs)	Comments	Total score (Method)	Disease duration (early – <6 months or <14 months median/<19 months mean, or long-standing)	Journal (year) (in order of publication)
Taskaynatan	CRPS (Budapest)	IVRSB with methylprednisolone 40 mg + lidocaine, 1/week × 3 weeks	A v P	NRS	Negative ES/CI not stated	Positive at 3 months, but not at 1 month	43	Early (mean 3.1 months)	Reg Anesth Pain Med (2004)
Rodriguez	CRPS (IASP)	Stellate block (1/week × 5 weeks) + physical and pharmacological therapy	A v C	Pain relief >50% at 1 month after treatment starts	Negative ES/CI not stated	Enriched patient group. Only those with >50% pain relief with a first stellate block were included. Only upper limb.	52	Early (mean 7 months)	Rev Soc Esp Dolor (2006)
Perez	CRPS (Budapest)	IV mannitol	A v P	VAS	Negative ES/CI not stated		80	Early (range 4–30 months; median – placebo group 14 months; active group 6.5 months)	J Pain (2008)
Munts	CRPS (IASP)	Intrathecal glycine	A v P	NRS	Negative for both pain and dystonia ES/CI not stated	CRPS with dystonia	77	Long-standing (mean 9 years)	Pain (2009)
Groeneweg	CRPS (Budapest)	Topical transdermal isosorbide dinitrate	A v P	VAS	Negative ES/CI not stated	Patients with cold limbs	75	Long-standing (mean 4 years)	J P Symp Man (2009)
Durmus	CRPS (IASP)	Electromagnetic field therapy (+ calcitonin and exercise in both groups)	A v P	VAS	Negative ES/CI not stated		56	Early (mean 51 days)	Disab & Rehab (2004)
Fischer	CRPS (Budapest)	Occlusal splints	A v C	NRS	Negative ES/CI not stated	Proof-of-concept trial with very small number of patients.	52	Long-standing (mean 38 months; range 8–80 months)	Clin J Pain (2008)
Duman	CRPS (Budapest)	Manual lymphatic drainage	A v C	VAS	Negative for pain ES/CI not stated		44.5	Early (mean 5.1 months)	Rheumatol Int (2009)
Munts	CRPS (IASP)	Single 60 mg bolus IT methylprednisolone	A v P	NRS	Negative ES/CI not stated	Trial stopped prematurely because no effect of treatment at 6 weeks.	75	Long-standing >6 months to <6 years	Eur J Pain (2010)
Eckmann	CRPS (IASP)	IVRB ketorolac + lignocaine	[c]A1 v A2 (control)[c] ×	NRS	Negative ES/CI not stated	Small, 10 patients with lower limb CRPS	59	Early (mean 10 months; range 1–29 months)	Clin J Pain 2011

NB. Enquiries with authors for Rodriguez paper: Appropriate randomization with sealed envelopes drawn by patients. RSD, reflex sympathetic dystrophy; CRPS, complex regional pain syndrome; IASP, International Association for the Study of Pain; VAS, visual analogue scale; NRS, numerical rating scale; VRS, verbal rating scale; NPS, neuropathic pain scale; IV, intravenous; LSB, lumbar sympathetic block; N/A, not applicable;

[a]With either no intervention in control group or some congruent intervention in both the active and control groups.

[b]Trials comparing two active treatments with a control.

[c]Trial with active control group. The active control intervention is assumed to reduce pain by itself and both groups received the active control intervention but the treatment group received the additional study treatment.

[d]Trial comparing two active treatments without a control group and with a resulting difference in outcome.

[e]The primary hypothesis was that iohexol may worsen the outcome. The improvement in outcome with iohexol was unexpected and would need to be confirmed. The authors conclude that iohexol use will not compromise LSB efficacy. The pain data represent a subsample of all post-block data. The selection of the sample was poorly described.

venous mannitol, oral tadalafil, occlusal splints, low-dose intravenous ketamine (two trials), topical transdermal isosorbide dinitrate, mirror therapy (two trials), iohexol [prior to lumbar sympathetic block (LSB) with lignocaine], botulinum toxin to the lumbar sympathetic chain, intrathecal glycine, low-dose intravenous immunoglobulin (IVIG), IVRB lignocaine with ketorolac, morphine with memantine and intrathecal methylprednisolone. Three treatments trialled during this review period had already been trialled before (in order of publication): stellate/sympathetic ganglion blockade with local anaesthetic, vitamin C for prevention of CRPS and manual lymphatic drainage; alternative bisphosphonates had also been investigated.

3.6 Trial outcomes

Of the 22 high-quality and 6 low-quality trials, 13 and 3, respectively, showed a significant effect of treatment compared with placebo, control (control = either no intervention, or congruent intervention in both the active and control groups) or a comparison treatment.[6] We give a synopsis of individual trials below, classified according to both outcome (positive vs. negative) and the type of intervention (drugs, procedures, rehabilitation). Short trial summaries are given in Table 4.

3.7 Positive trials

3.7.1 Drugs for pain relief (in order of publication date)

Bisphosphonates: IV pamidronate (60 mg) decreased pain compared with placebo in a high-quality trial (Robinson et al., 2004) in patients with mostly long-standing CRPS. Oral alendronate (40 mg daily for 8 weeks) reduced pain compared with placebo in a high-quality trial in patients with early CRPS with bone abnormalities on X-ray or three-phase bone scintigraphy (Manicourt et al., 2004).

In an upper limb, enriched group (non-responders to five stellate blocks with lignocaine and clonidine), IVRBs with 5 mg of parecoxib, 1 mg/kg lignocaine and 30 μg clonidine in 10 mL normal saline, plus systemic normal saline decreased pain more than either intravenous parecoxib (20 mg) with IV regional lidocaine and clonidine, or a control group (as the first intervention group, but without parecoxib), in a high-quality trial in long-standing CRPS (Frade et al., 2005). Blocks were given once a week for 3 weeks. The study had very small comparison groups and the reviewers had reservations about the study protocol (the rationale for combining parecoxib, lignocaine and clonidine), and the definition of the primary outcome (a positive result was only seen in week 3, but this had not been pre-specified; several parallel analyses for primary outcomes were performed).

Oral tadalafil (20 mg daily for 12 weeks) significantly reduced pain, which was a secondary outcome, compared with placebo in patients with CRPS of long-standing duration and a stably cold limb, in a high-quality trial (Groeneweg et al., 2008).

IV infusion of low-dose ketamine (4.5 days of continuous treatment or 10 consecutive working days of outpatient treatment) significantly reduced pain compared with placebo in one high-quality (Sigtermans et al., 2009) and one low-quality trial (Schwartzman et al., 2009) in long-standing CRPS. The reviewers noted that in the Schwartzman paper the primary outcome had not been defined.

In a small low-quality trial in long-standing CRPS, a lumber sympathetic block with combined 0.5% bupivacaine (10 mL) and botulinum toxin (75 U) provided longer pain relief than bupivacaine only in an enriched population of earlier responders to a block with bupivacaine (Carroll et al., 2009).

In a small high-quality trial, a single application of low-dose (0.5 g/kg) IVIG significantly reduced pain compared with placebo in long-standing CRPS (Goebel et al., 2010).

A small high-quality trial compared morphine (titrated from 10 mg OD (once daily) to 10 mg TDS (three times daily) over the first 5 days, then continued as 10 mg TDS for an additional 51 days) plus oral memantine (titrated from 5 mg OD to 20 mg BD (twice a day) from day 8 over 15 days, then maintained at 20 mg BD for additional 34 days) with morphine and placebo. Morphine with memantine was more effective than morphine and placebo in long-standing CRPS (Gustin et al., 2010)

3.7.2 Procedures for pain relief

SCS significantly reduced pain and improved quality of life, but did not improve function, up to 2 years after implantation, in a high-quality trial in long-standing CRPS (Kemler et al., 2000, 2004, 2006). From 3 years after implantation, the difference between the intervention and control groups was lost (Kemler et al., 2008).

rTMS decreased pain compared with placebo in a small high-quality trial in long-standing CRPS (Pleger

[6]One trial was for a prophylactic intervention, not treatment (Zollinger et al., 2007), giving 29 trials in total.

et al., 2004). A series of 10 rTMS (10 Hz) applications each lasting 1.2 s provided pain relief from 30 s after stimulation lasting for 45 min; the maximum effect was found at 15 min after stimulation. A second high-quality trial compared rTMS (10 Hz, 1/day for 10 days) with sham rTMS as an add-on therapy in long-standing CRPS. rTMS was more effective than sham rTMS. However, this effect did not persist at 1 week or 3 months (Picarelli et al., 2010).

3.7.3 Physiotherapy/rehabilitation interventions

In two high-quality studies in long-standing CRPS (Moseley, 2004, 2005) restricted to patients after wrist fracture, a physiotherapy intervention 'Graded Motor Imagery' decreased pain significantly compared with either control or another active treatment. Both trials were conducted in the same single-centre setting.

Another physiotherapy intervention, 'Mirror Therapy', decreased pain compared with placebo in early CRPS after stroke in a high-quality trial (Cacchio et al., 2009a); in a low-quality trial, mirror therapy reduced pain more than mental imagery in long-standing CRPS after stroke (Cacchio et al., 2009b).

3.7.4 Trials for prevention of CRPS

Vitamin C (200 mg/500 mg/1500 mg for 50 days) reduced the incidence of CRPS in a high-quality trial in patients after wrist fractures (Zollinger et al., 2007). Reviewers noted an insufficient description of patient selection criteria for this trial.

3.8 Negative trials

3.8.1 Drugs for pain relief

In a low-quality trial in long-standing CRPS, which investigated the administration of iohexol, prior to LSB with lidocaine, the primary hypothesis was that iohexol would worsen outcome (Tran et al., 2000). There was however an unexpected improvement in outcome. The authors conclude that iohexol will not compromise LSB efficacy. The trial used an enriched patient group of responders to either intravenous phentolamine or LSB. The reviewers noted concern about the trial interventions (LSBs should not be performed without contrast), and the post hoc nature of the findings (the trial had not been set up to prove efficacy, but rather to elicit a side effect of iohexol).

In a high-quality trial, intermediate-dose gabapentin (1800 mg) given over 3 weeks did not significantly reduce pain compared with placebo in long-standing CRPS (van de Vusse et al., 2004). The reviewers noted that this gabapentin dose is lower than that frequently recommended for the treatment of neuropathic pain (NICE, 2010).

Three IVRBs of 40 mg methylprednisolone in 10 mL of 2% lidocaine, given as one block per week for 3 weeks, were no more effective than saline blocks in a low-quality trial in early CRPS (Taskaynatan et al., 2004).

In an enriched patient group (>50% pain relief to a single stellate ganglion block), the addition of a series of five stellate ganglion blockades over 1 month to a combination of oral drug therapy and physiotherapy did not significantly reduce pain 1 month after the last injection, as compared with the combination therapy without injections, in a high-quality trial in early CRPS (Rodriguez et al., 2006).

IV mannitol (1 L of 10% solution over 4 h each day) given for 5 consecutive days was not effective for pain relief measured against placebo in a high-quality trial in early CRPS (Perez et al., 2008).

In long-standing CRPS with dystonia, intrathecal glycine given as a continuous infusion through a pump, following an up-titration protocol (maximum daily dose of 32 mg in 24 h), over 4 weeks, was not effective compared with intrathecal placebo in reducing pain and dystonia in a high-quality trial (Munts et al., 2009).

In long-standing cold CRPS topical transdermal isosorbide nitrate was not effective, compared with placebo, for pain relief in a high-quality trial (Groeneweg et al., 2009).

A single bolus administration of 60 mg intrathecal methylprednisolone was not more effective than placebo in a high-quality trial in long-standing CRPS (Munts et al., 2010).

In a small pilot study of high quality, in early lower limb CRPS, IVRB lignocaine (50 mL 0.5%), either alone or together with ketorolac (×4 injections of no ketorolac, 30, 60 or 120 mg ketorolac, 1 week apart, in random sequence), was compared. None of the ketorolac doses were effective to reduce pain 1 week after the respective injection when compared with the lignocaine injection (primary outcome). There was some short-term pain relief 1 day after injection in the pooled ketorolac group (Eckmann et al., 2011).

3.8.2 Procedures for pain relief

Electromagnetic field therapy, administered five times per week for 6 weeks with co-administration of 100 U of both intramuscular calcitonin (daily for 3 weeks and then once every other day for the next 3 weeks),

and exercise, was ineffective for pain relief in a high-quality trial, compared with calcitonin and exercise with sham electromagnetic field therapy in early CRPS (Durmus et al., 2004).

Occlusal splints were not effective in reducing pain in long-standing CRPS in a high-quality proof-of-concept trial (Fischer et al., 2008).

Manual lymphatic drainage did not reduce pain in a low-quality trial in early CRPS (Duman et al., 2009).

3.9 Levels of effectiveness for the investigated interventions (van Tulder method, Table 3)

3.9.1 Strong evidence

Physiotherapy/rehabilitation interventions taken together show strong evidence of effectiveness. Of the specific physiotherapy interventions investigated, GMI has strong evidence of effectiveness in CRPS. This evidence is based on two high-quality trials (Moseley, 2004, 2005). Both trials were restricted to patients after non-complicated wrist fractures. The reviewers note that GMI is a complex intervention (Paterson et al., 2009; Bennett and Closs, 2010), and that this grading result should be considered with caution until confirmatory trials from other groups are available. There is moderate evidence for the effectiveness of mirror therapy in patients with CRPS post stroke, based on two trials (Cacchio et al., 2009a,b) with differing disease durations (early CRPS/long-standing CRPS).

There is strong evidence for the efficacy of bisphosphonates, with one high-quality trial for IV pamidronate and one high-quality trial for oral alendronate. Oral alendronate at the trialled high dose is not recommended for use in some countries (BNF, 2011). The trials differed for included disease duration (long-standing vs. early CRPS) and additional patient characteristics (patients without vs. with confirmed bone abnormalities).

There is strong evidence for the effectiveness of rTMS in two high-quality trials in long-standing CRPS. (Pleger et al., 2004; Picarelli et al., 2010)

3.9.2 Moderate evidence

The review found moderate evidence for the efficacy of low-dose IV ketamine infusion in long-standing CRPS (Schwartzman et al., 2009; Sigtermans et al., 2009).

3.9.3 Limited evidence

There was limited evidence for the efficacy of oral tadalafil, low-dose IVIG, SCS and combined morphine with memantine in long-standing upper limb CRPS (Gustin et al., 2010), based on one positive high-quality trial in each case. The SCS trial was the only trial in this review period with more than 50 patients per treatment arm and a follow-up period of over 1 year.

3.10 Comparison between trials evaluated in 1966–2000 and 2000–2012

The 2002 and current reviews were conducted over consecutive episodes (1966–2000 and 2000–2012) using similar methodology. A summary of results from the Forouzanfar review is provided in Supporting Information Appendix S6. The evidence for interventions trialled during both periods is given in the following chapter. Supporting Information Appendix S7 provides an overview of all interventions trialled from 1966 to 2012, classified according to study outcomes, and including details about study populations and methodology scores.

3.11 Treatments trialled in both review periods (1966–2000 and 2000–2012)

Four high-quality trials with positive outcomes for bisphosphonates, oral alendronate (Manicourt et al., 2004), IV alendronate (Adami et al., 1997), IV pamidronate (Robinson et al., 2004), IV clodronate (Varenna et al., 2000), indicate their efficacy. These four trials were of three different substances using two different routes of administration, thus while there is strong evidence when combining these results, there is only limited evidence for each specific treatment. In three of these trials, only patients with bone abnormalities on X-ray and/or bone scintigraphy were included: Manicourt et al., Adami et al. and Varenna et al.

Two high-quality trials of sympathetic ganglion blockade with lidocaine had conflicting outcomes (Price et al., 1998; Rodriguez et al., 2006), see also Discussion section. Of note, the first study was conducted in long-standing CRPS, the second in early CRPS.

One low-quality trial (Duman et al., 2009) and one high-quality trial (Uher et al., 2000) of manual lymphatic drainage with negative outcomes indicate a moderate level of non-effectiveness of this treatment.[7]

Six trials of various physiotherapy/rehabilitation interventions were conducted, and all were positive:

[7]In the Uher et al. (2000) study, manual lymphatic drainage (MLD) together with exercise three times a week for 6 weeks was compared with exercise three times a week for 6 weeks only. In the Duman et al. (2009) study, MLD together with non-steroidal anti-inflammatory drugs (NSAIDs), physiotherapy (PT) and exercise for 3 weeks was compared with NSAIDs, PT and exercise only.

GMI (positive $n = 2$), mirror therapy (positive $n = 2$), qigong (positive) (Wu et al., 1999) and 'traditional' physiotherapy (which included information, practical advice and support; relaxation exercises; rest; connective tissue massage; transcutaneous electrical nerve stimulation; exercises to reduce pain; compensatory activities; instructions about body position[8])/ occupational therapy[9] (positive) (Oerlemans et al., 2000). The reviewers note that these heterogeneous interventions may have different modes of action.

4. Discussion and conclusions

We conducted a systematic review of the evidence from RCTs for the treatment or prevention of CRPS published between 2000 and 2012. We found that the evidence was generally weak. Few trials had assessed the same intervention (except GMI, mirror therapy and low-dose intravenous ketamine), and only one trial had more than 50 participants per treatment arm.

An earlier review of trials published between 1966 and 2000 had used a similar methodology as our review (Forouzanfar et al., 2002), thus comparison between, and combined assessment of these results is possible. We did not re-review these earlier trials as this would have been superfluous. When compared with results over the most recent two decades included in the earlier review, there has been a dramatic increase in the number of published trials per decade (1980–1989: 7 trials; 1990–1999: 17 trials; 2000–2009: 28 trials; 2010–2012: 5 trials). We note a trend away from trials on either local or regional percutaneous application of drugs from 17/28 trials (61%) in the earlier period to 12/29 trials (41.4%) in this review period. There has also been a statistically significant increase in the number of trials in populations with long-standing CRPS from 7/19[10] trials (37%) in the earlier period to 21/28 trials (75%) in this review period [$p = 0.02$ (Fisher exact test)].

[8]Description of treatments was taken from Oerlemans et al. (2003), Ned Tijdschr Fysiother; 113(5):15–19, which analysed the same data set as Oerlemans et al., 2000.

[9]Including splint treatment to reduce inflammation or provide support; treatment to normalize sensibility, improve functional ability through activity, improve independence of daily living by teaching patients to perform activities differently or with advice about aids and devices.

[10]Of the 26 trials in the earlier review period, 12 trials were in early CRPS, 7 in long-standing CRPS, and 7 trials were excluded for this analysis: in 5 the disease duration was not given and 2 trials were for prevention of CRPS. Of the 26 trials included from the current review period, 1 trial was excluded from this analysis: this trial was for prevention of CRPS.

The combined evidence can be summarized as follows. (1) There is strong evidence (six RCTs) that rehabilitation/physiotherapy interventions can reduce pain and improve function for people with CRPS; however, the specific methods varied across trials, and the evidence for each of these methods in isolation is unsatisfactory. The (formally strong) evidence from two positive high-quality trials of GMI (see also Daly and Bialocerkowsky, 2009), a complex physiotherapy intervention, warrants cautious interpretation, because in successful single-centre trials of complex interventions the specific effective ingredient can be difficult to discern (Paterson et al., 2009; Bennett and Closs, 2010). (2) There is strong evidence (four RCTs) for the use of bisphosphonate therapy. Of note, three of these trials were conducted in patients with <6 months duration which have regional bone changes as assessed by X-ray or bone scintigraphy. Long-term follow-up studies are missing, so that the requirement for repeat dosing is not established. The four trials had examined heterogeneous bisphosphonate preparations and had also used differing outcome measures. Nevertheless, the ubiquitously positive results suggest that the purported bisphosphonate targets, including osteoclasts and immune cells, may importantly contribute to causing CRPS (Drake et al., 2008). Although all four bisphosphonate trials were positive, it remains unknown whether the three specific drugs (clodronate, alendronate, pamidronate) or newer bisphosphonates (Russell, 2011) can be used interchangeably. (3) rTMS (two RCTs) was effective in two small trials, indicating that in CRPS, as in other painful conditions, direct modulation of cortical excitability can reduce pain (Picarelli et al., 2010). Treatment effects did not outlast application intervals, and further studies will be required to explore whether this method is feasible for application in clinical practice. (4) There is moderate evidence (two RCTs) for the efficacy of low-dose intravenous ketamine treatment; the interpretation of these results has recently been made more complicated by reports about incidences of liver failure with prolonged or repeated treatment (Noppers et al., 2011). However, both groups of patients had profound pain relief while the drug was applied, which reverted back to normal more slowly than the short ketamine half-life would have demanded; low-dose ketamine is understood to relieve pain through modulation at spinal cord NMDA receptors, and these results indicate a crucial role of central sensitization in sustaining CRPS pain (Latremoliere and Woolf, 2009). (5) There is strong evidence (four RCTs) suggesting that intravenous regional sympathetic blocks (IVRSBs) with guanethidine are no more effective than IVRSBs with normal saline or

lidocaine. (6) There is moderate evidence (two RCTs) for the non-efficacy of manual lymphatic drainage in early CRPS. (7) There is moderate evidence (two RCTs) for the efficacy of vitamin C to prevent CRPS after dorsal radius fracture. (8) There is limited evidence from one trial in each case for the efficacy of additional interventions (Supporting Information Appendix S7), and finally, (9) among the latter interventions, one trial that stands out because of its large size and long follow-up period suggests that SCS treatment can reduce pain for 2 to 3 years after implantation. (10) The evidence for local anaesthetic blockade of sympathetic ganglia in adults comes from two trials: one positive and one negative. The positive trial by Price et al. (reviewed in 2002) and the negative trial by Rodriguez (published in our review period) taken together provide limited evidence for the idea that although pain may be truly responsive to local anaesthetic injection to sympathetic ganglia, repeat injections at weekly intervals may not meaningfully hasten recovery; it remains unknown whether the time-limited pain relief obtained after such injections provides clinically meaningful benefit and/or whether more permanent interventions such as sympathectomies (Straube et al., 2010) could provide longer lasting relief.

Both reviews have assessed published trials. The risk for publication bias in systematic reviews is well documented: negative trials tend to be less published (PLoS Medical Editors, 2011), but mandatory registration should lessen this risk (De Angelis et al., 2004). For the current review, we searched the largest European and American trial registries. We found only one registered and recently completed, but not published, trial suggesting that publication bias may have been limited; however, trials conducted without intent to publish do not need to be registered and may have been missed. A recent consensus statement recommends that in trials in chronic pain, pain intensity should generally be the primary outcome (Dworkin et al., 2005). Our review has focused on assessing trials reporting pain intensity as either a primary or a secondary outcome. Additional trials have assessed the efficacy of interventions for the relief of CRPS-associated symptoms such as dystonia and allodynia, but not pain (Supporting Information Appendix S1), and a number of trials reported only composite outcomes, without separately reporting pain intensity. We excluded these latter two categories because we were concerned that trial results would be difficult to interpret; we cannot exclude the possibility that some of these interventions could be effective for relieving pain.

As in the 2002 review, we accepted evidence only from RCTs. It was not the purpose of this review to provide treatment recommendations, nor to claim that only interventions, for which RCT evidence exists, should be used in the treatment of CRPS. Further, it should be noted that the here-reviewed trials had small sample sizes, indicating a degree of imprecision about *any* estimates of effect sizes for these trials, and thus also about the classification of trials into 'positive' and 'negative'. Further, the classification into high-quality (50 points and higher) and low-quality studies was retained to provide a coherent framework between the current review and the earlier review; however, the utility of using this specific cut-off point should be viewed with some caution, as by using this threshold, some studies which had substantial limitations (Table 4) were classified as high quality, but should probably be termed low quality. Because of the limited availability of RCTs in CRPS, treatment recommendations need to be based additionally on non-RCT evidence: consideration of only RCT evidence would exclude drugs for neuropathic pain, or cognitive behavioural treatments, which would not be desirable. Of note, however, given the benign natural course of *early* CRPS (de Mos et al., 2009), positive trial outcomes derived from sources other than RCTs should not yield useful efficacy information[11] in this population. An additional limitation of our review is that it focuses on reviewing pain outcomes, while not assessing functional data. Most trials were short and functional measures, if used, varied widely (not shown). A systematic review of functional trial outcomes would appear valuable.

In summary, the level of available evidence from RCTs for the efficacy of medical intervention to relive pain for people with CRPS remains overall unsatisfactory. No evidence exists (positive or negative) for the efficacy of drugs recommended for the treatment of neuropathic pain, including opioids, antidepressants and gabapentinoids at recommended doses. Novel treatments have recently been effective in small RCTs, providing hope for an advance in clinical management over the coming decade. Confirmatory trials require larger patient groups, with longer follow-up periods. Some of these novel interventions appear to work in subgroups of patients only, so that innovative methods to identify responders are also important. Since CRPS is uncommon (de Mos et al., 2007),

[11]In this group, negative results (outcome compared with baseline) from well-conducted non-RCT trials may provide usable information.

network and multi-centre studies should facilitate more effective research.

Author contributions

L.C. devised and carried out the electronic searches of bibliographic databases, co-ordinated the reviewing process, scored and reviewed one-third of the included trials, tabulated the results, and contributed to the writing of the manuscript.

R.O. pre-filtered the identified trials, scored and reviewed one-third of the included trials, and contributed to the reviewing of all included trials and the writing of the manuscript.

H.C. pre-filtered the identified trials, scored and reviewed one-third of the included trials, and commented on the drafts of the manuscript.

B.S. and H.P. scored and reviewed one-third of the included trials and commented on the drafts of the manuscript.

A.G. devised the protocol for the review, pre-filtered the identified trials, scored and reviewed one-third of the included trials, and contributed to the reviewing of all included trials and the writing of the manuscript.

Acknowledgements

The authors acknowledge that members of the panel for the development of UK guidelines for the diagnosis and treatment of CRPS in adults, in primary and secondary care, contributed to their better understanding and interpretation of the results from this systematic review (L.Turner-Stokes and A.Goebel, 2011), and Dr. Jordi Perez for translation of an article from Spanish.

References

Adami, S., Fossaluzza, V., Gatti, D., Fracassi, E., Braga, V. (1997). Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. *Ann Rheum Dis* 56, 201–204.

Baron, R. (2004). Mechanistic and clinical aspects of complex regional pain syndrome (CRPS). *Novartis Found Symp* 261, 220–233.

Bennett, M.I., Closs, S.J. Methodological issues in nonpharmacological trials for chronic pain. Pain: Clinical Updates 18[2], 1–6. 2010. Seattle, IASP Press.

BNF. (2011). *BNF62 (2011)* (London: BMJ Group and Pharmaceutical Press).

Bruehl, S. (2010). An update on the pathophysiology of complex regional pain syndrome. *Anesthesiology* 113, 713–725.

Bruehl, S., Harden, R.N., Galer, B.S., Saltz, S., Bertram, M., Backonja, M., Gayles, R., Rudin, N., Bhugra, M.K., Stanton-Hicks, M. (1999). External validation of IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria. International Association for the Study of Pain. *Pain* 81, 147–154.

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

Cacchio, A., De Blasis, E., De Blasis, V., Santilli, V., Spacca, G. (2009a). Mirror therapy in complex regional pain syndrome type 1 of the upper limb in stroke patients. *Neurorehabil Neural Repair* 23, 792–799.

Cacchio, A., De Blasis, E., Necozione, S., di Orio, F., Santilli, V. (2009b). Mirror therapy for chronic complex regional pain syndrome type 1 and stroke. *N Engl J Med* 361, 634–636.

Carroll, I., Clark, J.D., Mackey, S. (2009). Sympathetic block with botulinum toxin to treat complex regional pain syndrome. *Ann Neurol* 65, 348–351.

Cepeda, M.S., Carr, D.B., Lau, J. (2005). Local anesthetic sympathetic blockade for complex regional pain syndrome. *Cochrane Database Syst Rev* (4) CD004598.

Daly, A.E., Bialocerkowski, A.E. (2009). Does evidence support physiotherapy management of adult complex regional pain syndrome type one? A systematic review. *Eur J Pain* 13(4), 339–353.

De Angelis, C., Drazen, J.M., Frizelle, F.A., Haug, C., Hoey, J., Horton, R., Kotzin, S., Laine, C., Marusic, A., Overbeke, A.J., Schroeder, T.V., Sox, H.C., Van Der Weyden, M.B. (2004). Clinical trial registration: A statement from the International Committee of Medical Journal Editors. *N Engl J Med* 351, 1250–1251.

de Mos, M., De Bruijn, A.G., Huygen, F.J., Dieleman, J.P., Stricker, B.H., Sturkenboom, M.C. (2007). The incidence of complex regional pain syndrome: A population based study. *Pain* 129(1-1), 12–20.

de Mos, M., Huygen, F.J., Hoeven-Borgman, M., Dieleman, J.P., Stricker, B.H., Sturkenboom, M.C. (2009). Outcome of the complex regional pain syndrome. *Clin J Pain* 25(7), 590–597.

de Vet, H.C., de Bie, R.A., van der Heijden, G.J., Verhagen, A.P., Sijpkes, P., Knipschild, P.G. (1997). Systematic reviews on the basis of methodological criteria. *Physiotherapy* 83, 284–289.

Drake, M.T., Clarke, B.L., Khosta, S. (2008). Bisphosphonates: Mechanism of action and role in clinical practice. *Mayo Clin Proc* 83(9), 1032–1045.

Duman, I., Ozdemir, A., Tan, A.K., Dincer, K. (2009). The efficacy of manual lymphatic drainage therapy in the management of limb edema secondary to reflex sympathetic dystrophy. *Rheumatol Int* 29, 759–763.

Durmus, A., Cakmak, A., Disci, R., Muslumanoglu, L. (2004). The efficiency of electromagnetic field treatment in complex regional pain syndrome type I. *Disabil Rehabil* 26, 537–545.

Dworkin, R.H., Turk, D.C., Farrar, J.T., Haythornthwaite, J.A., Jensen, M.P., Katz, N.P., Kerns, R.D., Stucki, G., Allen, R.R., Bellamy, N., Carr, D.B., Chandler, J., Cowan, P., Dionne, R., Galer, B.S., Hertz, S., Jadad, A.R., Kramer, L.D., Manning, D.C., Martin, S., McCormick, C.G., McDermott, M.P., McGrath, P., Quessy, S., Rappaport, B.A., Robbins, W., Robinson, J.P., Rothman, M., Royal, M.A., Simon, L., Stauffer, J.W., Stein, W., Tollett, J., Wernicke, J., Witter, J. (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 113, 9–19.

Eckmann, M.S., Ramamurthy, S., Griffin, J.G. (2011). Intravenous regional ketorolac and lidocaine in the treatment of complex regional pain syndrome of the lower extremity: A randomized, double-blinded, crossover study. *Clin J Pain* 27, 203–206.

Fischer, M.J., Reiners, A., Kohnen, R., Bernateck, M., Gutenbrunner, C., Fink, M., Svensson, P. (2008). Do occlusal splints have an effect on complex regional pain syndrome? A randomized, controlled proof-of-concept trial. *Clin J Pain* 24, 776–783.

Forouzanfar, T., Koke, A.J., van Kleef, M., Weber, W.E. (2002). Treatment of complex regional pain syndrome type I. *Eur J Pain* 6, 105–122.

Frade, L.C.P., Lauretti, G.R., Lima, I.C.P.R., Pereira, N.L. (2005). 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. *Anesth Analg* 101, 807–811.

Galer, B.S., Jensen, M.P. (1997). Development and preliminary validation of a pain measure specific to neuropathic pain: The neuropathic pain scale. *Neurology* 48, 332–338.

Goebel, A. (2011). Complex regional pain syndrome in adults. *Rheumatology (Oxford)* 50, 1739–1750.

Goebel, A., Baranowski, A.P., Maurer, K., Ghiai, A., McCabe, C., Ambler, G. (2010). Intravenous immunoglobulin treatment of complex regional pain syndrome: A randomized trial. *Ann Intern Med* 152, 152–158.

Groeneweg, G., Huygen, F.J., Niehof, S.P., Wesseldijk, F., Bussmann, J.B., Schasfoort, F.C., Stronks, D.L., Zijlstra, F.J. (2008). Effect of tadalafil on blood flow, pain, and function in chronic cold complex regional pain syndrome: A randomized controlled trial. *BMC Musculoskelet Disord* 9, 143.

Groeneweg, J.G., Huygen, F.J., Niehof, S.P., Wesseldijk, F., Bussmann, J.B., Schasfoort, F.C., Stronks, D.L., Zijlstra, F.J. (2009). No recovery of cold complex regional pain syndrome after transdermal isosorbide dinitrate: A small controlled trial. *J Pain Symptom Manage* 38, 401–408.

Gustin, S.M., Schwarz, A., Birbaumer, N., Sines, N., Schmidt, A.C., Veit, R., Larbig, W., Flor, H., Lotze, M. (2010). NMDA-receptor antagonist and morphine decrease CRPS-pain and cerebral pain representation. *Pain* 151, 69–76.

Harden,R.N., Swan, M., King, A., Costa, B., Barthel, J. (2006). treatment of complex regional pain syndrome: functional restoration. *Clin J Pain* 22, 420–424.

Harden, R.N., Bruehl, S., Stanton-Hicks, M., Wilson, P.R. (2007). Proposed new diagnostic criteria for complex regional pain syndrome. *Pain Med* 8, 326–331.

Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J., Gavaghan, D.J., McQuay, H.J. (1996). Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials* 17, 1–12.

Kalita, J., Vajpayee, A., Misra, U.K. (2006). Comparison of prednisolone with piroxicam in complex regional pain syndrome following stroke: A randomized controlled trial. *QJM* 99, 89–95.

Kemler, M.A., Barendse, G.A., van Kleef, M., de Vet, H.C., Rijks, C.P., Furnee, C.A., van den Wildenberg, F.A. (2000). Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med* 343, 618–624.

Kemler, M.A., de Vet, H.C., Barendse, G.A., van den Wildenberg, F.A., van Kleef, M. (2004). The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: Two years' follow-up of the randomized controlled trial. *Ann Neurol* 55, 13–18.

Kemler, M.A., de Vet, H.C., Barendse, G.A., van den Wildenberg, F.A., van Kleef, M. (2006). Spinal cord stimulation for chronic reflex sympathetic dystrophy – five-year follow-up. *N Engl J Med* 354, 2394–2396.

Kemler, M.A., de Vet, H.C., Barendse, G.A., van den Wildenberg, F.A., van Kleef, M. (2008). Effect of spinal cord stimulation for chronic complex regional pain syndrome type I: Five-year final follow-up of patients in a randomized controlled trial. *J Neurosurg* 108, 292–298.

Kozin, F., McCarty, D.J., Sims, J., Genant, H. (1976). The reflex sympathetic dystrophy syndrome. I. Clinical and histologic studies: Evidence for bilaterality, response to corticosteroids and articular involvement. *Am J Med* 60, 321–331.

Latremoliere, A., Woolf, C.J. (2009). Central sensitization: A generator of pain hypersensitivity by central neural plasticity. *J Pain* 10(9), 895–926.

Manicourt, D.H., Brasseur, J.P., Boutsen, Y., Depreseux, G., Devogelaer, J.P. (2004). Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity. *Arthritis Rheum* 50, 3690–3697.

Marinus, J., Moseley, G.L., Birklein, F., Baron, R., Maihofner, C., Kingery, W.S., Van Hilten, J.J. (2011). Clinical features and pathophysiology of complex regional pain syndrome. *Lancet Neurol* 10, 637–648.

Merskey, H., Bogduk, M. (1994). *Classification of Chronic Pain* (Seattle: IASP Press) p. 212.

Moseley, G.L. (2004). Graded motor imagery is effective for long-standing complex regional pain syndrome: A randomised controlled trial. *Pain* 108, 192–198.

Moseley, G.L. (2005). Is successful rehabilitation of complex regional pain syndrome due to sustained attention to the affected limb? A randomised clinical trial. *Pain* 114, 54–61.

Moseley, G.L. (2006) Graded motor imagery for pathologic pain: a randomised controlled trial. *Neurobiology* 67, 2129–2134

Munts, A.G., van der Plas, A.A., Ferrari, M.D., Teepe-Twiss, I.M., Marinus, J., Van Hilten, J.J. (2010). Efficacy and safety of a single intrathecal methylprednisolone bolus in chronic complex regional pain syndrome. *Eur J Pain* 14, 523–528.

Munts, A.G., van der Plas, A.A., Voormolen, J.H., Marinus, J., Teepe-Twiss, I.M., Onkenhout, W., van Gerven, J.M., van Hilten, J.J. (2009). Intrathecal glycine for pain and dystonia in complex regional pain syndrome. *Pain* 146, 199–204.

NICE. Neuropathic pain – pharmacological management: full guidance. 2010.

Noppers, I.M., Niesters, M., Aarts, L.P., Bauer, M.C., Drewes, A.M., Dahan, A., Sarton, E.Y. (2011). Drug-induced liver injury following a repeated course of ketamine treatment for chronic pain in CRPS type 1 patients: A report of 3 cases. *Pain* 152, 2173–2178.

Oerlemans, H.M., Oostendorp, R.A., de Boo, T., van der Laan, L., Severens, J.L., Goris, J.A. (2000). Adjuvant physical therapy versus occupational therapy in patients with reflex sympathetic dystrophy/complex regional pain syndrome type I. *Arch Phys Med Rehabil* 81, 49–56.

Oerlemans, H.M., Goris, R.J.A., Oostendorp, R.A.B. (2003) Physical therapy and complex regional pain syndrome type I / reflex sympathetic dystrophy: a randomised, controlled clinical trial. *Ned Tijdschr Fysiother* 113, 15–19.

Paterson, C., Baarts, C., Launso, L., Verhoef, M.J. (2009). Evaluating complex health interventions: A critical analysis of the 'outcomes' concept. *BMC Complement Altern Med* 9, 18.

Perez, R.S., Pragt, E., Geurts, J., Zuurmond, W.W., Patijn, J., van Kleef, M. (2008). Treatment of patients with complex regional pain syndrome type I with mannitol: A prospective, randomized, placebo-controlled, double-blinded study. *J Pain* 9, 678–686.

Perez, R.S., Zollinger, P.E., Dijkstra, P.U., Thomassen-Hilgersom, I.L., Zuurmond, W.W., Rosenbrand, K.C., Geertzen, J.H. (2010). Evidence based guidelines for complex regional pain syndrome type 1. *BMC Neurol* 10, 20.

Picarelli, H., Teixeira, M.J., de Andrade, D.C., Myczkowski, M.L., Luvisotto, T.B., Yeng, L.T., Fonoff, E.T., Pridmore, S., Marcolin,

M.A. (2010). Repetitive transcranial magnetic stimulation is efficacious as an add-on to pharmacological therapy in complex regional pain syndrome (CRPS) type I. *J Pain* 11, 1203–1210.

Pleger, B., Janssen, F., Schwenkreis, P., Volker, B., Maier, C., Tegenthoff, M. (2004). Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. *Neurosci Lett* 356, 87–90.

PLoS Medical Editors. (2011). Best practice in systematic reviews: The importance of protocols and registration. *PLoS Med* 8, e1001009.

Price, D.D., Long, S., Wilsey, B., Rafii, A. (1998). Analysis of peak magnitude and duration of analgesia produced by local anesthetics injected into sympathetic ganglia of complex regional pain syndrome patients. *Clin J Pain* 14, 216–226.

Robinson, J.N., Sandom, J., Chapman, P.T. (2004). Efficacy of pamidronate in complex regional pain syndrome type I. *Pain Med* 5, 276–280.

Rodriguez, R.F., Bravo, L.E., Tovar, M.A., Castro, F., Ramos, G.E., Daza, P. (2006). Study of the analgesic efficacy of stellate ganglion blockade in the management of the complex regional pain syndrome in patients with pain mediated by sympathetic nervous system: Preliminary study. *Rev Soc Esp Dolor* 4, 230–237.

Rowbotham, M.C. (2006). Pharmacologic management of complex regional pain syndrome. *Clin J Pain* 22, 425–429.

Russell, R.G. (2011). Bisphosphonates: The first 40 years. *Bone* 49, 2–19.

Schwartzman, R.J., Alexander, G.M., Grothusen, J.R., Paylor, T., Reichenberger, E., Perreault, M. (2009). Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: A double-blind placebo controlled study. *Pain* 147, 107–115.

Shang, Y.J., Ma, C.C., Cai, Y.Y., Wang, D.S., Kong, L.L. (2008). [Clinical study on acupuncture combined with rehabilitation therapy for treatment of poststroke shoulder-hand syndrome]. *Zhongguo Zhen Jiu* 28, 331–333.

Sigtermans, M.J., Van Hilten, J.J., Bauer, M.C., Arbous, M.S., Marinus, J., Sarton, E.Y., Dahan, A. (2009). Ketamine produces effective and long-term pain relief in patients with complex regional pain syndrome type 1. *Pain* 145, 304–311.

Stanton-Hicks, M., Janig, W., Hassenbusch, S., Haddox, J.D., Boas, R., Wilson, P. (1995). Reflex sympathetic dystrophy: Changing concepts and taxonomy. *Pain* 63, 127–133.

Stanton-Hicks, M.D., Burton, A.W., Bruehl, S.P., Carr, D.B., Harden, R.N., Hassenbusch, S.J., Lubenow, T.R., Oakley, J.C., Racz, G.B., Raj, P.P., Rauck, R.L., Rezai, A.R. (2002). An updated interdisciplinary clinical pathway for CRPS: report of an expert panel. *Pain Pract* 2, 1–16.

Straube, S., Derry, S., Moore, R.A., McQuay, H.J. (2010). Cervico-thoracic or lumbar sympathectomy for neuropathic pain and complex regional pain syndrome. *Cochrane Database Syst Rev* (7) CD002918.

Taskaynatan, M.A., Ozgul, A., Tan, A.K., Dincer, K., Kalyon, T.A. (2004). Bier block with methylprednisolone and lidocaine in CRPS type I: A randomized, double-blinded, placebo-controlled study. *Reg Anesth Pain Med* 29, 408–412.

Taylor, R.S. (2006). Spinal cord stimulation in complex regional pain syndrome and refractory neuropathic back and leg pain/failed back surgery syndrome: Results of a systematic review and meta-analysis. *J Pain Symptom Manage* 31, S13–S19.

Tran, K.M., Frank, S.M., Raja, S.N., El-Rahmany, H.K., Kim, L.J., Vu, B. (2000). Lumbar sympathetic block for sympathetically maintained pain: Changes in cutaneous temperatures and pain perception. *Anesth Analg* 90, 1396–1401.

Tran De, Q.H., Duong, S., Bertini, P., Finlayson, R.J. (2010). Treatment of complex regional pain syndrome: A review of the evidence. *Can J Anaesth* 57, 149–166.

Turner-Stokes, L., Goebel, A. (2011). Complex regional pain syndrome in adults: Concise guidance. *Clin Med* 11(6), 596–600.

Uher, E.M., Vacariu, G., Schneider, B., Fialka, V. (2000). [Comparison of manual lymph drainage with physical therapy in complex regional pain syndrome, type I. A comparative randomized controlled therapy study]. *Wien Klin Wochenschr* 112, 133–137.

van de Vusse, A.C., Stomp-Van Den Berg, S.G., Kessels, A.H., Weber, W.E. (2004). Randomised controlled trial of gabapentin in complex regional pain syndrome type 1. *BMC Neurol* 4, 13.

van Tulder, M.W., Koes, B.W., Bouter, L.M. (1997). Conservative treatment of acute and chronic nonspecific low back pain. A systematic review of randomized controlled trials of the most common interventions. *Spine* 22, 2128–2156.

Varenna, M., Zucchi, F., Ghiringhelli, D., Binelli, L., Bevilacqua, M., Bettica, P., Sinigaglia, L. (2000). Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. A randomized, double blind, placebo controlled study. *J Rheumatol* 27, 1477–1483.

Veldman, P.H., Reynen, H.M., Arntz, I.E., Goris, R.J. (1993). Signs and symptoms of reflex sympathetic dystrophy: Prospective study of 829 patients. *Lancet* 342, 1012–1016.

Wu, W.H., Bandilla, E., Ciccone, D.S., Yang, J., Cheng, S.C., Carner, N., Wu, Y., Shen, R. (1999). Effects of qigong on late-stage complex regional pain syndrome. *Altern Ther Health Med* 5, 45–54.

Zollinger, P.E., Tuinebreijer, W.E., Breederveld, R.S., Kreis, R.W. (2007). Can vitamin C prevent complex regional pain syndrome in patients with wrist fractures? A randomized, controlled, multicenter dose-response study. *J Bone Joint Surg Am* 89, 1424–1431.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. RCTs excluded from this review.
Appendix S2. IASP Diagnostic Criteria for CRPS I (International Association for the Study of Pain 1994) (Merskey and Bogduk, 1994).
Appendix S3. Veldman Diagnostic Criteria for CRPS (Veldman et al., 1993).
Appendix S4. Trial methodology – 15-item scoring system.
Appendix S5. Hierarchical list of quality scores for 29 RCTs included in the study.
Appendix S6. Summary of outcomes from the 2002 Forouzanfar review.
Appendix S7. Summary of results from systematic reviews of RCTs for treatment of pain in CRPS.