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Critical Review

# The Outcome of Complex Regional Pain Syndrome Type 1: A Systematic Review

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**Abstract:** **The purpose of this systematic review was to examine the outcome of complex regional pain syndrome (CRPS) type 1. We searched MEDLINE, Embase, and PsycINFO for relevant studies, and included 18 studies, with 3,991 participants, in this review. The following data were extracted: study details, measurement tools used, and rates or severity scores for the symptoms/signs of CRPS at baseline and follow-up, or in groups of patients with different disease durations. A quality assessment revealed significant limitations in the literature, with many studies using different diagnostic criteria. The 3 prospective studies demonstrated that for many patients, symptoms improve markedly within 6 to 13 months of onset. The 12 retrospective studies had highly heterogeneous findings, documenting lasting impairments in many patients. The 3 cross-sectional studies showed that rates of pain and sensory symptoms were highest among those with the longest duration of CRPS. Additionally, most studies showed that motor symptoms (stiffness and weakness) were the most likely to persist whereas sudomotor and vasomotor symptoms were the most likely to improve. Overall, this suggests that some CRPS patients make a good early recovery whereas others develop lasting pain and disability. As yet little is known about the prognostic factors that might differentiate between these groups.**

***Perspective:*** ***We found evidence that many CRPS patients recover within 6 to 13 months, but a significant number experience some lasting symptoms, and some experience chronic pain and disability. The quality of the evidence was poor. Future research should examine the factors associated with recovery and identify those at risk of poor outcomes.***



***Key words:*** *Complex regional pain syndrome, outcome, prognosis, recovery, systematic review.*

Complex regional pain syndrome (CRPS) is a painful condition that can occur after fracture, stroke, surgery or trauma, and most commonly affects a hand, wrist, foot, or ankle. In CRPS, pain is accompanied by a range of symptoms, including allodynia, hyperalgesia, swelling, and abnormalities in color, temperature, sweating, nail and hair growth, and movement.

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Traditionally, CRPS was considered a progressive condition with distinct "stages." For example, Bonica[10] described 3 stages. Stage 1, the "acute stage," was characterized by a painful, swollen, warm, red limb. In stage 2, the "dystrophic stage," the limb was said to cool and appear cyanotic, with changes to hair and nail growth, osteoporosis, stiffness, and muscle wasting. In stage 3, the "atrophic stage," irreversible atrophy of bones, muscles, and nails was described. However, relatively little research data have been offered to support the 3 specific stages, and at least 1 study has refuted the idea that 3 stages exist.[11] Long-term follow-ups of CRPS patients report contradictory findings regarding the outcome of the condition. A number of studies have found that although the nature of symptoms might fluctuate over time, CRPS tends to persist, and only a minority of patients recover from the condition.[14,15,21,41,44,47] For example, a prospective study of 42 patients with CRPS

after fracture found that no patient was symptom-free 12 months later.[6] A follow-up of 134 CRPS patients at a mean of 5.8 years after diagnosis found that 64% still met the International Association for the Study of Pain (IASP) diagnostic criteria for CRPS,[15] and 1 study of more than 600 CRPS patients showed that symptoms tended to be worse in those with a longer duration of CRPS compared to those with a shorter duration.[41] In addition, research has suggested that over time, CRPS patients can develop more widespread pain, and some researchers have described symptoms of CRPS "spreading" to affect multiple limbs.[41,46]

In contrast, there are also studies that present more optimistic data and suggest that the majority of patients will recover from the condition within 12 months.[8,17,24,38,49] A population-based study of medical records found that 74% of CRPS cases resolved, usually spontaneously, at a mean of 11.6 months post onset.[38] A prospective study requiring patients to have no treatment found that of the 30 participants, only 3 had severe symptoms and had to withdraw from the study for treatment, and of the 27 remaining participants, only 1 continued to have CRPS at the 1-year follow-up.[49] Several studies have also shown that the majority of CRPS patients will return to employment following the condition.[17,18]

This review aims to examine these discrepancies in the literature, to synthesize the published data concerning the course of CRPS symptoms over time, and to answer the following questions: In what proportion of CRPS patients do symptoms persist? To what extent do CRPS symptoms persist? We chose to limit the review to CRPS type 1 (CRPS-1, without a major nerve injury) because CRPS type 2 (CRPS-2) is associated with a specific nerve injury that likely affects outcome. We hypothesized that the majority of patients would show improvements in CRPS symptoms with time, but some would display chronic severe symptoms.

## Methods

### Selection of Studies

We systematically reviewed prospective, retrospective, and cross-sectional studies that provided data on the outcome of CRPS type 1. A literature search was conducted using the databases MEDLINE, Embase, and PsycINFO, from inception until April 4, 2012 (search date). We used the search terms recommended for systematic reviews on prognosis[2]: "exp epidemiologic studies," "incidence.sh," "follow-up studies.sh," "prognos:.sh," "predict:.tw," OR "course:.tw" AND "complex regional pain syndrome.mp," "Reflex sympathetic dystrophy.mp," OR "algodystrophy.mp." The search was limited to peer-reviewed journals and to studies including human subjects. The personal electronic libraries of the researchers were also searched for possible references. The reference lists of all relevant papers were searched by hand and an electronic search for citing articles of each paper was also conducted to ensure that all possible references were obtained.

Studies were considered for inclusion in the systematic review if they

1. Reported on "complex regional pain syndrome type 1," "reflex sympathetic dystrophy" (RSD), "algodystrophy," or "sudeck's dystrophy." Studies with patients combined from several diagnostic groups (eg, CRPS-1 and CRPS-2) were included if >80% of the sample had CRPS-1;
2. Had the stated aim of investigating the course, natural history, or outcomes of CRPS; or
3. Had one of the following characteristics:
   a. Reported on rates or severity of CRPS symptoms/signs or presence of CRPS diagnosis at more than 1 time point, where the time points are at least 6 months apart, or
   b. Provided cross-sectional or correlational data comparing the symptoms/signs of CRPS between patients with differing CRPS duration or correlating symptom severity with duration, or
   c. Were retrospective studies documenting self-report of how symptoms changed over time, or
   d. Were retrospective studies or audits documenting residual symptoms/signs in a follow-up of a cohort more than 6 months after the CRPS patients were identified. Cohorts had to have been previously assembled or patients previously identified, so that the review only included retrospective studies that had a chance of capturing CRPS cases that had resolved.

Studies were excluded if they 1) had a sample size of less than 10; 2) were not published in full article format or data could not be extracted from the article; 3) conducted in pediatric samples or in adult samples where the CRPS onset was during childhood (as there is suggestion that CRPS can manifest differently in children and adolescents); 4) published in languages other than English, French, or German; or 5) had follow-up or response rates <50%.

### Quality and Relevance Assessment and Data Extraction

To assess study quality and relevance of studies for this review, we used a modified version of the quality evaluation method recommended for systematic reviews of prognostic variables.[12,28] Few studies assessed prognostic variables. Therefore, our review focused on clarifying the course of CRPS, so we excluded quality items on prognostic factor measurement and confounder measurement.

We assessed quality and relevance on the following 4 sources of bias: study participation (sampling method described, sample described, inclusion/exclusion criteria described, diagnostic criteria described, response rate, representative sample, assembled at common time point >3 months, follow-up >6 months), study attrition (attrition described, attrition adequate, information on drop-outs), outcome measurement (outcomes defined, objective, measured appropriately), and analysis (relevant statistical analysis conducted, and statistical analysis appropriate). For each question, each study was scored

positive (Y), negative (N), or unclear (?). For retrospective and cross-sectional studies, attrition items were scored not applicable (N/A). A detailed description of the quality assessment criteria is available in Supplementary Table 1 in the supplementary information online.

We extracted data on the study population, diagnostic criteria, symptom duration at baseline and follow-ups (where applicable), the measurement tools used to assess each of the symptoms/signs of CRPS, and the mean and standard deviation scores on those measures at each time point. The symptoms/signs investigated were pain, sensory symptoms, function (range of motion/stiffness and limb strength), temperature asymmetry, color asymmetry, swelling, abnormal sweating, and hair and nail growth abnormalities. We also extracted data on scores or measures of general recovery from CRPS. As a number of studies did not report mean scores, but rather the proportion of the sample with each symptom/sign either present or absent, for these studies, the percentage of the sample with the symptom/sign at each time point was recorded.

### Data Synthesis

As there was significant heterogeneity in research methods, it was not possible to pool data quantitatively in any meaningful way. Instead, a qualitative analysis and synthesis of the data is presented here. We present the results of the prospective, retrospective, and cross-sectional studies separately.

## Results

### Studies Selected

The literature search yielded 1,741 papers. The titles, abstracts, and, where necessary, full text of these were screened by the primary author (D.J.B.). Ninety of these were selected for a closer review and were examined in detail. Of these, 18 studies (with 19 publications) met the inclusion and exclusion criteria and were selected for this review (Table 1). The second author screened any of the studies where it was unclear whether they met the inclusion/exclusion criteria, and a decision was made by consensus.

Of the 18 studies included in the review, there were 3 prospective studies, 12 retrospective studies, and 3 cross-sectional or correlational studies. The median sample size of the studies was 71, but samples ranged from 17 to 888. The total number of participants included in this review is 3,991. The study characteristics are described in Table 1. Few studies used the same diagnostic criteria. Three used the 1994 IASP criteria,[33] 2 used the "Budapest" criteria (now also known as the new IASP criteria),[26] 3 used the criteria described by Zyluk,[49] and the rest used their own criteria or did not describe the criteria used. This reflects the changing taxonomy of CRPS over the years. Earlier studies used criteria for algodystrophy or RSD, whereas later studies tended to use the newer criteria for CRPS. There are large variations between the criteria, so, for example, studies that used the 1994 IASP criteria would have captured many more patients than studies that used the new IASP (Budapest) criteria.[14]

### Quality Assessment

The results from the quality and relevance assessment are presented in Table 2. In keeping with guidelines on quality assessment for systematic reviews of this nature, we chose not to create a "quality score" for each study, but instead discuss the quality of the studies qualitatively.[12,28] We note 4 major sources of bias in the included studies:

1. Unrepresentative Samples: As shown in Tables 1 and 2, most studies used samples that are unlikely to represent the CRPS population as a whole: some recruited only patients with a particular "trigger" for their CRPS, such as a fracture, which has been suggested to influence outcome.[38] Some recruited from specialist centers where patients with more severe cases of CRPS are likely to be referred, others included only patients with a previous "good outcome," which is also likely to influence later prognosis, and 1 study only included those with CRPS for more than 1 year. We determined that only 6 out of the 18 included samples met our criteria for using a "representative sample." In addition, only 3 studies met our criteria for being considered an "inception" cohort (ie, samples selected at a common time point less than 3 months after developing their CRPS). Thus, most of the studies likely failed to include any CRPS patients who could have recovered in the first few months of their condition.
2. Attrition: Loss to follow-up is major source of bias for the studies included in this review, particularly if those lost to follow-up are those with a likely better or poorer outcome. Only 6 of our 18 included studies could be scored for attrition, and of these, only 2 met our minimum criteria (<20% attrition). Three of the studies were cross-sectional (which meant that any patients who had recovered were not included), and 9 were retrospective follow-ups of a previously identified cohort. For these retrospective studies, we did not score them for "attrition" but rather for "response rate" (ie, the percentage of the previously identified cohort that was included in the study). Of these 9 studies, 4 had response rates below our required cut-off of 75%, and the other 5 did not report response rate clearly in the published article. Thus, attrition is a major and obvious source of bias in the included studies.
3. Measurement: Inadequate measurement of outcomes is a source of bias for this review. We assessed whether outcome measures were defined, whether any measures were objective, and whether they were measured appropriately. We found that 15 of the 18 papers defined their outcomes, 11 studies included at least 1 objective measure (ie, not self- or physician report), and 9 studies used some kind of standardized measure or scale. Overall, the studies performed better for this source of bias than for other major sources of bias, but the huge variation

## Table 1. Characteristics of the Included Studies

| Reference | Setting, Location, and Publication Year | Sample and Method | Diagnostic Criteria Used | Mean CRPS Duration at Baseline/ Cohort Assembly | Mean CRPS Duration at Follow-Up/ Time of Survey |
|---|---|---|---|---|---|
| Prospective studies | | | | | |
| Atkins et al[3] | Hospital Casualty Department, Sheffield, United Kingdom, 1989 | Assessed 109 unselected Colles fracture patients at 9 wk and 6 mo. Reports on persisting symptoms in 19 of the 27 patients with features of algodystrophy at baseline. | Own | 9 wk | 6 mo |
| Bickerstaff and Kanis[8] | Hospital Casualty Department, Sheffield, United Kingdom, 1994 | Assessed 274 Colles fracture patients at 7 wk, then monthly until symptoms abated (6 mo for asymptomatic patients). Included 77 who developed algodystrophy. No mention of response/ dropout rates. Reports the percentage of algodystrophy patients with persisting symptoms at 6 and 12 mo. | From Atkins et al[4] | 7 wk | 6 and 12 mo |
| Zyluk[49] | Surgical Department, Pomeranian Medical University, Poland, 1998 | Assessed 30 RSD patients at 1, 2, 6, and approx. 13 mo. Patients were required to receive no treatment. Three patients with severe symptoms withdrew for treatment, so the study reports on the rates of symptoms in the remaining 27. | From Zyluk[49] | At time of diagnosis: mean of 12 wk | 6 and 13 mo postdiagnosis |
| Retrospective studies | | | | | |
| Subbarao and Stillwell[45] | Clinic/setting not described, United States, 1981 | Chart review of 125 upper limb RSD patients who had been discharged a mean of 14 mo earlier. Follow-up questionnaires sent to 123. Of those, 77 (63%) responded. Paper reports on rates of symptoms noted in this questionnaire. | From Pak et al[35] | 22 wk | 22 mo |
| Gougeon et al[25] | French Society of Rheumatology, France, 1982 | File review of 573 RSD cases from a survey of society members, 370 files selected for review. Of these, 227 files mentioned the duration of disease until resolution. Reports on percentage whose symptoms had resolved by 6, 12, and 36 mo. | Not described | n/a | Followed up until cured or 3 y max |
| Fialka et al[20] | Physical Medicine & Rehabilitation Department, Vienna, Austria, 1991 | Followed 17 patients with lower limb RSD post-fracture, for a mean of 39 mo. Performed physical assessment at follow-up. Reports on remaining symptoms, as well as scintigraphy. | Own | 14 wk | 3.5 y |

**Table 1. Continued**

| Reference | Setting, Location, and Publication Year | Sample and Method | Diagnostic Criteria Used | Mean CRPS Duration at Baseline/ Cohort Assembly | Mean CRPS Duration at Follow-Up/ Time of Survey |
|---|---|---|---|---|---|
| Ehrler et al[19] | Functional Rehabilitation Centre, Strasbourg, France, 1995 | Follow-up questionnaire sent to 47 algodystrophy patients who had taken part in a study 9 y earlier. 25 (53%) responded. Reports on percentage that continue to experience pain, stiffness, and reduced strength. | Not described | 2 groups: 1 = 1 wk, 2 = 28 wk | Both groups 9 y later |
| Laulan et al[32] | Orthopedic Services, University Hospital Trousseau, Tours, France, 1997 | Recruited all 125 distal radius fracture patients seen over a 7-mo period for surgical treatment and followed-up at 12 mo. Of the 26 who had "definite algodystrophy" at 12 wk, all were followed-up. Reports on those with stiffness and pain at 12 mo. | Own | n/a | 12 mo postfracture |
| Geertzen et al[22,23] | Department of Rehab., University Hospital Groningen, The Netherlands, 1998 | Invited all 93 patients treated for RSD from 1988–1994 for follow-up. 65 (70%) responded. Reports on measures of pain, quality of life and physical function. | Own | n/a | 5.5 y |
| Galer et al[21] | University of Washington Multidisciplinary Pain Center, USA, 2000 | Questionnaire sent to 55 CRPS patients treated from 1997 to 1998. 31 (56%) responded. Asked patients to describe which symptoms had improved, worsened or remained unchanged. | 1994 IASP[33] | n/a | 3.3 y |
| Zyluk[50] | Surgical Dept, Pomeranian Medical University, Poland, 2001 | Chart review of all 146 patients treated for RSD from 1986 to 1997. Assessed the 94 (64%) with a previous good response to treatment, at mean 11 mo post-treatment. Paper describes remaining symptoms. | From Zyluk[50] | Not stated, majority duration <4 mo (17 wk) | 11 mo posttreatment completed |
| Bejia et al[7] | Rheumatology Department, University Hospital Monastir, Tunisia, 2005 | Reviewed 60 algodystrophy cases seen from 1989 - 2003. Classified the outcome for each patient (poor/ moderate/good/very good), and reports the percentage left with atrophy and pain. | Not described | 13 wk | 15 mo |
| de Mos et al[15] | Integrated Primary Care Info. Project (GP Database), Erasmus Medical Centre, Rotterdam, The Netherlands, 2009 | Identified all 259 patients diagnosed with CRPS a minimum of 2 y earlier, from 48 clinics in GP database. Visited and assessed 62% of these patients. 40 later | 1994 IASP[33] | 1st mention in GP database; confirmed by patients | 5.8 y |

**Table 1. Continued**

| Reference | Setting, Location, and Publication Year | Sample and Method | Diagnostic Criteria Used | Mean CRPS Duration at Baseline/ Cohort Assembly | Mean CRPS Duration at Follow-Up/ Time of Survey |
|---|---|---|---|---|---|
| | | identified as not appropriate (never had CRPS/developed CRPS before the study period). Final sample: 102 CRPS patients (100 CRPS-1, 2 CRPS-2). Reports on percentage with symptoms/signs of CRPS at assessment. | | | |
| Savas et al[39] | Department Physical Medicine & Rehab, Suleyman Demireal University Medical School, Turkey, 2009 | Physical examination of all 30 CRPS-1 patients previously discharged with a good outcome 18 mo later. Reports on remaining symptoms at this assessment. | From Zyluk[50] | Unclear | 18 mo posttreatment |
| Sharma et al[44] | RSD Association of America Website, United States, 2009 | Asked RSD website users to complete online survey. Received 1359 responses. 35% excluded (likely never met diagnostic criteria). 888 responses included. Reports percentage describing remission at some point, percentage pain-free, and symptom change over time. | Modified Budapest[26] (used symptom report only as no physical examination) | n/a | 5.5 y |
| Cross-sectional or correlational studies | | | | | |
| Veldman et al[47] | Department of Surgery, Nijmegen University Hospital, The Netherlands, 1993 | Recorded symptoms reported by 829 consecutive RSD patients. Assessed symptom prevalence in groups according to CRPS duration. | From Veldman et al[47] | Group 1: 0–2 mo (n = 156)<br>Group 2: 2–6 mo (n = 242)<br>Group 3: 6–12 mo (n = 200)<br>Group 4: >12 mo (n = 231) | |
| Schwartzman et al[41] | Pain Clinic, Drexel University College of Medicine, United States, 2009 | Retrospectively analyzed questionnaires completed by 656 CRPS-1 & 2 patients seen over a 10.5-y period. Correlated symptom severity scores with CRPS duration, reported on percentage with particular symptoms at different stages of CRPS duration. | Budapest[26] | 1–46-y range. No mean duration reported. | |
| De Boer et al[14] | Outpatient clinics of 5 hospitals participating in the TREND knowledge consortium (Trauma Related Neuronal Dysfunction), The Netherlands, 2011 | Replicated the Veldman et al[47] study with a group of 692 ambulatory CRPS-1 patients. | 1994 IASP[33] | Group 1: 0–2 mo (n = 48)<br>Group 2: 2–6 mo (n = 211)<br>Group 3: 6–12 mo (n = 70)<br>Group 4: >12 mo (n = 352) | |

in measurement practices and lack of objective measures still likely affected results.

4. Statistics: Only 7 of the 18 studies performed relevant statistical testing, for example, looking for statistically significant reductions in symptom severity over time or comparing differences in measures of the affected and unaffected limbs at a follow-up. All 7 studies that performed statistical testing were deemed to use statistics appropriately. However, a possible source of bias is the lack of statistical testing in the 11 other studies. This means that we did not know if differences between groups in the cross-sectional studies, or changes in symptom severity over time in prospective studies, could be chance findings, and had to take the raw data on its merit.

## Results From Prospective Studies

The 3 prospective studies presented the most optimistic outcome data and demonstrated consistent symptom improvements over time.[3,8,49] Two of these studies systematically measured the symptoms/signs of CRPS early after diagnosis and then again at a 12- to 13-month follow-up,[8,49] whereas the other study briefly noted data from a 6-month follow-up.[3] The 2 prospective studies that measured pain or tenderness found that the proportion of CRPS patients with pain reduced from 100% at first assessment to 18% and 7% respectively at the 12- to 13-month follow-up.[8,49] The 2 studies that assessed the presence of swelling reported rates of 87 to 100% at first assessment, which reduced to 12 to 15% at the final follow-up.[8,49] Only 1 of the prospective studies measured changes in temperature disturbance, limb discoloration, sweating abnormalities, trophic changes to hair and nails, and sensory disturbances, and this study noted significant reductions in rates of signs over the course of 13 months.[49] One study found significant reductions in rates of "vasomotor instability" (a combination of abnormalities in limb color, temperature, and sweating) over the course of 12 months, from 91% at baseline to 29% at follow-up.[8] Another study grouped symptoms into a category labeled "vasomotor instability or swelling" and found that 42% of patients experienced these symptoms at the 6-month follow-up.[3]

The symptoms/signs that were least likely to resolve in the prospective studies were stiffness and limb strength. Bickerstaff and Kanis[8] found that 65% of patients continued to have stiffness at 12 months, and the grip strength of the affected limb was equivalent to 45% of the strength of the unaffected limb. This contrasted with a grip strength ratio of 80% in Colles' fracture patients who did not develop algodystrophy. Zyluk[49] reported that 89% of RSD patients had reduced grip strength at the 13-month follow-up and reported that grip strength was 45% that of the unaffected limb. Zyluk[49] also found that stiffness was highly prevalent, with 78% of RSD patients experiencing "stiffness in the morning" at the 13-month follow-up. Atkins et al[3] reported lower rates of joint stiffness at the 6-month follow-up (21%), but it is unclear from the results they present whether joint stiffness may also have affected the 42% of patients noted to have "vasomotor instability or swelling."

Only 1 of the prospective studies had an overall measure of CRPS severity, the "Zyluk assessment of result." This study reported that 73% of patients had a good result (no pain and full finger flexion), 13% had a moderate outcome (pain after load and loss of flexion of less than 3 cm), whereas 13% had a poor result (persistent severe pain and loss of flexion greater than 3 cm).[49]

Of note, 2 of the prospective studies used the same criteria for "algodystrophy" and the other used criteria for "reflex sympathetic dystrophy." All 3 prospective studies required 4 different symptoms/signs of CRPS to be present in order to meet diagnostic criteria, although the algodystrophy criteria were broader as a wider range of symptoms were accepted.

## Results From Retrospective Studies

### Measures of Overall Rates of CRPS Symptoms or Severity

There were 12 retrospective studies included in the review. Seven reported on results of an overall measure of CRPS presence or severity, with the majority of these studies quantifying the percentage of an original cohort who continued to have symptoms/signs of CRPS at a long-term follow-up assessment. The results are presented in Table 3. This shows that the outcomes were highly variable and are presented here in order from the most to the least positive. Gougeon et al[25] found that all but 22% of algodystrophy patients were "cured" at the 3-year follow-up according to a chart review. A 9-year follow-up questionnaire sent to algodystrophy patients reported that 40% of patients had not "normalized."[19] Another study of algodystrophy patients indicated that 58% had "sequelae" with an elevated algodystrophy score calculated from a clinical and radiologic examination at 12 months postfracture.[32] A study of CRPS patients reported that 64% continued to meet the 1994 IASP criteria for CRPS at an examination at a mean of 5.8 years postdiagnosis.[15] Finally, a physical examination of CRPS patients who had previously had a good outcome found that 90% continued to experience symptoms 18 months after treatment.[39] Overall, these findings are highly heterogeneous, with ratings as low as 22% and as high as 90% for those who continue to have symptoms at long-term follow-up.

One study rated patients' outcome according to a clinical grading system and found that 63% of algodystrophy patients had a very good or good outcome, 29% had a moderate outcome, and 9% had a poor outcome according to a chart review.[7] Another interviewed patients about their clinical course and found that 30% considered themselves recovered, 54% rated their symptoms as stable, and 16% stated that their symptoms were progressive at a mean of 5.8 years after diagnosis.[15]

One retrospective study reported on a measure of overall symptom severity in a cohort of patients examined at a mean of 5.5 years.[22,23] They used the "RSD score"—a 60-point rating scale—and reported that although the score for RSD patients' unaffected hands was 0.7/60 (on a scale of 0–60 where 0 = no RSD and 60 = worst RSD), on the affected side it was a mean of 6/60. They also reported that quality of life scores among patients were similar to population norms.

### Measures of Pain

Ten retrospective papers reported on measures of pain among cohorts of patients followed up at least 1 year after diagnosis, and these are presented in Table 4. Five of these studies reported on the percentage of patients who continued to experience pain, and these results were highly variable. The most positive results showed that only 19% of algodystrophy patients continued to experience pain at 1 year; however, 27% of the "algodystrophy" sample in this study had never experienced pain at any time, which questions the

## Table 2. Results of the Quality and Relevance Assessment for the Included Studies

| | Sampling Method Described? | Sample Described? | Inclusion/ Exclusion Criteria Described? | Diagnostic Criteria Described? | Response Rate >75%? | Representative Sample? | Assembled at Common Time Point <3 Mo? | Follow-Up at Least 6 Mo? | Attrition Described? | Attrition Adequate (<20%)? | Information About Completers vs Dropouts? | Outcomes Defined? | Outcomes Objective? | Outcomes Measured Appropriately? | Relevant Statistical Analysis Conducted? | Analysis Appropriate? |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Prospective studies | | | | | | | | | | | | | | | | |
| Atkins et al[3] | Y | Y | Y | Y | ? | N, fracture | Y | N | Y | N | N | N | N | ? | N | n/a |
| Bickerstaff and Kanis[8] | Y | N | N | Y | ? | N, fracture | Y | Y | Y | Y | n/a | Y | Y | Y | Y | Y |
| Zyluk[49] | Y | Y | N | Y | ? | Y | N | Y | Y | N | Y | Y | Y | Y | N | n/a |
| Retrospective studies | | | | | | | | | | | | | | | | |
| Subbarao and Stillwell[45] | Y | Y | Y | Y | N | Y | N | Y | Y | N | N | Y | N | N | N | n/a |
| Gougeon et al[25] | Y | N | N | N | ? | ? | N | Y | n/a | n/a | n/a | N | ? | ? | N | n/a |
| Fialka et al[20] | N | Y | Y | Y | ? | ? | N | Y | n/a | n/a | n/a | Y | Y | Y | Y | Y |
| Ehrler et al[19] | N | N | N | N | ? | ? | N | Y | Y | N | N | N | Y | ? | N | n/a |
| Laulan et al[32] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | N | N | n/a |
| Geertzen et al[22,23] | Y | Y | Y | Y | N | Y | N | Y | n/a | n/a | n/a | Y | Y | Y | Y | Y |
| Galer et al[21] | Y | Y | Y | Y | N | N, pain center | N | n/a | n/a | n/a | n/a | Y | N | Y | N | n/a |
| Zyluk[50] | Y | Y | Y | Y | N | N, good outcome | N | Y | n/a | n/a | N | Y | Y | Y | N | n/a |
| Bejia et al[7] | Y | Y | N | N | ? | ? | N | n/a | n/a | n/a | n/a | Y | N | ? | N | n/a |
| de Mos et al[15] | Y | Y | Y | Y | N | Y | n/a | Y | n/a | n/a | n/a | Y | Y | ? | Y | Y |
| Savas et al[39] | Y | Y | Y | Y | ? | N, good outcome | N | Y | n/a | n/a | n/a | Y | Y | Y | Y | Y |
| Sharma et al[44] | Y | Y | Y | Y | ? | N, online support group | N | N | n/a | n/a | n/a | Y | N | N | N | n/a |
| Cross-sectional studies | | | | | | | | | | | | | | | | |
| Veldman et al[47] | Y | Y | Y | Y | Y | Y | N | n/a | n/a | n/a | n/a | Y | Y | ? | N | n/a |
| Schwartzman et al[41] | Y | Y | Y | Y | Y | N, chronic | N | N | n/a | n/a | n/a | Y | N | Y | Y | Y |
| de Boer et al[14] | Y | Y | Y | Y | ? | N, regional referral center | N | N | n/a | n/a | n/a | Y | Y | Y | Y | Y |

Abbreviations: Y, positive; N, negative; ?, unclear.

similarity of this sample to others diagnosed with RSD or CRPS.[32] An assessment of CRPS patients at a mean of 5.8 years after diagnosis found that 32% still reported experiencing pain.[15] Two postal questionnaire studies found that 36% of algodystrophy patients still reported pain at a 9-year follow-up,[19] and 47% of RSD patients had hand pain at 22 months.[45] Studies that examined patients at follow-up found that 71% of RSD patients with a previously good outcome still had pain 11 months posttreatment,[50] and of CRPS patients, 86% had pain on movement and 76% had pain at rest 18 months post-treatment.[39]

Three retrospective studies reported results of measures of pain intensity. Savas et al[39] found that on a visual analog scale (0–10 cm), the mean pain score of CRPS patients was 2.8 ± 2.0 cm at a follow-up of 18 months post-treatment. Geertzen et al[22,23] reported even lower pain severity ratings at 5.5-year follow-up of RSD patients, with a mean visual analog score of 1.2 ± 1.8 cm. Fialka et al[20] reported low-moderate pain intensity among a group of RSD patients at a 42 month follow-up: on a scale of 0 (no pain) to 5 (intolerable pain), the mean score was 2.1 ± 1.1 cm.

Two retrospective self-report studies asked groups of CRPS patients to recall how pain had changed over time. Galer et al[21] found that 29% of CRPS patients believed their pain had improved over time, 42% described no change, and 29% indicated that their pain had worsened. A survey of RSD patients found that, on average, patients believed their pain had improved slightly since first developing their symptoms, but 79% stated that their symptoms had never gone into remission.[44] This last study was limited as it surveyed patients who were current users of an RSD website, so any who had recovered were unlikely to be included. The results of the retrospective studies that measured the prevalence or intensity of pain are presented in Table 4.

## Measures of Function

Eight retrospective studies reported on follow-up measures of limb function among cohorts of CRPS patients. All of these studies showed that limb strength and/or stiffness continue to be affected in the long term. For example, Geertzen et al[22,23] found that there were small but statistically significant differences in the range of motion between the affected and unaffected limbs of RSD patients at a mean follow-up time of 5.5 years. They also reported that the grip strength of the RSD affected hand was 73% that of the unaffected hand, and that 62% of patients were limited in the activities of daily living. Similar significant range of motion and strength differences between the affected and unaffected limbs of CRPS patients were reported by Savas et al[39] at a mean of 18 months posttreatment. Fialka et al[20] found that 58.8% of patients had a slightly reduced range of motion, but none exhibited a markedly reduced range of motion at the 39-month follow-up. Zyluk[50] found that 28% of RSD patients had "morning stiffness" and 78% described decreased function of the hand 11 months after treatment. Grip strength of the affected hand was 37% of the strength of the unaffected side. Ehrler et al[19] reported that 36% of algodystrophy patients indicated that they had reduced

**Table 3. Results of Retrospective Studies Measuring General Outcomes of CRPS**

| Reference | Sample | Mean Follow-Up Time Point | Measure | Result |
|---|---|---|---|---|
| Bejia et al[7] | 60 algodystrophy patients | 15 mo | Criteria of French Society for Rheumatologists | Very good result: 16%; good result: 46.5%; moderate result: 28.7%; poor result: 8.8% |
| Gougeon et al[25] | 227 algodystrophy patients | Until cured, max 3 y | Chart review to determine % "cured" | 21.6% not "cured" after 3 y |
| Ehrler et al[19] | 25 algodystrophy patients | 9 y | Questionnaire to determine % "normalized" | 60% "normalized"; 40% symptomatic |
| Laulan et al[32] | 26 algodystrophy patients post–distal radius fracture | 12 mo | % with "sequelae" on physical examination | 57.7% had "sequelae" |
| De Mos et al[15] | 102 CRPS patients | 5.8 y | % who still meet 1994 IASP Criteria for CRPS | 64% meet 1994 IASP criteria |
| Savas et al[39] | 30 CRPS patients with previous good outcome | 18 mo after treatment | % who met own criteria for CRPS<br>% who were symptom-free | 0 met criteria for CRPS; 10% were symptom-free, 90% symptomatic |
| Geertzen et al[22,23] | 65 RSD patients | 5.5 y | RSD Score (min = 0, max = 64, worse scores indicate more severe RSD); Short-form 36 (quality of life) | Unaffected side = 0.7 ± 1.5; affected side = 5.6 ± 8.6; SF-36 scores similar to population norms |

strength in the limb, and 28% described stiffness 9 years after diagnosis. Subbarao and Stillwell[45] found that 51% of their sample experienced stiffness in the hand at the 22-month follow-up. Of the 102 patients visited by de Mos et al,[15] at a mean of 5.8 years since CRPS onset, 59 to 60% described a reduced range of motion or weakness of the limb, and these were observed by the researchers in 41 to 44%. Galer et al[21] surveyed CRPS patients and asked them to recall the course of symptoms over time. They reported that weakness was noted to have improved by 48% of patients, but 25% noted that weakness tended to worsen and 23% noted no change. Overall, the retrospective studies that report on functional outcomes concur with the findings of the prospective studies, indicating that functional limitations such as weakness, stiffness, and reduced range of motion may be quite prevalent in the long term for CRPS patients.

## Diagnostic Criteria Used in the Retrospective Studies

The diagnostic criteria used by the studies once again differed greatly. Three of the retrospective studies did not describe their criteria. Four required 4 symptoms/signs from a list of varying possible clinical features.[22,23,39,44,50] Two studies required 3 symptoms/signs from a list of possible clinical features along with particular radiologic findings.[20,32] Two studies used the broad 1994 IASP criteria.[15,21] One study described a range of symptoms/signs but did not state which were required for diagnosis.[45] It appears that studies that used criteria for "algodystrophy" tended to produce more optimistic results than studies that examined "RSD" or "CRPS." Also, studies that conducted a chart review produced more optimistic results than studies that examined patients at follow-up.

## Results From Cross-Sectional Studies

Three cross-sectional studies were included in the review. Two of the studies took samples of patients with diagnoses of RSD or CRPS and divided them into 4 groups on the basis of their duration (less than 2 months, 2–6 months, 6–12 months, and more than 12 months).[14,47] They measured the percentage of each group with each of the symptoms of CRPS and reported these rates. One of the studies compared these 4 groups for statistically significant differences in the rates of symptoms.[14] The other study measured symptoms as well as CRPS duration and performed correlations to see whether symptom prevalence or severity significantly correlated with CRPS duration.[41] These 3 studies had large sample sizes in comparison with the majority of the other papers (656–829 subjects).

The cross-sectional studies generally reported poorer outcomes than the prospective studies and the retrospective studies. For example, for pain, the 2 comparative studies reported that 85 to 92% of RSD/CRPS patients had pain during the first 2 months, and this increased steadily so that among those with CRPS for more than 1 year the rates were 95 to 97%.[14,47] The correlational study reported a significant correlation of r = 0.6 for the numerical pain rating scale scores and CRPS duration, indicating that pain intensity increases with CRPS duration.[41] The cross-sectional studies reported similar patterns of increasing rates for sensory symptoms such as allodynia and hyperesthesia, although the actual rates of symptoms were lower than those for pain.[14,47] The comparative studies

**Table 4. Results of Retrospective Studies Measuring Pain Outcomes in CRPS**

| Reference | Sample | Mean Follow-Up Time Point | Measure | Result |
|---|---|---|---|---|
| Laulan et al[32] | 26 algodystrophy patients post–distal radius fracture | 12 mo | % with pain | 19% |
| De Mos et al[15] | 102 CRPS patients | 5.8 y postdiagnosis | % reporting spontaneous pain | 32% |
| Ehrler et al[19] | 25 algodystrophy patients | 9 y | % with pain | 36% |
| Subbarao and Stillwell[45] | 77 RSD patients | 22 mo | % with pain in hand | 41% |
| Zyluk[50] | 94 RSD patients with previous "good" outcome | 11 mo posttreatment | % not completely pain-free | 71% |
| Savas et al[39] | 30 CRPS-1 patients with previous "good" outcome | 18 mo posttreatment | % with hand pain after use; % with hand pain at rest; Mean VAS pain intensity | 86%, 76%; 2.8 ± 2.0 cm |
| Geertzen et al[22,23] | 65 RSD patients | 5.5 y | Mean VAS pain intensity last 24 hours | 1.2 ± 1.8 cm |
| Fialka et al[20] | 17 lower limb RSD patients | 42 mo | Mean 0–5 pain-rating (0 = no pain, 5 = intolerable pain) | 2.1 ± 1.1 |
| Galer et al[21] | 31 CRPS patients | 3.3 y | Self-report—has pain changed over time? | Improved: 29%; No change: 42%; Worse: 29% |
| Sharma et al[44] | 888 CRPS patients using RSD Association America Website | 5.5 y | Self-report (retrospective): pain NRS at onset of symptoms and now | Onset estimate: 8.2/10; current intensity: 6.9/10 |

Abbreviations: VAS, visual analog scale; NRS, numerical rating scale.

showed that the proportion of patients experiencing temperature disturbance, limb discoloration, and swelling tended to decrease with increasing CRPS duration,[14,47] but this contrasted with the results of the correlational study, which reported significant positive correlations between rates of these symptoms and CRPS duration.[41] The results of the cross-sectional studies are presented in Table 5.

Each of the 3 cross-sectional studies used different diagnostic criteria for CRPS. One of the studies used Veldman's criteria, which required the presence of at least 4 symptoms/signs of CRPS from a list of 5 possible clinical features, and also required that symptoms/signs worsened with use of the limb and that pain was present in a larger and more distal area of the limb than the original injury or surgery.[47] Schwartzman reported using the Budapest criteria, which are much stricter.[41] The third study used the 1994 IASP criteria for CRPS and also reported on the relatively low number of patients in their cohort who would have met Veldman's criteria (42%) and the Budapest criteria (38%), and that the proportion of patients meeting these different criteria differed depending on the CRPS duration.[14] Thus, it is likely that the patient group captured differs greatly among the 3 cross-sectional studies.

## Discussion

The 18 studies reviewed here document highly variable outcomes of CRPS. The quality assessment revealed a number of significant limitations in the literature, which are discussed below. Bearing this in mind, we first comment on the general findings. The best rates of recovery were shown by the prospective studies, which found that the proportion of patients with pain, swelling, limb discoloration, and temperature disturbance reduced dramatically within 6 to 13 months. However, functional outcomes such as weakness, stiffness, and limited range of motion persisted in a majority of patients for more than 1 year. In contrast, the cross-sectional studies found that rates of pain, sensory symptoms, and motor dysfunction were highest among those with the longest duration of CRPS, which could be interpreted to mean that these symptoms progress and worsen over time. However, because cross-sectional studies cannot capture cases that have resolved, this interpretation would be inappropriate. Instead, these results can only indicate that there is a cohort of CRPS patients with long-term symptoms including pain, sensory disturbance, and impaired limb function.

The retrospective studies also showed that it is not uncommon for patients to have sequelae including pain and limb dysfunction many years after a diagnosis of CRPS. However, the studies' findings were highly disparate, and there were several possible reasons for this. Studies that conducted careful interviews and examinations tended to identify more symptoms than those that conducted chart reviews or posted questionnaires. Studies that measured symptom severity showed that some persisting symptoms are fairly mild. For example, Geertzen et al[22,23] found at follow-up that average pain scores were 1.2/10, and range of motion was 84 to 99% of the unaffected limb. It is unclear whether such mild symptoms would have been categorized as "present" or "absent" in studies that dichotomized patients, and this likely contributed to the variability in results.

There were some common findings across all 3 types of studies included in the review. First, the vasomotor and sudomotor symptoms of CRPS (discoloration, temperature disturbance, altered sweating, and edema) tend to be most common in the early stages of the condition and had the greatest likelihood of resolving. Second, pain and sensory symptoms persisted in some patients but not all, and long-term follow-ups show fairly low rates of mean pain intensity. Third, we found that motor symptoms such as weakness, stiffness, and limited range of motion are the symptoms most likely to persist in the long term.

Overall, this review shows that CRPS has a highly variable course, with some patients experiencing a relatively

**Table 5. Results of Cross-Sectional and Correlational Studies on the Course of CRPS**

| Reference | Group | Pain | Allodynia | Hyperesthesia | Temperature Disturbance | Discoloration | Edema | Altered Sweating | Reduced Strength |
|---|---|---|---|---|---|---|---|---|---|
| De Boer et al[14] | <2 mo | 85% | 31% | 21% | 68% | 62% | 60% | 31% | 33% |
| | 2–6 mo | 87% | 28% | 28% | 58% | 65% | 45% | 18% | 43% |
| | 6–12 mo | 93% | 41% | 39% | 57% | 62% | 49% | 20% | 52% |
| | ≥12 mo | 95% | 45% | 41% | 51% | 48% | 38% | 20% | 67% |
| | Between-group differences | * | * | * | ns | * | * | ns | * |
| Veldman et al[47] | <2 mo | 92% | | 69% | 98% | 97% | 86% | 57% | |
| | 2–6 mo | 88% | | 75% | 91% | 96% | 80% | 56% | |
| | 6–12 mo | 97% | | 72% | 89% | 90% | 61% | 42% | |
| | ≥12 mo | 97% | | 85% | 91% | 84% | 55% | 40% | |
| Schwartzman et al[41] | | NRS correlated with duration (r = 0.6*), SF-McGill did not correlate with duration (ns). | Intensity of touch allodynia correlated with duration (r = 0.5*) | n/a | % with temperature disturbance in each category correlated with duration (r = 0.4*) | % with color disturbance in each category correlated with duration (r = 0.5*) | % with edema in each category correlated with duration (r = 0.5*) | No correlation between % with altered sweating in each category and duration (r = 0.2, ns) | No correlation between % with loss of strength in each category and duration (r = 0.2, ns) |

Abbreviations: ns, not significant; NRS, numerical rating scale; SF-McGill, Short-Form McGill Pain Questionnaire.
*$P < .01$ (statistically significant difference).

brief syndrome (with some sequelae such as weakness and stiffness) whereas others experience lasting pain and symptoms. Interestingly, studies have documented high prevalence rates for CRPS after events such as fracture or surgery (up to 36%),[4,27,37,43] and it might be that having features of CRPS briefly after such events is quite common; nevertheless, many symptoms resolve spontaneously, as was found by Zyluk.[49] However, in severe cases of CRPS, disability may last years,[41] and invasive treatments such as spinal cord stimulation[42] or amputation[9] are performed. This suggests that there is huge variability in the course of CRPS and lends support to the idea the subtypes of CRPS patients might exist. Two studies[11,15] performed cluster analyses and showed that there were 3 subtypes of CRPS patients, including a group with florid symptoms across all categories. De Mos et al[15] showed that this group experienced the poorest outcomes. Clinically, it would be useful to be able to identify those at risk of poor outcomes early in the trajectory of their CRPS, so that treatments can be targeted for these individuals.

Relatively few studies have assessed prognostic factors in CRPS, and a recent systematic review concluded that there were few quality studies and most of the evidence on prognostic factors is contradictory, although they did identify that sensory disturbance and cold skin temperature are associated with poor outcomes.[48] The studies included in this review listed the following prognostic factors associated with poor outcome: longer pain duration,[31,34] more intense pain,[20] delay to receive treatment,[7,19] male sex,[7] female sex,[25] younger age,[7] a more severe fracture, poorer grip strength, and low mobility.[32] The following have been reported to predict good outcome: having a fracture as the initiating event, the absence of sensory symptoms, the presence of swelling,[38] having a warm limb in the early stages, no delay between the injury and CRPS onset,[7] and having a single joint involved.[25] Research in other pain conditions has identified the importance of psychosocial factors for predicting the transition from acute to chronic pain. For example, factors such as depression, expectations, pain-related fear, and avoidance of movement predict poor outcome in low back pain.[13,30] As yet, it appears that little research has assessed whether psychological factors predict the transition from the acute to the chronic stages in CRPS. Although studies that have assessed whether psychosocial factors predict the onset of CRPS after fracture or surgery have produced mixed results,[5,16,27,29,36] future researchers may wish to assess the role of such factors in CRPS recovery. Another factor that has been shown to predict CRPS following fracture and CRPS recurrence following surgery is activity of the sympathetic nervous system.[1,40] It may also be valuable to assess whether sympathetic nervous system activity predicts the course or outcome of the condition.

## Limitations

This review highlighted several limitations in the literature. At the most, 3 studies agreed on a diagnostic criteria,[14,15,21] and many studies either followed their own criteria or did not describe them. Although considerable efforts have been made by researchers to develop a common name (ie, "complex regional pain syndrome") and diagnostic criteria (eg, the 1994 IASP criteria and the "new IASP" or "Budapest criteria"), even some studies published since this time have not used these terms or criteria. The differences in the criteria used, not to mention the way such criteria are interpreted, likely contributed to the variation in study results. For example, many studies assessing "algodystrophy" reported more favorable outcomes than those assessing RSD or CRPS. As the diagnostic criteria for algodystrophy often required fewer signs and symptoms or did not require the presence of pain,[3,32] this suggests that those with a more limited set of symptoms at the outset might make a fuller recovery. A recently published study that used the stricter Budapest diagnostic criteria found that of those with CRPS-1 after fracture, none were symptom-free at 12 months.[6] This study did not meet the inclusion criteria for this systematic review and only briefly mentions its 12-month outcome data, but it does contrast strongly with the positive data reported by the 3 prospective studies included in this review, which all used "looser" diagnostic criteria. It is important that future research use a common diagnostic criteria for CRPS, and that researchers adopt a consistent set of measurement tools for assessing the signs and symptoms of CRPS.

Another major finding of this review was that the literature as a whole suffers from several sources of bias, and higher-quality studies are needed to understand the outcomes of CRPS. First, few studies included samples that could be considered "representative" of the CRPS population as a whole, and many did not adequately describe their recruitment processes. Future studies should seek to recruit from a wide variety of settings to include a broad range of CRPS patients and should state whether samples are consecutive patients or selected in another manner. Even when such processes were described, the samples recruited were often unrepresentative. For example, 2 studies recruited only patients who had previously responded well to treatment,[39,50] which would be expected to bias results, and another study excluded severe cases who had to withdraw for treatment.[49] Second, several studies suffered from high attrition or low response rates. This is particularly problematic where there is a difference between those who do and those who do not participate. It is possible that those who have recovered would be less inclined to complete a follow-up than those who are still symptomatic and therefore motivated to support research into their condition. Future studies should try to reduce barriers to participation to ensure adequate participant recruitment and retention. The other limitations of the literature included differences in measurement tools used and lack of relevant statistical testing. Also, the review process was limited in that we used just 1 reviewer to search the literature, with a second reviewer assessing suitability for inclusion when there was any doubt.

In conclusion, we found evidence from prospective studies that the rates of symptoms of CRPS reduce significantly over the first 6 to 13 months, but the results from retrospective studies indicate that the outcomes of CRPS are highly variable, and the cross-sectional studies demonstrate that there are a group of patients for whom pain and sensory symptoms persist in the long term. Overall, the quality of the evidence was poor, and the data should be interpreted with caution. At present, there are few studies that have assessed prognostic factors in CRPS, and such studies could help to identify those at risk of poor outcomes as well as help researchers identify possible target variables for treatment.

## Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpain.2014.01.500.

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Critical Review

# The Effects of Graded Motor Imagery and Its Components on Chronic Pain: A Systematic Review and Meta-Analysis

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**Abstract:** **Graded motor imagery (GMI) is becoming increasingly used in the treatment of chronic pain conditions. The objective of this systematic review was to synthesize all evidence concerning the effects of GMI and its constituent components on chronic pain. Systematic searches were conducted in 10 electronic databases. All randomized controlled trials (RCTs) of GMI, left/right judgment training, motor imagery, and mirror therapy used as a treatment for chronic pain were included. Methodological quality was assessed using the Cochrane risk of bias tool. Six RCTs met our inclusion criteria, and the methodological quality was generally low. No effect was seen for left/right judgment training, and conflicting results were found for motor imagery used as stand-alone techniques, but positive effects were observed for both mirror therapy and GMI. A meta-analysis of GMI versus usual physiotherapy care favored GMI in reducing pain (2 studies, n = 63; effect size, 1.06 [95% confidence interval, .41, 1.71]; heterogeneity, $I^2$ = 15%). Our results suggest that GMI and mirror therapy alone may be effective, although this conclusion is based on limited evidence. Further rigorous studies are needed to investigate the effects of GMI and its components on a wider chronic pain population.**

***Perspective:*** ***This systematic review synthesizes the evidence for GMI and its constituent components on chronic pain. This review may assist clinicians in making evidence-based decisions on managing patients with chronic pain conditions.***



***Key words:*** *Graded motor imagery, GMI, mirror therapy, motor imagery, left/right judgments, chronic pain, systematic review.*

Rapid advances in our understanding of the role of the brain in chronic pain have seen the development of treatments for chronic pain that directly target cortical reorganization.[30,44] The first of these treatments was developed in response to remarkable findings in amputees with phantom limb pain (PLP), which showed that pain was associated with reorganization of the primary sensory cortex contralateral to the amputated limb. The normal representation of the amputated hand had been invaded by the representation of the lip.[11] This cortical reorganization has also been demonstrated for chronic low back pain, in which representation of the painful side of the back was enlarged and shifted medially as compared with representation in healthy controls.[10] That primary sensory cortex receptive fields can be modified by tactile stimuli with a behavioral relevance (for example, eating or braille) is now well accepted.[12] Flor et al aimed to exploit this plasticity in amputees with PLP by 2 weeks of sensory discrimination training, in which participants discriminated between stimuli of different frequencies and at different locations on their stump.[9,13] Their randomized controlled trial (RCT)

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showed normalization of cortical organization and a clinically important reduction of pain. This process, from discovery of altered sensory cortex organization to targeted sensory discrimination training for clinical benefit, has been repeated in complex regional pain syndrome (CRPS).[15,17,32,34]

As well as physiological evidence of disrupted somatotopic representation in chronic pain, there is also behavioral evidence of disrupted spatial representation—disrupted processing of stimuli delivered to healthy body parts held in the affected space,[31] the abnormality of the perceived size of the painful body part,[19,20,27,29] and poor voluntary movement and motor imagery performance.[1,5,6,25,28,37-39] One treatment that was developed to directly target these cortical disruptions is graded motor imagery (GMI), a 3-stage treatment that aims to gradually engage cortical motor networks without triggering the protective response of pain. This treatment gets its theoretical framework from the principle established in the physical therapies, of graded increase in activity. This principle is adapted in GMI to cater to both the overly sensitive nociception system and the disrupted cortical mechanisms mentioned above. GMI was developed initially for an application to chronic limb pain or PLP but has been extended clinically to chronic back pain, where a component of GMI has been used for some time.[43]

The first stage of the GMI program is left/right judgments of photographs that depict the affected area. For limb pain, this involves viewing an image of a limb and judging whether that image depicts a left or a right limb. Functional brain imaging studies in healthy subjects have shown that this task selectively activates the premotor cortex without activating primary motor areas.[35,41,45] The second stage, motor imagery, requires imagined movement of the area. These imagined movements have been demonstrated to activate motor cortical areas similar to those activated in the actual execution of that movement.[8] For the final stage, mirror therapy, patients place their affected limb inside a mirror box and watch movements of their nonaffected limb in the mirror, giving the illusion of a moving, but pain-free, affected limb. This task activates the motor cortex and also provides a strong visual input to the cortex that the movements are occurring normally and without impediment.[18] While functional brain imaging studies have supported the proposed cortical activation for each stage of GMI in healthy subjects, no studies have investigated cortical activation of GMI stages in pain patients. These imaging studies nonetheless provide support for the possibility that similar sequential activation of cortical areas within each stage of the GMI program could occur in pain patients.

Both GMI and its components have been used in the clinical setting to treat chronic pain conditions such as CRPS, PLP, and back pain. However, an issue that remains to be addressed is whether the evidence supports or negates the use of GMI or its components in the treatment of a wider chronic pain population. A recent systematic review evaluating interventions for treating CRPS supported the use of GMI.[7] However, a recent clinical audit of CRPS multimodal management including but not limited to GMI clearly showed no benefit of treatment.[14] These conflicting findings, and that GMI has not, to our knowledge, been empirically evaluated in a wider chronic pain population, highlight the importance of systematic evaluation of the entire literature concerning GMI and its components. The aim of this review and meta-analysis was to synthesize all available literature regarding the efficacy of GMI programs, or any of the 3 constituent components, on chronic pain. The results of this systematic review will enable clinicians to make evidence-based decisions on the use of GMI with chronic pain patients.

## Methods

### Data Sources

For this review, several health-based databases were searched from their relative inception through January 2012. The electronic search was performed using the following databases: Medline (via OvidSP), Embase (via Ovid SP), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, Academic Search Premier, Web of Science, Allied and Complementary Medicine, PubMed, the Cochrane Collaboration, and the Physiotherapy Evidence Database (PEDro). A sensitive search was completed using a combination of key words and relevant subject headings for GMI, its components, and chronic pain. The relevant subject headings were determined specific to each database. The complete Medline search strategy is provided in Appendix A. Searches were limited to English language and humans only. To attempt to identify grey literature (specifically nonindexed published trials, conference abstracts, and book chapters), experts were contacted and asked to contribute any materials not identified by database search. The references of all relevant articles were also hand-searched for further articles. We did not search clinical trials registers for unpublished studies.

### Study Selection

Four reviewers (K.J.B., A.T., M.J.C., and H.B.L.) were paired and each pair independently screened the titles and abstracts of half of the potential studies—thus, all papers were screened by 2 people. Results of the screening process were compared within pairs. In this process, studies were retained if they evaluated GMI or at least 1 component of GMI. Following initial screening, the full texts of potentially relevant studies were retrieved and reviewed independently by 2 reviewers (K.J.B. and A.T.). Studies were retained if they met the following criteria: human adult subjects (>18 years of age); clinically validated pain measure used; RCT; and subjects all had a chronic pain condition lasting longer than 3 months. No restrictions were placed on the comparison group used (ie, placebo, wait list control, or other active treatment). Any discrepancies were resolved through

discussion, or if necessary, through consultation with a third independent reviewer.

### Outcome Measures

Pain intensity ratings were the primary outcome of interest for this review. This included self-reported measures such as the McGill Pain Questionnaire, a visual analog scale (VAS), a numerical rating scale (NRS), a neuropathic pain scale, or a categorical rating of pain (such as mild, moderate, severe). A rating of pain using 1 of these measures was required immediately preintervention and immediately postintervention. Follow-up pain ratings were a secondary outcome of interest for this review.

### Risk of Bias Assessment and Data Extraction

Two reviewers (K.J.B. and A.T.) independently assessed the risk of bias of included studies using the Cochrane Collaboration's risk of bias tool. For the category of "other" sources of bias, the reviewers were particularly concerned with similarity of pain scores at baseline, as this is recommended by other quality assessment tools such as PEDro.[36] In the "other" source of bias category we also included evaluation of sample sizes (ie, less than 50 participants per treatment arm considered a high risk of bias).[22] These items were added as we anticipated that studies identified were likely to be small and, as such, these factors were more likely to represent a significant source of bias.

For all eligible studies, data extraction was completed independently by 2 reviewers using a customized data extraction form. This data extraction form was piloted before use. Data extracted included participant characteristics such as age, gender, pain condition, and length of pain; the outcome measure used; the control and treatment intervention choices and their length (minutes per each session), frequency (sessions per day/week), and total duration (weeks of intervention); baseline and immediate postintervention pain scores; and follow-up pain scores if provided. Any disagreements regarding risk of bias or data extraction were resolved through discussion or, if necessary, through consultation with a third independent reviewer. If necessary, authors were contacted to provide further information.

### Data Synthesis

We sought to pool data for pain relief from studies where adequate data were available. We planned a priori to pool data from studies comparing GMI programs with usual care or no treatment, and to perform separate meta-analyses for studies that investigated similar individual components of GMI.

Data were pooled using Review Manager 5 software[4] using a random effects inverse-variance approach. A random effects model was chosen as it was anticipated and subsequently confirmed that there would be differences in the populations and interventions studied that would suggest that the effects might differ somewhat across studies. Using the postintervention means of each group and the pooled postintervention standard deviations of pain scores, the standardized mean difference (Hedge's g) was calculated for each study to allow comparison between studies. Effect sizes were interpreted according to Cohen[40] ($\leq$.2 small, .5 moderate, $\geq$.8 large). We used the chi-square test to detect statistically significant heterogeneity and the $I^2$ statistic to estimate the amount of heterogeneity. When heterogeneity was high, we did not pool the outcomes. Further, we considered it inappropriate to pool data from studies that used full GMI programs with those that used individual components of GMI because it does not follow that the different types of interventions should be estimating the same effect size. We therefore planned separate meta-analyses for these types of studies considering both short-term (immediately postintervention or the closest measure presented to that point) and follow-up (>4 weeks postintervention) time points. We undertook a sensitivity analysis to investigate the influence of using a random effects model by reanalyzing the data using a fixed effects model.

In studies that evaluated a comprehensive GMI program, the effect sizes for the first component (ie, left/right judgments stage) were also calculated using postintervention scores when individual participant data were present. It was decided, a priori, that effect sizes would not be calculated for the second or third GMI treatment components (motor imagery and mirror therapy, respectively) because in these latter components, the methodological tenets of the RCT study design do not hold. Specifically, participants are not re-randomized following each component stage, so there are preintervention pain differences between groups in the latter stages. That the responses of the latter components were due to carryover effects or continuing improvement from the previous treatment could therefore not be ruled out. We did not establish any a priori sensitivity or subgroup analyses because we anticipated identifying inadequate data to support this process.

## Results

### Study Description

The initial literature search yielded 6,160 records following the removal of duplicates. Six thousand fifteen studies were excluded in the initial screening of title and abstracts. One hundred thirty-nine studies were then excluded following review of the full text. The most prevalent reason for exclusion was that articles did not include primary research data; primarily, these were reviews, conference abstracts, and book chapters, all presented in a narrative form. Other reasons for exclusion were studies that recruited sample populations without chronic pain or did not evaluate pain outcome measures, were not of RCT design, were non-English studies, and that recruited children. The screening and review process is shown in a PRISMA flow-diagram in Fig 1. Key data of the remaining 6 RCTs included are summarized in Table 1.

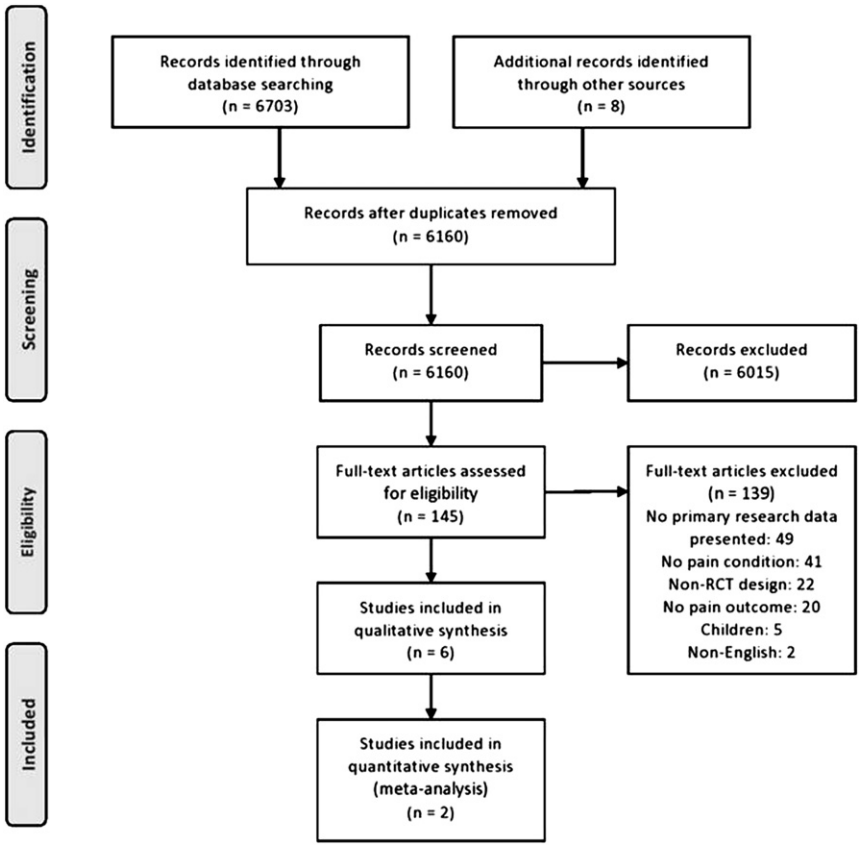


**Figure 1.** The PRISMA flow-diagram describing the screening and review process.

## Characteristics of Included Studies

Three studies evaluated the effects of GMI on chronic pain.[23,24,26] Two of these studies compared a 6-week program of GMI to usual physiotherapy care.[23,24] The third study compared an ordered program of GMI to an unordered program of GMI.[26] Participants were instructed to spend 10 minutes of each waking hour on the intervention. All studies collected follow-up data: 1 study at 6 weeks postintervention,[24] 1 study at 12 weeks postintervention,[26] and 1 study at 6 months postintervention.[23] These studies used varying methods of collecting participant pain scores. The author of each study was contacted, and NRS data for each participant's pain level was provided. These NRS data were used in the analyses. Only 1 study[23] provided data on adherence to the treatment program. This study found that both GMI and usual care groups had adherence rates of 75%.

Three other studies evaluated individual components of GMI.[2,3,21] No studies primarily evaluated left/right judgments; however, 2 studies[23,24] evaluating GMI provided sufficient data to enable calculation of effect sizes for the 2 weeks of left/right judgment training. Two studies[2,3] evaluated the effects of motor imagery. Three studies[2,3,21] evaluated the effects of mirror therapy on chronic pain. The time spent on the intervention differed between studies. In 1 study, participants completed 5 1-hour sessions of mirror therapy a week.[21] In the second study, participants spent 30 minutes per day doing either mirror therapy or motor imagery, depending on their group allocation.[2] In the third study, participants spent 15 minutes per day doing either mirror therapy or motor imagery, depending on their group allocation.[3] Follow-up data from these studies were collected at either 4 weeks[2,3] or 6 months.[21] All 3 studies used 100-mm VAS data to report participants' pain levels.

## Characteristics of Included Populations

The participants in each study had experienced pain for greater than 3 months. The chronic pain conditions included CRPS,[2,23,24,26] PLP,[3,23] and pain following stroke.[21] Studies including children were excluded from this review. The mean age in each study ranged from 32 to 57 years. Overall, there were more females (n = 90) than males (n = 81) in the included studies.

## Risk of Bias of Included Studies

The results of the risk of bias assessment are shown in Table 2 (see also the Supplementary graph for a representation of risk of bias results). The study appraised to be at lowest risk of bias was that by Moseley,[23] which met every criterion except the blinding of therapists and participants and the "other" category, for its small sample size. None of the 6 included RCTs met the blinding of therapists and participants criterion. In therapy trials such as these, direct participant-therapist involvement means that blinding is not feasible; hence, all 6 RCTs had nonblinded therapists and participants. While

**Table 1. Study Characteristics Data for Randomized Controlled Trials of Graded Motor Imagery or Its Components for Chronic Pain**

| Study | Participants | Condition | Intervention | Outcome Measures |
|---|---|---|---|---|
| Studies evaluating the components of GMI | | | | |
| Michielsen et al[21] | n = 40<br>Mean age = 57*<br>Gender = 50% male | Chronic pain following stroke (mean time since stroke 3.9 years) | Exp: 6-week bilateral hand movement with mirror therapy program. Practiced 5x/week, 1 hour per session.<br>Con: 6-week bilateral hand movements. Practiced 5x/week, 1 hour per session. | 100-mm VAS†<br>Follow-up: 6 months |
| Cacchio et al[2] | n = 24<br>Median age = 62 (53 to 71)‡<br>Gender = 46% male | CRPS | Exp: 4-week mirror therapy program, 30 min daily.<br>Con: 4-week covered mirror program, 30 min daily.<br>Exp2: 4 weeks of motor imagery, 30 min daily. | 100-mm VAS<br>Follow-up: 4 weeks |
| Chan et al[3] | n = 22<br>Mean age = 29 ± 8.8§<br>Gender = 100% male | PLP | Exp: 4-week mirror therapy program, 15 min daily.<br>Con: 4-week covered mirror program, 15 min daily.<br>Exp2: 4 weeks of motor imagery, 15 min daily. | 100-mm VAS†<br>Follow-up: 4 weeks |
| Studies evaluating GMI | | | | |
| Moseley[23]¶ | n = 50<br>Mean age = 41 ± 16§<br>Gender = 36% male | CRPS, PLP following amputation or brachial plexus avulsion | Exp: laterality retraining, motor imagery, mirror therapy. 2 weeks each component, 10 min for each waking hour.<br>Con: usual physiotherapy/other treatment. | MPQ, NRS†<br>Follow-up: 6 months |
| Moseley[26] | n = 20<br>Mean age = 32 ± 11§<br>Gender = 30% male | CRPS type 1 | Exp: sequential GMI. 2 weeks each component, 10 min for each waking hour.<br>Con: nonsequential GMI: MI, left/right, MI. 2 weeks each component, 10 min for each waking hour.<br>Con2: nonsequential GMI: left/right, mirror, left/right. 2 weeks each component, 10 min for each waking hour. | NPS, NRS†<br>Follow-up: 12 weeks |
| Moseley[26]¶ | n = 13<br>Mean age = 57 ± 19§<br>Gender = 30% male | CRPS type 1 | Exp: sequential GMI. 2 weeks each component, 10 to 15 min for each waking hour.<br>Con: usual physiotherapy/other treatment. | NPS, NRS†<br>Follow-up: 6 weeks |

Abbreviations: Exp, experimental group; Exp2, secondary control group; Con, control group; Con2, secondary control group; n, number recruited (prior to drop-out or loss to follow-up); MPQ, McGill Pain Questionnaire; NPS, neuropathic pain scale; MI, motor imagery; left/right, left/right judgments; mirror, mirror therapy.
*Range or standard deviation not provided.
†Data used to calculate effect sizes.
‡Range.
§Standard deviation.
¶Due to the presence of individual participant postintervention data, the left/right judgments component of treatment was also examined.

blinding in these trials is not feasible, it is still an inherent source of bias that must be highlighted for every study. No study was free of additional bias, as all studies had sample sizes less than 50. Michielsen et al[21] presented additional bias in that they failed to report any baseline similarities or differences between groups on pain scores. Two other studies also failed to report whether groups had similar baseline pain levels.[2,3] The lack of this information has implications for the validity of the observed effect sizes as it is uncertain whether differences found between groups may have been influenced by baseline group differences. These same studies also failed to provide information regarding whether the person who determined participant eligibility was blinded to treatment allocation. Given the lack of participant/therapist blinding due to nature of the interventions within the studies, all studies were considered to have some inherent bias.

## Outcomes

Four authors were contacted to gain additional information required to calculate the effect size of their intervention.[2,3,21,23,24,26] One author could not be contacted, so the effect size for this study could not be calculated.[2] The effect sizes for the remaining studies are presented in Table 3.

## GMI Program

Three studies evaluated the effects of a 6-week GMI program on chronic pain, with all finding that GMI reduced pain when compared to usual physiotherapy care[23,24] and unordered GMI.[26] The 2 studies comparing GMI to

**Table 2. Risk of Bias Assessment of Included Randomized Controlled Trials**

| | Random Allocation | Concealed Allocation | Blinding of Participants/ Therapists | Outcome Assessors | Incomplete Data | No Selective Outcome Reporting | Free of Additional Bias |
|---|---|---|---|---|---|---|---|
| Michielsen et al[21] | Y | Y | N | Y | Y | Y | N |
| Cacchio et al[2] | U | U | N | N | U | Y | N |
| Chan et al[3] | U | U | N | N | U | Y | N |
| Moseley[23] | Y | Y | N | Y | Y | Y | N |
| Moseley[26] | Y | U | N | Y | Y | Y | N |
| Moseley[24] | Y | U | N | Y | Y | N | N |

Abbreviations: Y, yes, low risk of bias; N, no, high risk of bias; U, unclear, uncertain risk of bias.

usual physiotherapy care both found large effect sizes (1.70 [95% confidence interval (CI), .36, 3.04][24] and .89 [95% CI, .31, 1.47][23]). In the study that compared a course of GMI to an unordered course of GMI,[26] moderate-to-large effects in favor of the ordered GMI were found (.73 [95% CI, −.41, 1.87] and .99 [95% CI, −.19, 2.17]).

The immediate postintervention results of the 2 studies comparing GMI with usual care were pooled.[23,24] The results of the study evaluating GMI versus unordered GMI[26] were not included in the meta-analysis because the control group intervention had pronounced differences; this heterogeneity meant that pooling of these data was not appropriate. The heterogeneity of the pooled studies was low ($I^2$ = 15%) and produced a large pooled effect size (1.06 [95% CI, .41, 1.71]; Fig 2). While the statistical heterogeneity of the studies was low, it must be noted that the chronic pain population in each study differed slightly; 1 included only CRPS participants[24] and the other a mix of CRPS, PLP, and pain after brachial plexus avulsion.[23] Sensitivity analysis using fixed effects, rather than random effects, meta-analysis had no substantive impact on our findings ($I^2$ = 0%; effect size, .97 [95% CI, .52, 1.42]; test for overall effect, $P < .0001$).

Follow-up data also suggest an effect of GMI further reducing pain, with large effect sizes reported at 6 months for GMI when compared to usual physiotherapy care (1.59 [95% CI, .28, 2.90][24] and 1.68 [95% CI, 1.02, 2.33]),[23] and also at 12 weeks for GMI when compared to an unordered GMI program (1.35 [95% CI, .09, 2.60] and 1.31 [95% CI, .06, 2.55]).[26] Pooling of these effect estimates was not considered appropriate as the follow-up in each study was conducted at a markedly different time point.

## *Left/Right Judgments*

No studies were found that evaluated left/right judgments as the primary intervention, although 2 studies

**Table 3. Effect Sizes (95% CI) for GMI and Its Components on Chronic Pain When Compared to Control Groups**

| | | Number of Participants | | Postintervention Pain (Mean ± SD) | | |
|---|---|---|---|---|---|---|
| Study | Control | Control | Intervention | Control | Intervention | Effect Size (95% CI) |
| Laterality judgment task | | | | | | |
| Moseley[23] | Usual care | 25 | 25 | 54 ± 13 | 48 ± 14 | .44 (−.12, 1.00) |
| Moseley[24] | Usual care | 6 | 7 | 61 ± 10 | 57 ± 15 | .29 (−.81, 1.39) |
| MI | | | | | | |
| Cacchio et al[2] | Covered mirror therapy | 8 | 8 | — | — | —* |
| Chan et al[3] | Covered mirror therapy | 6 | 6 | 34 ± 22 | 58 ± 20 | −1.05 (−2.30, .19) |
| Mirror therapy | | | | | | |
| Michielsen et al[21] | Bilateral hand movements | 19 | 17 | 9.2 ± 14 | 8.8 ± 10.8 | .03 (−.62, .69) |
| Cacchio et al[2] | Covered mirror therapy | 8 | 8 | — | — | —* |
| | MI | 8 | 8 | — | — | —* |
| Chan et al[3] | Covered mirror therapy | 6 | 6 | 34 ± 22 | 17 ± 21 | .73 (−.46, 1.92) |
| | MI | 6 | 6 | 58 ± 20 | 17 ± 21 | 1.85 (.40, 3.29)† |
| GMI | | | | | | |
| Moseley[23] | Usual care | 25 | 25 | 47 ± 16 | 33 ± 15 | .89 (.31 to 1.47)† |
| Moseley[26] | MI, left/right, MI | 6 | 7 | 40 ± 10 | 33 ± 8 | .73 (−.41, 1.87) |
| | Left/right, mirror, left/right | 6 | 7 | 42 ± 9 | 33 ± 8 | .99 (−.19 to 2.17) |
| Moseley[24] | Usual care | 6 | 7 | 58 ± 12 | 38 ± 10 | 1.70 (.36, 3.04)† |

Abbreviations: MI, motor imagery; left/right, left/right judgments; mirror, mirror therapy.

NOTE. The effect sizes are standardized mean differences, calculated using Hedge's g (ie, the difference in postintervention pain scores between control and intervention groups divided by the pooled standard deviation of the 2 groups, each weighted for sample size). Effect sizes are grouped according to intervention type. Positive effect sizes indicate a lower pain score in the intervention group, favoring the intervention group. Negative effect sizes indicate a lower pain score in the control group, favoring the control group.

*Did not provide postintervention pain data for control or intervention groups.

†$P < .05$; For all Moseley studies, pain scores and effect estimates are for NRS results.

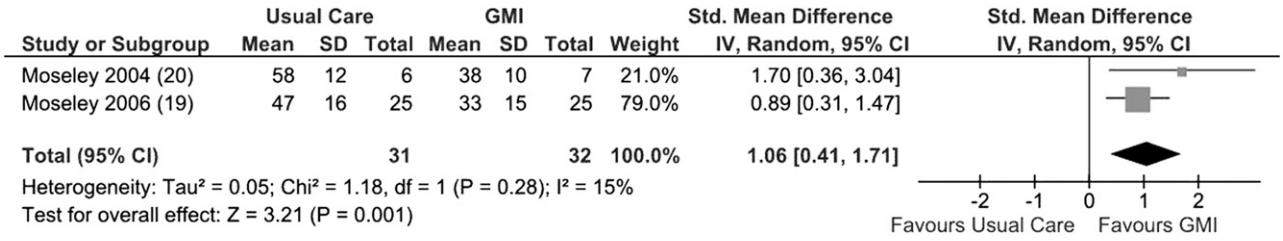


**Figure 2.** The pooled effect estimate for GMI versus usual care. Abbreviations: SD, standard deviation; CI, confidence interval.

investigated the effects of left/right judgments as part of a GMI program on chronic pain.[23,24] Neither study found statistically significant effect estimates for left/right judgments reducing pain when compared to usual care. However, the effect estimates produced were positive, albeit small (.29 [95% CI, −.81, 1.39][24] and .44 [95% CI, −.12, 1.00][23]). The heterogeneity of the pooled studies was low ($I^2$ = 0%) and produced a similarly small effect estimate (.41 [95% CI, −.09, .91]; Fig 3). Sensitivity analysis using fixed effects, rather than random effects, meta-analysis again had no substantive impact on our findings ($I^2$ = 0%; effect size, .41 [95% CI, −.09, .91]; test for overall effect, $P$ = .11).

### Motor Imagery

None of the included studies had a primary aim of evaluating the effects of motor imagery on chronic pain. However, in 2 studies, motor imagery was used as a secondary control group[2,3] and was compared to covered mirror therapy (in which the participant is instructed to look at a mirror that is covered with a cloth so as to offer no reflection; controlling for attention). These studies found contrasting results. Chan et al[3] found covered mirror therapy to be much more effective at reducing pain when compared to motor imagery, with a large effect size found (−1.05 [95% CI, −2.30, .19]). Interestingly, participants receiving motor imagery treatment had increased pain levels (compared to baseline pain). Similar findings were reported by Cacchio et al,[2] in which 6 out of 8 participants experienced increased pain levels following 4 weeks of motor imagery. However, Cacchio et al[2] found no difference between motor imagery and covered mirror therapy (5 of 8 participants had increased pain in covered mirror therapy group). All pain assessments were immediately postintervention; no short- or long-term follow-up data were available. Both studies had small sample sizes and had a high risk of bias.

### Mirror Therapy

A total of 3 studies evaluated mirror therapy as a standalone treatment in chronic pain; in each study, mirror therapy was the primary treatment evaluated.[2,3,21] All 3 studies found positive effects of mirror therapy in reducing pain, despite using different control groups. The effect sizes ranged from trivial (.03 [95% CI, −.62, .69],[21] bilateral hand movement control group) to moderate (.73 [95% CI, −.46, 1.92],[3] covered mirror control group) to large (1.85 [95% CI, .40, 3.29],[3] motor imagery control group). Notably, this final effect size was the only statistically significant finding in the mirror therapy analyses. This finding was further supported by Cacchio et al,[2] who reported 7 of 8 participants in the mirror therapy group experiencing decreased pain levels (compared to only 1 of 8 participants in the covered mirror group and only 2 of 8 participants in the motor imagery group having decreased pain levels).

The pooling of studies of mirror therapy demonstrated high levels of heterogeneity ($I^2$ = 63%) but no effect ($P$ = .07). Visual inspection of the forest plot showed that the 1 study that utilized a different comparison condition[3] (motor imagery as opposed to covered mirror therapy) was the most likely source of this variance. Post hoc sensitivity analysis removing this study from the analysis reduced this heterogeneity substantially ($I^2$ = 2%) and continued to demonstrate no effect ($P$ = .51). Sensitivity analysis using fixed effects, rather than random effects, meta-analysis again had no substantive impact on our findings ($I^2$ = 63%; effect size, .42 [95% CI, −.011, .95]; test for overall effect, $P$ = .12).

Only 1 study presented follow-up data,[21] reporting a small, nonsignificant effect size (.34 [95% CI, −.29, .96]) of mirror therapy compared to bilateral hand movements in patients with pain following stroke at 6 months follow-up. All 3 studies were considered to have a high risk of bias.

## Discussion

This is the first review to systematically evaluate the effect of GMI or its components on pain outcomes in people with chronic pain. The limited number of small RCTs available have found mixed results for the effects of GMI or its components on chronic pain. Of the six RCTs

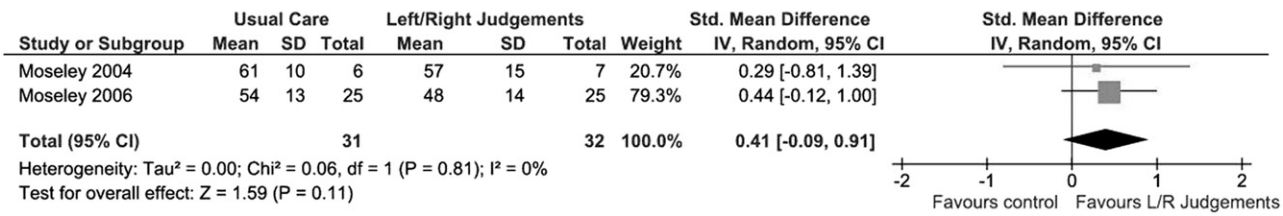


**Figure 3.** The pooled effect estimate for left/right judgments versus usual care. Abbreviation: L/R, left/right.

identified, all contained some inherent bias. A key finding of this review was that the majority of studies evaluated the effect of GMI or its components in CRPS or PLP, so it is unclear how GMI might relate to other chronic pain conditions. We will first consider our findings with respect to individual components of GMI and then consider our findings with respect to full GMI programs.

## *Effect of Individual GMI Components on Pain*

### Left/Right Judgments

Left/right judgments as a sole treatment appear to have no effect on chronic pain.[23,24] That all effect sizes were positive raises the possibility that even the pooled data were underpowered to detect an effect, but one might conclude that such a small effect is of little clinical consequence.

Because left/right judgments have never been used as a stand-alone treatment for chronic pain, there have been no studies that evaluate only left/right judgments as a treatment for chronic pain. Because only data from the first stage of a GMI program can currently be used to evaluate the effect of left/right judgments, there are no data available on the long-term effect of this treatment. While left/right judgments alone may not produce statistically significant effects, they are an integral part of the sequential GMI program that our results suggest may be effective. Nonetheless, the clinical importance for left/right judgments per se remains to be shown.

### Motor Imagery

Motor imagery appears less effective at treating chronic pain than covered mirror therapy.[2,3] Covered mirror therapy was utilized in these studies as an inactive control condition. That 2 studies found an increase in pain relative to baseline following motor imagery and 1 observed greater improvements in an inactive control group suggests that motor imagery might have the potential to increase pain intensity. These findings are consistent with those of a separate pre-/posttreatment trial not included in this review, in which motor imagery increased pain and swelling in those with chronic arm pain[33] and speaks against the use of motor imagery alone as a treatment for chronic pain.

### Mirror Therapy

Mirror therapy is arguably the most studied component of GMI in terms of its effects on pain; however, much of the available literature concerns case studies, which were excluded from this review. The results of the included studies were consistently positive in favor of mirror therapy reducing pain[2,3,21] although there is wide variance in the reported effect sizes.

This variance may reflect differences between studies in the patient group and the choice of control treatment. For example, Michielsen et al[21] recruited chronic pain patients with very low baseline pain scores, which are atypical of chronic pain populations and provide minimal room for improvement, creating the possibility of a floor effect. In contrast, the baseline pain scores for participants in the Chan et al[3] study were high, providing the opportunity for greater pain reductions and therefore a larger effect size. Both the Chan et al[3] and Cacchio et al[2] studies suggest that mirror therapy is substantially more effective than motor imagery. However, motor imagery appeared to increase participants' pain levels, so the difference might reflect both the worsening in the control motor imagery group and the improvement in the mirror therapy group.

One important consideration when interpreting the effect of mirror therapy relative to a covered mirror control condition is the possible impact of variable placebo effects. That is, covering the mirror might imply to the patient that the mirror is the powerful component of treatment and, as such, the covered mirror condition might not be perceived as credible by the patient. As stated, blinding of therapists and participants in therapy interventions such as mirror therapy is nearly impossible. Through matching the frequency and duration of therapy sessions for both the covered and active mirror groups, all studies achieved structural equivalence, which is particularly important in situations where indistinguishable placebo controls are not possible.[16] While covered mirror therapy as a control may not be ideal, it is a pragmatic control.

## *Effect of Full GMI Programs on Pain*

Our results suggest that a GMI program likely has moderate effects when compared to unordered GMI[26] and large effects when compared to usual physiotherapy care.[23,24] Both of the 2 identified studies evaluating GMI versus usual physiotherapy found a large effect size[23,24] and clearly support the efficacy of GMI, at least as delivered within 1 clinical center.

Recently published clinical audit data appear to contradict the GMI findings of this review. Prospective audit data from 32 patients treated at 2 interdisciplinary centers showed no reduction in pain after a multimodal approach that included GMI[14]; indeed, some patients (30% in 1 center and 50% in the other) actually reported an increase in their pain intensity following treatment. The authors proposed that variations in GMI protocol from other studies and logistic constraints may have led to the poor result. Nonetheless, this study, while less robust than an RCT, highlights that independent replication of the results of Moseley[24] and Moseley[23] in controlled trials remains a research priority.

That GMI produced moderate effects when compared to an unordered program of GMI[26] is interesting. The order of GMI components seems to be important, which is consistent with its proposed mechanism.[42] Moreover, that there is such an effect relative to an unordered treatment control group[23,24] suggests against the possibility that the effects of GMI are largely due to a placebo response. That is, unordered GMI might be a more appropriate placebo control treatment in future studies because it would capture much of the novelty of GMI, but it appears to have little effect. That this finding arises from a single small trial indicates that it also requires independent replication.

Given the limited data available, it is difficult to draw firm conclusions, but these data and those relating to the ordering of GMI components suggest that the gradual and progressive nature of GMI may be clinically important. Motor imagery particularly demands attention. Not only was no significant benefit observed with motor imagery, but unlike with left/right judgments, there was no suggestion in the data of a trend toward pain relief with this intervention and some evidence to suggest a worsening of pain. This leads to the inevitable question of whether GMI might be more effective without a motor imagery stage. To our knowledge, no study has currently investigated this.

The majority of the evidence pertains to patients with CRPS, and we identified little evidence pertaining to the efficacy of GMI for other chronic pain conditions. Caution is advised when extrapolating these findings to the broader chronic pain population.

### *Limitations*

Non-English studies were not included due to lack of translation resources, and we did not search clinical trials registers for unpublished studies. However, experts in the area of GMI/chronic pain were consulted regarding any missing relevant publications or active research groups and did not identify any relevant contributions, so we would suggest that the chance of missing a study would seem low. The number of RCTs included was small, and the majority had a high risk of bias. The limited number of studies published in this area also raises the possibility of publication bias.

In terms of the evidence of the effectiveness of full GMI programs for reducing chronic pain, perhaps the strongest limitation is that all of the included trials were completed by 1 research group with which we ourselves are affiliated.[23,24,26] To increase confidence in our findings, the need for further trials of GMI by independent research groups cannot be overstated. There was significant heterogeneity between the included study populations; the type and duration of chronic pain varied, and studies used a range of methods for sourcing and recruiting participants. Lastly, there were very few long-term follow-ups (ie, all follow-ups were 6 months or earlier), which suggests that the effectiveness of these treatments in the longer term remains unknown.

In conclusion, while the results of this systematic review suggest that the effectiveness of GMI and its components is encouraging in CRPS and PLP, no evidence exists for these treatments in a wider chronic pain population. It is critical to acknowledge that more work is required—the theoretical framework underlying these treatments suggests the value of additional trials in a wider chronic pain population. It is difficult to be certain of the findings because there are very few studies of mixed risk of bias available. Differing methodologies and samples within each study significantly limits the generalizability of these findings to people with CRPS or PLP, although there seems to be good reason to extend this line of investigation into different chronic pain populations.

## Supplementary Material

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpain.2012.09.007.

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# Appendix A

## Full Medline search strategy (23/3/11)

1. exp "Imagery (Psychotherapy)"/
2. graded motor imagery.mp.
3. exp Physical Therapy Modalities/
4. physiotherapy.mp.
5. physical therapy.mp.
6. device therapy.mp.
7. Occupational Therapy/
8. Rehabilitation/
9. Functional Laterality/
10. laterality.mp.
11. left right judg$.mp.
12. exp Pattern Recognition, Visual/
13. visual pattern recognition.mp.
14. Discrimination (Psychology)"/
15. discrimination.mp.
16. Imagination/
17. imagined movement.mp.
18. mental imagery.mp.
19. mental movement.mp.
20. visual imagery.mp.
21. exp Kinesthesis/
22. kinaesthetic imagery.mp.
23. kinesthetic imagery.mp.
24. mirror therapy.mp.
25. Feedback, Sensory/
26. mirror visual feedback.mp.
27. user-computer interface/
28. Therapy, Computer-Assisted/
29. virtual reality therapy.mp.
30. user computer interface.mp.
31. mirror box therapy.mp.
32. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. Pain/
34. 32 and 33
35. limit 34 to human

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# Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II (Review)

Smart KM, Wand BM, O'Connell NE

Smart KM, Wand BM, O'Connell NE.
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*Cochrane Database of Systematic Reviews* 2016, Issue 2. Art. No.: CD010853.
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[Intervention Review]

# Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II

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## ABSTRACT

### Background

Complex regional pain syndrome (CRPS) is a painful and disabling condition that usually manifests in response to trauma or surgery. When it occurs, it is associated with significant pain and disability. It is thought to arise and persist as a consequence of a maladaptive pro-inflammatory response and disturbances in sympathetically-mediated vasomotor control, together with maladaptive peripheral and central neuronal plasticity. CRPS can be classified into two types: type I (CRPS I) in which a specific nerve lesion has not been identified, and type II (CRPS II) where there is an identifiable nerve lesion. Guidelines recommend the inclusion of a variety of physiotherapy interventions as part of the multimodal treatment of people with CRPS, although their effectiveness is not known.

### Objectives

To determine the effectiveness of physiotherapy interventions for treating the pain and disability associated with CRPS types I and II.

### Search methods

We searched the following databases from inception up to 12 February 2015: CENTRAL (the Cochrane Library), MEDLINE, EMBASE, CINAHL, PsycINFO, LILACS, PEDro, Web of Science, DARE and Health Technology Assessments, without language restrictions, for randomised controlled trials (RCTs) of physiotherapy interventions for treating pain and disability in people CRPS. We also searched additional online sources for unpublished trials and trials in progress.

### Selection criteria

We included RCTs of physiotherapy interventions (including manual therapy, therapeutic exercise, electrotherapy, physiotherapist-administered education and cortically directed sensory-motor rehabilitation strategies) employed in either a stand-alone fashion or in combination, compared with placebo, no treatment, another intervention or usual care, or of varying physiotherapy interventions compared with each other in adults with CRPS I and II. Our primary outcomes of interest were patient-centred outcomes of pain intensity and functional disability.

**Data collection and analysis**

Two review authors independently evaluated those studies identified through the electronic searches for eligibility and subsequently extracted all relevant data from the included RCTs. Two review authors independently performed 'Risk of bias' assessments and rated the quality of the body of evidence for the main outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

**Main results**

We included 18 RCTs (739 participants) that tested the effectiveness of a broad range of physiotherapy-based interventions. Overall, there was a paucity of high quality evidence concerning physiotherapy treatment for pain and disability in people with CRPS I. Most included trials were at 'high' risk of bias (15 trials) and the remainder were at 'unclear' risk of bias (three trials). The quality of the evidence was very low or low for all comparisons, according to the GRADE approach.

We found very low quality evidence that graded motor imagery (GMI; two trials, 49 participants) may be useful for improving pain (0 to 100 VAS) (mean difference (MD) −21.00, 95% CI −31.17 to −10.83) and functional disability (11-point numerical rating scale) (MD 2.30, 95% CI 1.12 to 3.48), at long-term (six months) follow-up, in people with CRPS I compared to usual care plus physiotherapy; very low quality evidence that multimodal physiotherapy (one trial, 135 participants) may be useful for improving 'impairment' at long-term (12 month) follow-up compared to a minimal 'social work' intervention; and very low quality evidence that mirror therapy (two trials, 72 participants) provides clinically meaningful improvements in pain (0 to 10 VAS) (MD 3.4, 95% CI −4.71 to −2.09) and function (0 to 5 functional ability subscale of the Wolf Motor Function Test) (MD −2.3, 95% CI −2.88 to −1.72) at long-term (six month) follow-up in people with CRPS I post stroke compared to placebo (covered mirror).

There was low to very low quality evidence that tactile discrimination training, stellate ganglion block via ultrasound and pulsed electromagnetic field therapy compared to placebo, and manual lymphatic drainage combined with and compared to either anti-inflammatories and physical therapy or exercise are not effective for treating pain in the short-term in people with CRPS I. Laser therapy may provide small clinically insignificant, short-term, improvements in pain compared to interferential current therapy in people with CRPS I.

Adverse events were only rarely reported in the included trials. No trials including participants with CRPS II met the inclusion criteria of this review.

**Authors' conclusions**

The best available data show that GMI and mirror therapy may provide clinically meaningful improvements in pain and function in people with CRPS I although the quality of the supporting evidence is very low. Evidence of the effectiveness of multimodal physiotherapy, electrotherapy and manual lymphatic drainage for treating people with CRPS types I and II is generally absent or unclear. Large scale, high quality RCTs are required to test the effectiveness of physiotherapy-based interventions for treating pain and disability of people with CRPS I and II. Implications for clinical practice and future research are considered.

## PLAIN LANGUAGE SUMMARY

**Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II**

**Background**

Complex regional pain syndrome (CRPS) is a painful and disabling condition. Most commonly it affects a person's arm and hand or leg and foot and may occur after a traumatic injury. There are two types of CRPS: CRPS I in which there is no nerve injury, and CRPS II in which there is a nerve injury. Guidelines recommend physiotherapy, which could include different kinds of exercise therapy or electrotherapy for instance, along with other medical treatments for treating the pain and disability associated with CRPS. However, we do not know how well these treatments work.

**Review question**

Which types of physiotherapy treatment are effective for reducing the pain and disability associated with CRPS in adults?

**Study characteristics**

We searched for clinical trials of physiotherapy up to 12 February 2015. We included 18 trials that had 739 participants with CRPS I. In most of these trials the participants had CRPS I of the arm and hand. We did not find any clinical trials that included participants with CRPS II.

**Key results**

Overall we did not find any good quality clinical trials of physiotherapy aimed at reducing the pain and disability of CRPS I in adults. Most included trials were not well designed and contained only small numbers of patients. We did find some low quality trials suggesting that two broadly similar types of rehabilitation training, known as 'graded motor imagery' (GMI) and 'mirror therapy', might be useful for reducing the pain and disability associated with CRPS I after traumatic events or surgery or a stroke. From the limited evidence available it appears that some types of electrotherapy, such as ultrasound and pulsed electromagnetic field therapy, as well as a type of massage therapy known as manual lymphatic drainage, are not effective. Most studies did not report on adverse events and so we do not know if these treatments have any harmful side-effects.

On the whole, because of the limited number and low quality of available trials for the various physiotherapy treatments, we cannot be sure if any of the physiotherapy treatments we evaluated are effective for treating the pain and disability of CRPS I in adults. It is possible that some treatments, such as GMI or mirror therapy, might be effective. Further high quality clinical trials of physiotherapy are needed in order to find out if any of the different types of physiotherapy treatment are effective at improving pain and disability in people with CRPS.

# BACKGROUND

## Description of the condition

Complex regional pain syndrome (CRPS) is a persistent, painful and disabling condition that usually, but not exclusively, manifests in response to acute trauma or surgery (Goebel 2011; Shipton 2009). The International Association for the Study of Pain (IASP) introduced the diagnostic label 'CRPS' in the 1990s in order to standardise inconsistencies in terminology and diagnostic criteria (Merskey 1994). Two sub-categories of CRPS have been described: CRPS type I (CRPS I) (formerly and variously referred to as reflex sympathetic dystrophy (RSD), algodystrophy, Sudek's atrophy) in which no nerve lesion is present and CRPS type II (CRPS II) (formerly referred to as causalgia, algoneurodystrophy), in which a co-existing nerve lesion (as determined by nerve conduction studies or surgical inspection for example) is present (Coderre 2011; Todorova 2013).

CRPS is characterised by symptoms and signs typically confined to a body region or limb, but which may become more widespread (van Rijn 2011). The diagnostic criteria for CRPS originally proposed by the IASP (Merskey 1994) have since been revised in response to their low specificity and potential to over-diagnose cases of CRPS. The Budapest criteria proposed by Harden 2010 have enhanced diagnostic accuracy and are now widely accepted (Goebel 2011). The diagnosis of CRPS is clinical (Goebel 2011) and the cardinal features include:

1. continuing pain disproportionate to any inciting event;
2. the presence of clusters of various symptoms and signs reflecting sensory (e.g. hyperaesthesia, allodynia), vasomotor (e.g. asymmetries of temperature or skin colour, or both), sudomotor (e.g. oedema or altered sweating or both), motor (e.g. reduced range of motion, tremor) or trophic (e.g. altered hair or nails, or both) disturbances; and
3. the absence of any other medical diagnosis that might better account for an individual's symptoms and signs.

The pathophysiological mechanisms underlying CRPS are not fully understood (Harden 2010). Current understanding implicates multiple mechanisms including complex contributions from a maladaptive pro-inflammatory response and a disturbance in sympathetically mediated vasomotor control, together with maladaptive peripheral and central neuronal plasticity (Bruehl 2010; Bruehl 2015; Marinus 2011; Parkitny 2013). Furthermore, mechanisms, and in consequence symptoms and signs, may vary between individuals and within individuals over the time course of the disorder, thus heightening the complexity (Marinus 2011).

The incidence of CRPS is not accurately known but population estimates indicate an incidence of somewhere between five and 26 cases per 100,000 person-years (Marinus 2011). A likely conservative 11-year period prevalence rate for CRPS of 20.57 per 100,000 people has been reported (Sandroni 2003). CRPS is three to four times more likely to occur in women than in men, and although it may occur at any time throughout the lifespan it tends to occur more frequently with increasing age (Shipton 2009). Genetic susceptibility may serve as an aetiological risk factor for the de-

velopment of CRPS (de Rooij 2009). In individuals who develop CRPS after a fracture, intra-articular fracture, fracture-dislocation, pre-existing rheumatoid arthritis, pre-existing musculoskeletal comorbidities (e.g. low-back pain, arthrosis) (Beerthuizen 2012) and limb immobilisation (Marinus 2011) may increase the risk of its development. Psychological traits, such as depression, anxiety, neuroticism and anger, have so far been discounted as risk factors for the development of CRPS (Beerthuizen 2009: Lohnberg 2013), although further prospective studies are required to substantiate this assertion (Harden 2013).

People with CRPS experience significant suffering and disability (Bruehl 2010; Lohnberg 2013). Preliminary data suggest that interference with activities of daily living, sleep, work and recreation is common and further contributes to a diminished quality of life (Galer 2000; Geertzen 1998; Kemler 2000; Sharma 2009).

Studies into the course of CRPS present contradictory findings. Whilst some studies have reported complete and partial symptom resolution within one year (Sandroni 2003; Zyluk 1998), other studies have indicated more protracted symptoms and impairments lasting from three to nine years (de Mos 2009; Geertzen 1998; Vaneker 2006). In addition, emerging evidence suggests that people with CRPS of an upper limb (which develops less often in response to a fracture) and whose affected limb is colder than the contralateral limb, may experience significantly longer disease duration than people with CRPS of a lower limb (which occurs more commonly after fracture) and whose affected limb is warmer than the contralateral limb (de Mos 2009).

Although guidelines for the treatment of CRPS recommend an interdisciplinary multimodal approach, comprising pharmacological and interventional pain management strategies together with rehabilitation, psychological therapy and educational strategies (Goebel 2012; Harden 2013; Perez 2010; Stanton-Hicks 2002), determining the optimal approach to therapy remains clinically challenging (Cossins 2013; O'Connell 2013).

## Description of the intervention

Guidelines recommend the inclusion of a variety of physiotherapy interventions as part of the multimodal treatment of CRPS (Goebel 2012; Perez 2010; Stanton-Hicks 2002) but their effectiveness is not known. Physiotherapy has been defined as "the treatment of disorders with physical agents and methods" (Anderson 2002) and for CRPS could include any of the following interventions employed either as stand-alone interventions or in combination: manual therapy (e.g. mobilisation, manipulation, massage, desensitisation); therapeutic exercise and progressive loading regimens (including hydrotherapy); electrotherapy (e.g. transcutaneous electrical nerve stimulation (TENS), therapeutic ultrasound, interferential, shortwave diathermy, laser); physiotherapist-administered education (e.g. pain neuroscience education); as well as cortically directed sensory-motor rehabilitation strategies (e.g. graded motor imagery (GMI), mirror therapy, sensory motor retuning, tactile discrimination training).

## How the intervention might work

The precise mechanisms of action through which various physiotherapy interventions are purported to relieve the pain and disability associated with CRPS are not fully understood. Theories underpinning the use of manual therapies to relieve pain include the induction of peripheral or central nervous system-mediated analgesia, or both (Bialosky 2009; Goats 1994). Therapeutic exercise may induce analgesia, via endorphin-mediated inhibition (Nijs 2012), and improve function, and by extension disability, by restoring range of movement at affected joints and improving neuromuscular function (Kisner 2002). Theories underlying the use of electrotherapy modalities for pain relief variously include spinal cord-mediated electro-analgesia, heat- or cold-mediated analgesia and anti-inflammatory effects (Atamaz 2012; Robertson 2006). Pain neuroscience education may reduce pain and disability by helping individuals to better understand the biological processes underlying their pain in a way that positively changes pain perceptions and attitudes (Louw 2011). Other rehabilitation strategies, such GMI or mirror therapy, may provide pain relief or increase mobility, or both, by ameliorating maladaptive somatosensory and motor cortex reorganisation (Moseley 2005; Moseley 2012).

## Why it is important to do this review

A number of systematic reviews suggest that physiotherapy interventions (e.g. exercise, GMI, TENS) employed in combination with medical management may be beneficial in reducing the pain and disability associated with CRPS (Daly 2009; Smith 2005). However, the inclusion of non-randomised clinical trials and case series designs, together with the exclusion of studies involving people with CRPS II as well as those published in a language other than English, may have biased these conclusions. Furthermore, the methodologies used for conducting systematic reviews have been substantially revised in recent years, such as those recommended within the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for describing the strength of the evidence (Balshem 2011), which has not been utilised in previous reviews. Given the limitations of existing systematic reviews, together with the availability of potentially numerous physiotherapy treatment strategies for CRPS, an up-to-date systematic review of the evidence from randomised clinical trials for the effectiveness of these interventions may assist clinicians in their treatment choices and inform future clinical guidelines that may be of use to policymakers and those who commission health care for people with CRPS.

## OBJECTIVES

To determine the effectiveness of physiotherapy interventions for treating pain and disability associated with CRPS types I and II.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included randomised controlled trials (RCTs) (including those of parallel, cluster-randomised and cross-over design) published in any language. Translators identified by the Managing Editor of the Cochrane Pain, Palliative and Supportive Care Group evaluated studies published in a language other than English. We excluded studies in which participants were not randomised to intervention groups.

#### Types of participants

We included trials of adults, aged 18 years or older, diagnosed with CRPS I or II, or with an alternative diagnostic label for these conditions (e.g. RSD, causalgia). We grouped trials according to diagnosis (i.e. CRPS I and II, or mixed). Since the use of formal diagnostic criteria for CRPS is inconsistent across studies (Reinders 2002), we included trials that used established or validated diagnostic criteria, including the Veldman criteria (Veldman 1993), the International Association for the Study of Pain (IASP) criteria (Merskey 1994), Bruehl criteria (Bruehl 1999), Budapest criteria (Harden 2010) and Atkins criteria (Atkins 2010), as well as studies that either predate these criteria or use non-standard diagnostic criteria.

#### Types of interventions

We included all randomised controlled comparisons of physiotherapy interventions, employed in either a stand-alone fashion or in combination, compared with placebo, no treatment, another intervention or usual care, or of varying physiotherapy interventions compared with each other, which were aimed at treating pain or disability, or both, associated with CRPS. We included trials in which non-physiotherapists (e.g. occupational therapists) delivered such physiotherapy interventions, as defined in 'Description of the intervention', and reported the professional discipline of the clinician delivering the intervention. After the publication of our Cochrane protocol, (Smart 2013) we decided to exclude studies that evaluated non-physiotherapy based interventions (e.g. pharmacological) in which all arms received the same physiotherapy intervention (differing only in the application of the non-physiotherapy component) as they are unlikely to offer any insight into the value of physiotherapy management (see Differences between protocol and review).

#### Types of outcome measures

##### Primary outcomes

1. Changes in pain severity/intensity as measured using a visual analogue scale (VAS), numerical rating scale (NRS), verbal rating scale or Likert scale;
2. changes in disability as measured by validated self-report questionnaires/scales or functional testing protocols.

We presented and analysed primary outcomes as change on a continuous scale or in a dichotomised format as the proportion of participants in each group who attained a predetermined threshold of improvement. For example, we judged cut-points from which to interpret the likely clinical importance of (pooled) effect sizes according to provisional criteria proposed in the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement (Dworkin 2008). Specifically, reductions in pain intensity compared with baseline were judged as follows:

1. less than 15%: 'no important change';
2. 15% or more: 'minimally important change';
3. 30% or more: 'moderately important change';
4. 50% or more: 'substantially important change'.

We planned to use the cut-points for 'minimally', 'moderately' and 'substantially' important changes to generate dichotomous outcomes, the effect size for which we would have expressed as the risk ratio (or relative risk (RR)) but a lack of data did not permit any such analyses.

##### Secondary outcomes

We planned to analyse the following secondary outcome measures where such data were available:

1. changes in composite scores for CRPS symptoms;
2. changes in health-related quality of life (HRQoL) using any validated tool;
3. changes in patient global impression of change (PGIC) scales;
4. incidence/nature of adverse effects.

We planned to analyse and present secondary outcomes as change on a continuous scale or in a dichotomised format but a lack of data did not permit any such analyses. For example, equivalent measures of treatment effect with respect to PGIC have been defined as: 'much' or 'very much' improved (moderate benefit) and very much' improved (substantial benefit) (Dworkin 2008). Future updates may allow such analyses where relevant data are available.

## Search methods for identification of studies

### Electronic searches

We identified relevant RCTs by electronically searching the following databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, Issue 1 of 12, 2015;
2. Database of Abstracts of Reviews of Effects in the Cochrane Library, Issue 1 of 4 2015;
3. Health Technology Assessments in the Cochrane Library, Issue 1 of 4 2015;
4. MEDLINE (OVID) (1966 to 11 February 2015);
5. EMBASE (OVID) (1974 to 11 February 2015);
6. CINAHL (EBSCO) (1982 to 11 February 2015);
7. PsycINFO (OVID) (1806 to 11 February 2015);
8. LILACS; (1982 to 15 February 2015);
9. PEDro; (1929 to 15 February 2015);
10. Web of Science (ISI);(1945 to 15 February 2015).

The Trials Search Co-ordinator of the Cochrane Pain, Palliative and Supportive Care Group devised the search strategies. She and the review authors ran these searches. We used a combination of controlled vocabulary, i.e. medical subject headings (MeSH) and free-text terms. The search strategies are in Appendix 1.

### Searching other resources

#### Reference lists

On completion of the electronic searches we searched the reference lists of all eligible studies in order to identify additional relevant studies. In addition we screened the reference lists of key physiotherapy textbooks and previous systematic reviews.

#### External experts

We sent the list of included trials to a content expert to help identify any additional relevant studies.

#### Unpublished data

In order to minimise the impact of publication bias we searched the following registers and databases to identify unpublished research as well as research in progress:

1. OpenGrey (System for Information on Grey Literature in Europe);
2. Dissertation Abstracts (ProQuest);
3. National Research Register Archive;
4. Health Services Research Projects in Progress;
5. Current Controlled Trials Register (incorporating the meta-register of controlled trials and the International Standard Randomised Controlled Trial Number);
6. ClinicalTrials.gov;
7. International Clinical Trials Registry Platform;
8. Pan African Clinical Trials Registry;
9. EU Clinical Trials Register.

## Data collection and analysis

### Selection of studies

Two review authors (KMS and BMW) independently assessed the titles and abstracts of studies we identified by the search strategy for eligibility. If the eligibility of a trial was unclear from the title and abstract, we assessed the full-text article. We excluded trials that did not match the inclusion criteria (see the 'Criteria for considering studies for this review' section). We resolved any disagreements between review authors regarding a study's inclusion by discussion. If we could not resolve disagreements, a third review author (NEO) assessed relevant studies and we made a majority decision. Trials were not anonymised prior to assessment. We obtained potentially relevant studies identified in the first round of screening in full text and independently assessed these for inclusion using the same process outlined above. We did not apply any language restrictions.

### Data extraction and management

Two review authors (KMS and BMW) independently extracted data from all included trials. We extracted data using a standardised and piloted form. We resolved any discrepancies and disagreements by consensus. In cases where we could not achieve consensus, a third review author (NEO) assessed the trial and we took a majority decision. We extracted the following data from each included trial:

1. country of origin;
2. study design;
3. study population (including diagnosis, diagnostic criteria used, symptom duration, age range, gender split);
4. type of noxious initiating event: surgery, fracture, crush injury, projectile, stab injury, other or no event;
5. type of tissue injured: nerve, soft tissue, bone;
6. presence of medicolegal factors (that may influence the experience of pain and the outcomes of therapeutic interventions);
7. concomitant treatments that may affect outcome: medication, procedures etc.;
8. sample size: active and control/comparator groups;
9. intervention (including type, parameters (e.g. frequency, dose, duration), setting and professional discipline of the clinician delivering the therapy);
10. type of placebo/comparator intervention;
11. outcomes (primary and secondary) and time points assessed;
12. adverse effects;

13. author conflict of interest statements;
14. assessment of risk of bias.

### Assessment of risk of bias in included studies

We assessed the overall risk of bias for each included trial on the basis of an evaluation of key domains using a modified version of the Cochrane 'Risk of bias' assessment tool. We classified risk of bias as either 'low' (low risk of bias for all key domains), 'unclear' (unclear risk of bias for one or more key domains) or 'high' (high risk of bias for one or more key domains), as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We also considered experimental design-specific (e.g. cross-over study designs) 'Risk of bias' issues where appropriate (Higgins 2011b). We assessed the following key domains of risks of bias for each included trial using either 'yes', 'no' or 'unclear' judgements:

1. random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as either: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated); or high risk of bias (studies using a quasi/non-random process (e.g. odd or even date of birth; hospital or clinic record number);

2. allocation concealment (checking for possible selection bias). The method used to conceal allocation to group prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods used as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated); or high risk of bias (studies that do not conceal allocation (e.g. open list));

3. blinding of study participants and personnel (checking for possible performance bias). We assessed the methods used to blind participants and care providers as either: low risk of bias (participants and care providers blinded to allocated intervention and unlikely that blinding broken; or no/incomplete blinding but judged that both intervention arms reflect active interventions of relatively equal credibility delivered with equal enthusiasm); unclear risk of bias (insufficient information provided to permit a judgement of low/high risk of bias); or high risk of bias (participants and care providers not blinded to the allocated intervention and interventions are clearly identifiable as control and experimental; or participants and care providers blinded to the allocated intervention but likely that blinding was broken);

4. blinding of outcome assessment (self reported outcomes) (checking for possible detection bias). We assessed the methods used to blind study participants self-reporting outcomes (e.g. pain severity) from knowledge of which intervention a participant received. We assessed the methods as either: low risk of bias (participants blinded to allocated intervention and unlikely that blinding broken; or no/incomplete blinding but judged that both intervention arms reflect active interventions of relatively equal credibility delivered with equal enthusiasm); unclear risk of bias (insufficient information provided to permit a judgement of low/high risk of bias); or high risk of bias (participants not blinded to the allocated intervention and interventions are clearly identifiable as control and experimental; or participants blinded to the allocated intervention but likely that blinding was broken);

5. blinding of outcome assessment (investigator-administered outcomes) (checking for possible detection bias). We assessed the methods used to blind researchers undertaking outcome assessments (e.g. functional testing protocols) from knowledge of which intervention a participant received. We assessed the methods as at either: low risk of bias (researchers blinded to allocated intervention and unlikely that blinding broken); unclear risk of bias (insufficient information provided to permit a judgement of low/high risk of bias); high risk of bias (researchers not blinded to the allocated intervention; or researcher blinded to the allocated intervention but likely that blinding was broken);

6. incomplete outcome data (drop out) (checking for possible attrition bias). We first assessed for risk of attrition bias by evaluating participant drop out rates according to judgements based on the following criteria: low risk of bias (less than 20% drop out and appears not to be systematic, with numbers for each group and reasons for drop out reported); unclear risk of bias (less than 20% drop out but appears to be systematic or numbers per group and reasons for drop out not reported); high risk of bias (greater than or equal to 20% drop out);

7. incomplete outcome data (method of analysis) (participants analysed in the group to which they were allocated) (checking for possible attrition bias). We further assessed for risk of attrition bias by separately evaluating the appropriateness of the method of analysis employed, using the following criteria: low risk of bias (participants analysed in the group to which they were allocated (intention-to-treat (ITT) or as an available case analysis); unclear risk of bias (insufficient information provided to determine if analysis was based on the principle of ITT or per protocol); or high risk of bias (if per protocol analysis used or where available data is not analysed or participant's data were included in group to which they were not originally assigned to);

8. selective reporting (checking for possible reporting bias). We assessed studies for selective outcome reporting using the following judgements: low risk of bias (study protocol available and all pre-specified primary outcomes of interest adequately reported or study protocol not available but all expected primary outcomes of interest adequately reported or all primary outcomes numerically reported with point estimates and measures of variance for all time points); unclear risk of bias (insufficient information provided to permit a judgement of low/high risk of bias); or high risk of bias (incomplete reporting of

pre-specified primary outcomes or point estimates and measures of variance for one or more primary outcome not reported numerically (e.g. graphically only) or one or more primary outcomes reported using measurements, analysis methods or subsets of data that were not pre-specified or one or more reported primary outcomes were not pre-specified or results for a primary outcome expected to have been reported were excluded);

9. other bias. We assessed studies for other potential sources of bias. We determined judgements regarding low/unclear/high risk of bias according to the potential confounding influence of identified factors, for example: low risk of bias (appears free of other potentially serious sources of bias e.g. no serious study protocol violations identified); unclear risk of bias (other sources of bias may be present but there is either insufficient information to assess whether an important risk of bias exists or insufficient rationale or evidence regarding whether an identified problem will introduce bias); or high risk of bias (results may have been confounded by at least one potentially serious risk of bias, e.g. a significant baseline imbalance between groups; a serious protocol violation; use of 'last observation carried forward' when dealing with missing data).

We also evaluated included trials for the additional sources of bias associated with:

1. sample size; and
2. duration of follow-up, as recommended by Moore 2010.

Small studies are more prone to bias because of their inherent imprecision and due to the effects of publication biases (Dechartres 2013; Moore 2012; Nüesch 2010). Inadequate length of follow-up may produce an overly positive view of the true clinical effectiveness of interventions, particularly in persistent conditions (Moore 2010). These additional criteria were not considered 'key domains' and therefore did not inform judgements of a trial's overall risk of bias. We assessed these trials according to the following criteria:

1. sample size (checking for possible biases confounded by small sample size): we assessed trials as being at low risk of bias (greater than or equal to 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (less than 50 participants per treatment arm);
2. duration of follow-up (checking for possible biases confounded by a short duration of follow-up): we assessed trials as being at low risk of bias (follow-up of greater than or equal to eight weeks); unclear risk of bias (follow-up of two to seven weeks); or high risk of bias (follow-up of less than two weeks).

Two review authors (KMS and BMW) independently undertook the 'Risk of bias' assessments, and resolved any disagreements by discussion. If they could not reach an agreement, a third review author (NEO) undertook a 'Risk of bias' assessment and we took a majority decision.

### Measures of treatment effect

We presented treatment effect sizes using appropriate metrics. We calculated the risk ratio (RR) with 95% confidence intervals (CIs) for dichotomised outcome measures, and the number needed to treat (NNT) as an absolute measure of treatment effect where possible.

We expressed the size of treatment effect on pain intensity, as measured with a VAS or NRS, using the mean difference (MD) (where all studies utilised the same measurement scale) or the standardised mean difference (SMD) (where studies used different scales). In order to aid interpretation of the pooled effect size we planned to back-transform the SMD value to a 0 to 100 mm VAS format on the basis of the mean standard deviation (SD) from trials using a 0 to 100 mm VAS where possible.

We analysed the data using Review Manager (RevMan) (RevMan 2014). We plotted the results of each RCT with available data as point estimates with corresponding 95% CIs and displayed them using forest plots. If included trials demonstrated clinical homogeneity we performed a meta-analysis to quantify the pooled treatment effect sizes using a random-effects model. We did not perform a meta-analysis when clinical heterogeneity was present. Similarly we presented secondary outcomes, though we did not consider them for meta-analysis.

### Unit of analysis issues

All included trials randomised participants at the individual participant level. We planned to meta-analyse estimates of treatment effect (and their standard errors (SE)) from cluster-RCTs employing appropriate statistical analyses using the generic inverse-variance method in RevMan (RevMan 2014), as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Where we considered such trials to have employed inappropriate analyses, we planned to utilise methods for 'approximately correct analysis' where possible (Higgins 2011b). In addition, we planned to enter cross-over trials into a meta-analysis when it was clear that data were free from carry-over effects, and to combine the results of cross-over trials with those of parallel trials by imputing the post-treatment between-condition correlation coefficient from an included trial that presented individual participant data and use this to calculate the SE of the SMD. These data may be entered into a meta-analysis using the generic inverse-variance method (Higgins 2011b). Issues concerning cluster-RCTs and crossover trials did not arise as we did not identify any cluster-RCTs that met the inclusion criteria of this review and we did not conduct any quantitative analyses on the one included crossover trial. We may include such analyses where relevant data are available in future updates of this Cochrane review.

### Dealing with missing data

We attempted to contact the authors of included trials when numerical data were unreported or incomplete. If trial authors only

presented data in graphical form, we did not attempt to extract the data from the figures. If SD values were missing from follow-up assessments but were available at baseline, we used these values as estimates of variance in the follow-up analyses.

### Assessment of heterogeneity

We evaluated the included trials for clinical homogeneity regarding study population, treatment procedure, control intervention, timing of follow-up and outcome measurement. For trials that were sufficiently clinically homogenous to pool, we formally explored heterogeneity using the Chi² test to investigate the statistical significance of any heterogeneity, and the I² statistic to estimate the amount of heterogeneity. Where significant heterogeneity (P value < 0.1) was present, we planned to explore subgroup analyses (see the 'Differences between protocol and review' section).

### Assessment of reporting biases

We planned to test for the possible influence of publication bias on trials that utilised dichotomised outcomes by estimating the number of participants in trials with zero effect required to change the NNT to an unacceptably high level (defined as an NNT of 10), as outlined by Moore 2008. An absence of relevant data meant that we did not undertake any analyses. Instead, we considered the possible influence of small study/publication biases on review findings as part of our 'Risk of bias' assessment (see the 'Assessment of risk of bias in included studies' section) and as part of our Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessments (Guyatt 2011a) of the quality of evidence (see the 'Data synthesis' section). We may include such analyses in future updates of this Cochrane review where relevant data are available.

### Data synthesis

Where possible, we grouped extracted data according to diagnosis (CRPS types I or II, or mixed), intervention, outcome (i.e. pain, disability) and duration of follow-up (short-term: zero to less than two weeks postintervention; mid-term: two to seven weeks postintervention; and long-term: eight or more weeks postintervention). Regarding intervention, we planned to pool data from trials that investigated the same single therapy separately for each therapy. We planned to pool trials of multimodal physiotherapy programmes together.

For all analyses, we report the outcome of the 'Risk of bias' assessments. Where we found inadequate data to support statistical pooling, we performed a narrative synthesis of the evidence. We were only able to combine trials through meta-analysis for one type of intervention (graded motor imagery (GMI)) because of insufficient data and clinical heterogeneity. We conducted a qualitative analysis of all trial findings and used the GRADE approach to assess the quality of evidence (Guyatt 2011a; Guyatt 2011b).

To ensure consistency of GRADE judgements we applied the following criteria to each domain equally for all key comparisons of the primary outcome:

1. limitations of studies: we downgraded once if more than 25% of the participants were from trials we classified as being at high risk of bias;
2. inconsistency: we downgraded once if heterogeneity was statistically significant and the I² statistic value was greater than 40%. When a meta-analysis was not performed we downgraded once if the trials did not show effects in the same direction;
3. indirectness: we downgraded once if more than 50% of the participants were outside the target group;
4. imprecision: we downgraded once if there were fewer than 400 participants for continuous data and fewer than 300 events for dichotomous data;
5. publication bias: we downgraded once where there was direct evidence of publication bias or if estimates of effect based on small scale, industry sponsored studies raised a high index of suspicion of publication bias.

Two review authors (KS and NO) made the judgement of whether these factors were present or not. We considered single trials to be inconsistent and imprecise, unless more than 400 participants were randomised for continuous outcomes or more than 300 for dichotomous outcomes. We applied the following definitions of the quality of the evidence (Balshem 2011):

1. high quality: we are very confident that the true effect lies close to that of the estimate of the effect;
2. moderate quality: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
3. low quality: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect;
4. very low quality: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

### Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses based on the type of CRPS (i.e. I, II or mixed) and its temporal characteristics (i.e. acute (defined as symptoms and signs of CRPS of zero to 12 weeks duration) and chronic (symptoms and signs of CRPS lasting 13 weeks). However, we did not undertake them due to the insufficient number of included trials.

### Sensitivity analysis

We planned to perform sensitivity analyses on risk of bias (investigating the influence of excluding studies classified at high risk of bias) and choice of meta-analysis model (investigating the influence of using a fixed-effect analysis). We did not perform them

as insufficient data were available (see the 'Differences between protocol and review' section).

# RESULTS

## Description of studies

See the 'Characteristics of included studies' and 'Characteristics of excluded studies' sections.

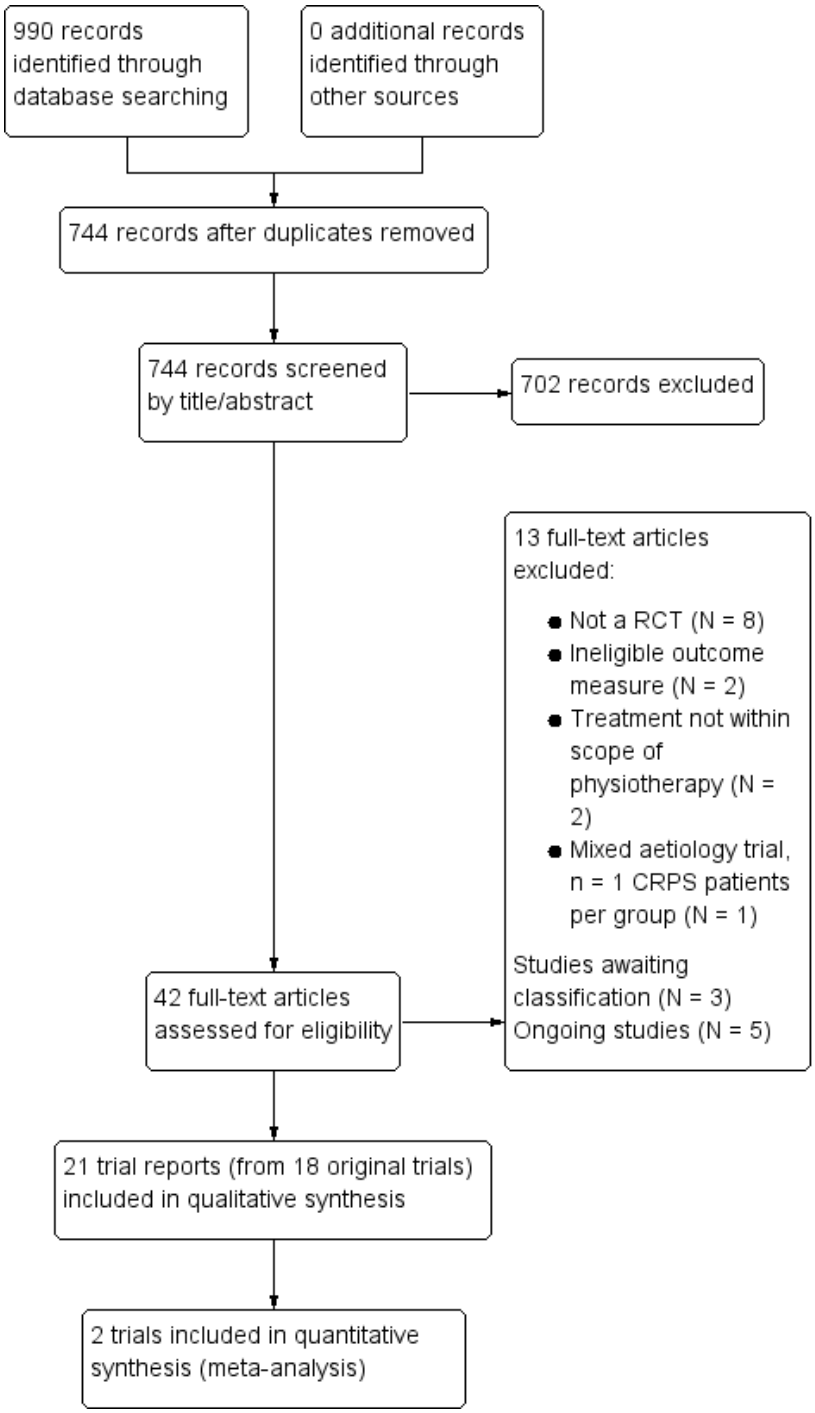
### Results of the search

We conducted the literature search up to 12 February 2015 and identified 990 papers that comprised original research studies, reviews and poster abstracts, of which 744 remained after we removed duplicates. After we screened titles and abstracts, we discarded 702 records because they did not meet the inclusion criteria of this Cochrane review. We retrieved 42 records for full-text screening. We deemed 21 trial reports from 18 original trials for inclusion (Askin 2014; Aydemir 2006; Cacchio 2009a; Cacchio 2009b; Dimitrijevic 2014; Duman 2009; Durmus 2004; Hazneci 2005; Jeon 2014; Li 2012; Moseley 2004; Moseley 2005; Moseley 2006; Moseley 2009; Mucha 1992; Oerlemans 1999; Schreuders 2014; Severens 1999; Uher 2000). Four published trial manuscripts reported data pertaining to a single included trial (Oerlemans 1999).

One additional trial is awaiting submission for publication (ISRCTN39729827), one trial is available only as a conference abstract (Mete-Topcuoglu 2010) and we were unable to contact the authors of one registered trial (NCT00625976). These three trials are awaiting classification (see the 'Characteristics of studies awaiting classification' table).

In addition, we identified five ongoing trials (see the ' Characteristics of ongoing studies' section). We have presented a flow diagram outlining the trial screening and selection process (Figure 1). Two review authors (KMS and BMW) reported study details in the 'Characteristics of included studies' and 'Risk of bias' tables for two papers published in the Turkish language (Aydemir 2006; Hazneci 2005) based on an English translation of the original trial report; and one review author (BMW) reported study details in the 'Characteristics of included studies' and 'Risk of bias' tables for two papers published in the German language (Mucha 1992; Uher 2000).

**Figure 1. Study flow diagram.**



## Included studies

We have provided the details of all included trials in the 'Characteristics of included studies' tables. We extracted relevant data from eight included trials (Askin 2014; Aydemir 2006; Cacchio 2009a; Dimitrijevic 2014; Duman 2009; Durmus 2004; Hazneci 2005; Li 2012). We contacted or attempted to contact the corresponding authors of 10 trials on three occasions in order to obtain missing outcomes data (Cacchio 2009b; Jeon 2014; Moseley 2004; Moseley 2005; Moseley 2006; Moseley 2009; Mucha 1992; Oerlemans 1999; Schreuders 2014; Uher 2000). One trial author responded and supplied data for an outcome measure of 'impairment' but we were unable to extract outcome data linked to 'pain intensity' from the supplied data (Oerlemans 1999); one trial author responded stating that they were unable to supply the relevant data (Schreuders 2014); and there was no response from the other trial authors we had contacted.

### Design

All included trials were RCTs, and 17 essentially used a parallel-group design. Whilst the selected participants in three trials crossed over from comparator to intervention groups (Cacchio 2009b; Moseley 2004; Mucha 1992), none employed a true randomised crossover design and we analysed them up to the point of crossover as parallel group-designs. One trial employed a within-subject randomised crossover design (Moseley 2009). Twelve trials included two intervention arms (Cacchio 2009a; Dimitrijevic 2014; Duman 2009; Durmus 2004; Hazneci 2005; Jeon 2014; Li 2012; Moseley 2004; Moseley 2006; Mucha 1992; Schreuders 2014; Uher 2000), five trials included three arms (Askin 2014; Aydemir 2006; Cacchio 2009b; Moseley 2005; Oerlemans 1999) and one study used four arms (Moseley 2009). No cluster-RCTs met the inclusion criteria of this Cochrane review.

### Participants

The 18 trials included a total of 739 participants and the total number of participants per trial ranged from 10 to 135. All 18 trials included participants with CRPS I using a range of diagnostic criteria, most commonly using those of Bruehl 1999. There were no trials that included participants with CRPS II. Fourteen trials included participants with CRPS I of the upper limb (Askin 2014; Aydemir 2006; Cacchio 2009a; Cacchio 2009b; Duman 2009; Durmus 2004; Hazneci 2005; Li 2012; Moseley 2004; Moseley 2005; Moseley 2009; Mucha 1992; Oerlemans 1999; Schreuders 2014), two with either upper or lower limb CRPS I (Dimitrijevic 2014; Moseley 2006), one with CRPS I of the lower limb (Uher 2000) and one trial included participants with either upper, lower, multi-limb or whole body CRPS I (Jeon 2014). Participants developed CRPS I linked to a range of aetiologies including onset post fracture, soft-tissue injuries, stroke, surgery, carpal tunnel syndrome as well as of idiopathic onset. Participants had acute symptoms (less than or equal to three months) of CRPS I in six trials (Cacchio 2009a; Dimitrijevic 2014; Durmus 2004; Hazneci 2005; Li 2012; Mucha 1992), chronic symptoms (greater than three months) in seven trials (Duman 2009; Jeon 2014; Moseley 2004; Moseley 2005; Moseley 2006; Moseley 2009; Schreuders 2014), a mix of acute and chronic symptoms in two trials (Askin 2014; Oerlemans 1999), and three trials did not report the duration of symptoms (Aydemir 2006; Cacchio 2009b; Uher 2000). Trials were undertaken across a range of geographical locations including: Turkey (N = 5); Australia (N = 4); Italy, Germany, the Netherlands (N = 2 each); China, Serbia, and South Korea (N = 1 each).

### Interventions

We have provided a detailed description of the interventions delivered in each included trial in the 'Characteristics of included studies' table. The types of physiotherapy interventions delivered were heterogenous across the included trials and included various electrotherapy modalities (ultrasound, TENS, laser, interferential therapy, pulsed electromagnetic field therapy), cortically-directed sensory-motor rehabilitation strategies (GMI, mirror therapy, virtual body swapping, tactile sensory discrimination training), exercise (active, active-assisted, passive, stretching, strengthening, mobilising, functional; supervised and unsupervised), manual lymphatic drainage (MLD) and pain management advice. Five trials directly compared an active and placebo intervention (Askin 2014; Aydemir 2006; Cacchio 2009a; Cacchio 2009b; Durmus 2004). Six trials evaluated electrotherapy modalities (Askin 2014; Aydemir 2006; Dimitrijevic 2014; Durmus 2004; Hazneci 2005; Mucha 1992), eight trials evaluated cortically-directed sensory-motor rehabilitation strategies (Cacchio 2009a; Cacchio 2009b; Jeon 2014; Moseley 2004; Moseley 2005; Moseley 2006; Moseley 2009; Schreuders 2014), two trials evaluated MLD (Duman 2009; Uher 2000) and two trials evaluated general rehabilitation therapies (Li 2012; Oerlemans 1999).

## Excluded studies

We have listed the details regarding the 13 trial reports that we excluded in the 'Characteristics of excluded studies' table. The main reasons for exclusion were that the studies were either not RCTs (N = 8), investigated clinically irrelevant outcome measures (N = 2), tested interventions that fell outside the scope of physiotherapy (N = 2) or included participants with mixed aetiologies with only

one participant with CRPS I in each of the two arms of the trial (N = 1).

## Risk of bias in included studies

We presented a summary of the 'Risk of bias' assessments for all included trials in Figure 2 and Figure 3. We judged the overall risk of bias as being 'high' for 15 trials (Askin 2014; Cacchio 2009a; Cacchio 2009b; Dimitrijevic 2014; Duman 2009; Jeon 2014; Li 2012; Moseley 2004; Moseley 2005; Moseley 2006; Moseley 2009; Mucha 1992; Oerlemans 1999; Schreuders 2014; Uher 2000) and 'unclear' for three trials (Aydemir 2006; Durmus 2004; Hazneci 2005). We did not judge any of the included trials as having an overall 'low' risk of bias.

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

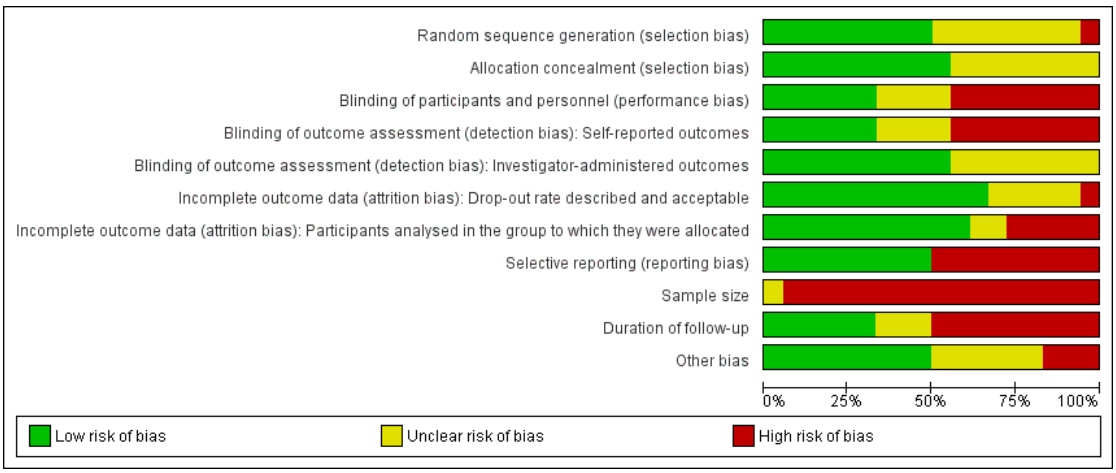
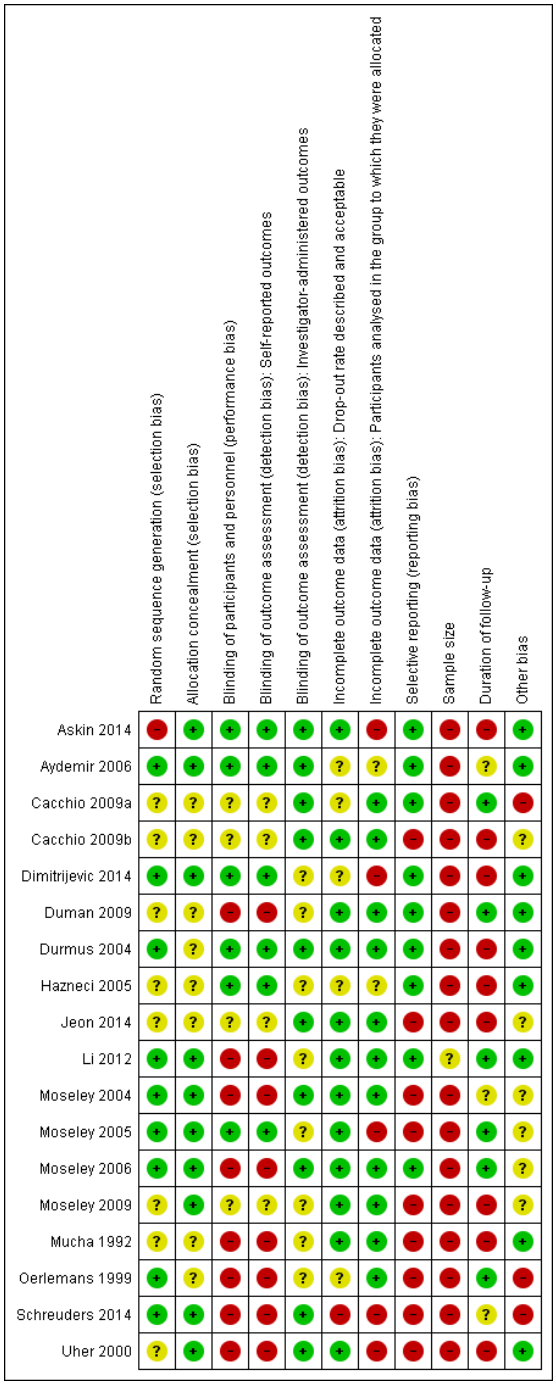


**Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included trial.**



### Allocation

Only seven out of the 18 trials reported using, or were judged to have used, adequate methods to generate a random sequence and conceal allocation (Aydemir 2006; Dimitrijevic 2014; Li 2012; Moseley 2004; Moseley 2005; Moseley 2006; Schreuders 2014) and as such we judged them as being of 'low' risk of selection bias. The risk of selection bias was 'unclear' in 10 trials (Cacchio 2009a; Cacchio 2009b; Duman 2009; Durmus 2004; Hazneci 2005; Jeon 2014; Moseley 2009; Mucha 1992; Oerlemans 1999; Uher 2000) where the methods used to generate the allocation sequence or where the method of allocation concealment were not adequately reported enough in order to allow a judgement of 'high' or 'low' risk of bias. One trial, Askin 2014, used a quasi-randomisation method and we judged it as having a 'high' risk of selection bias.

### Blinding

We judged six trials to have a 'low' risk of performance bias (Askin 2014; Aydemir 2006; Dimitrijevic 2014; Durmus 2004; Hazneci 2005; Moseley 2005), where participants were adequately blinded to their intervention or where we considered a lack of blinding to have been unlikely to have biased trial outcomes. Eight trials were at 'high' risk of performance bias and consequently detection biases because of inadequate or a lack of blinding (Duman 2009; Li 2012; Moseley 2004; Moseley 2006; Mucha 1992; Oerlemans 1999; Schreuders 2014; Uher 2000). We judged three trials, all of which tested the efficacy of electrotherapy-based modalities, as at 'low' risk of detection bias because they successfully blinded participants and outcome assessors (Askin 2014; Aydemir 2006; Durmus 2004).

### Incomplete outcome data

Twelve trials either had no drop-outs or a drop-out rate of less than 20% and as such we judged them as having a 'low' risk of attrition bias secondary to drop-outs (Askin 2014; Cacchio 2009b; Duman 2009; Durmus 2004; Jeon 2014; Li 2012; Moseley 2004; Moseley 2005; Moseley 2006; Moseley 2009; Mucha 1992; Uher 2000). In five trials the risk of attrition bias was 'unclear' either because the drop-out rate was not reported (Aydemir 2006; Hazneci 2005) or the drop-out rate between groups was unequal and the effect of which was uncertain (Cacchio 2009a; Dimitrijevic 2014; Oerlemans 1999). One trial, with an overall drop-out rate of 44%, had a 'high' risk of attrition bias (Schreuders 2014). We judged 11 trials (Cacchio 2009a; Cacchio 2009b; Duman 2009; Durmus 2004; Jeon 2014; Li 2012; Moseley 2004; Moseley 2006; Moseley 2009; Mucha 1992; Oerlemans 1999), two trials (Aydemir 2006; Hazneci 2005) and five trials (Askin 2014; Dimitrijevic 2014; Moseley 2005; Schreuders 2014; Uher 2000) respectively as being at 'low', 'unclear' and 'high' risk of attrition bias as a consequence of their adopted method of analysis.

### Selective reporting

We judged a total of nine trials as being of 'high' risk of reporting bias; three trials because of inadequate or incomplete reporting of primary outcomes, or both (Jeon 2014; Oerlemans 1999; Uher 2000) and six trials because the trial authors presented data in graphical format only, i.e. point estimates with measures of variation were not reported (Cacchio 2009b; Moseley 2004; Moseley 2005; Moseley 2009; Mucha 1992; Schreuders 2014). The other nine trials adequately reported outcome data and we judged them as being at 'low' risk of reporting bias (Askin 2014; Aydemir 2006; Cacchio 2009a; Dimitrijevic 2014; Duman 2009; Durmus 2004; Hazneci 2005; Li 2012; Moseley 2006).

### Other potential sources of bias

We considered three trials to be at 'high' risk of other potential sources of bias; one trial because it was published as a 'Letter to the Editor' and not as a full trial report (Cacchio 2009b); one trial because violations of the random sequence generation were permitted (Oerlemans 1999); and one trial because it did not report the baseline data of three participants excluded from the analysis and because of a likely highly significant baseline imbalance in duration of symptoms between groups (Schreuders 2014). The 15 other trials appeared to be free of other potential sources of bias.

#### Sample size

None of the included trials had intervention arms with 200 or more participants per treatment arm. One trial randomised 60 participants to each trial arm and we judged it as being at 'unclear' risk of bias (Li 2012). The remaining 17 trials had less than 50 participants per trial arm and we judged them as being at 'high' risk of bias based on this criterion.

#### Duration of follow-up

Nine trials employed a follow-up period of less than two weeks and we judged them as being at 'high' risk of bias based on this criterion (Askin 2014; Cacchio 2009b; Dimitrijevic 2014; Durmus 2004; Hazneci 2005; Jeon 2014; Moseley 2009; Mucha 1992; Uher 2000). Six trials employed a follow-up period of eight or more weeks and we judged them as being at 'low' risk of bias (Cacchio 2009a; Duman 2009; Li 2012; Moseley 2005; Moseley 2006; Oerlemans 1999). Three trials reported a follow-up period of two to seven weeks and we judged them as being at 'unclear' risk of bias (Aydemir 2006; Moseley 2004; Schreuders 2014).

## Effects of interventions

### Multimodal physiotherapy

One three-arm trial, Oerlemans 1999, (135 participants), which we judged as being at 'high' risk of bias based on a number of criteria, compared a physiotherapy programme (pain management advice, relaxation exercises, connective tissue massage, TENS and exercise) plus medical treatment according to a fixed pre-established protocol, to an occupational therapy (OT) programme (splinting, de-sensitisation, functional rehabilitation) plus medical management and to a control intervention, described as 'social work' (SW), (attention, advice) plus medical management in participants with CRPS I of the upper limb secondary to mixed aetiologies. The trial authors did not adequately report details regarding the nature of the interventions and did not standardise the number of treatment sessions given with the intensity and frequency of treatment adjusted to the individual needs of participants. The trial authors did not report the overall duration of the treatment periods for each trial group.

According to the trial authors, adjuvant physiotherapy, and to a lesser extent, OT were superior to SW for reducing pain according to all four measures of pain intensity at three months post-recruitment, and for reducing pain from effort of use of the affected extremity at six months. However, there were no significant between-group differences for any measure of pain intensity at 12 months follow-up. Numerical data (i.e. group means and standard deviations (SD) for each time-point) for the four self-reported measures of pain intensity (current pain, pain from effort of use of the affected extremity, least and worst pain experienced in the preceding week) were not reported, and the trial authors have not provided these data. Consequently, no further analyses of these measures were possible and we could not determine effect sizes.

Physiotherapy demonstrated a small but statistically significant between-group improvement in impairment at 12 months compared to SW (impairment level sum score, five to 50 scale; mean difference (MD) 3.7, 95% (CI) −7.13 to −0.27, P = 0.03; but not OT.

The trial authors did not report numerical data from other outcomes of interest, including measures of function (Radboud Skills Questionnaire, modified Greentest, Radboud Dexterity Test), HRQoL (Sickness Impact Profile) and adverse events although Oerlemans 1999 state that there were no between-group differences in function or well-being at 12 months follow-up.

### Quality of the evidence

There is very low quality evidence (RCT evidence: high, downgraded once for methodological limitations, once for imprecision and once for inconsistency) that physiotherapy plus medical treatment may be more effective at reducing pain at short- (three months) but not long-term follow-up (12 months) compared to a control intervention of SW and that physiotherapy plus medical treatment may be more effective at reducing impairment compared to SW at long-term follow-up in the treatment of CRPS I of the upper limb.

### Cortically directed sensory-motor rehabilitation strategies

#### Graded Motor Imagery

We included four separate trials of GMI, all of which were small trials (13 to 37 participants) judged to be at 'high' risk of bias. Two trials compared the same GMI protocol to control interventions of standard care (Moseley 2004; Moseley 2006); one compared a different GMI protocol plus conventional treatment (occupational and therapy physiotherapy) to conventional treatment alone (Schreuders 2014); and one compared three different GMI protocols to each another (Moseley 2005).

Moseley 2004 (N = 13) compared a six-week GMI programme (consisting of two weeks of limb laterality recognition followed by two weeks of imagined movements followed by two weeks of mirror-box therapy) to 12 weeks of ongoing medical management (predominantly physiotherapy) in participants with longstanding CRPS I of the upper limb post wrist fracture. Moseley 2006 compared the same GMI programme to physical therapy and usual care in a combined cohort of 14 participants with phantom-limb pain and 37 participants with CRPS I of the upper or lower limb of mixed aetiologies. Schreuders 2014 (N = 18) compared a six-week GMI programme (consisting of one week of limb laterality recognition, followed by one week of imagined movements, followed by four weeks of mirror-box therapy) plus conventional care (physiotherapy and OT) to conventional care alone in participants with longstanding CRPS I of the upper limb (aetiology not reported).

Moseley 2004 reported a statistically significant improvement in pain, as measured by the Neuropathic Pain Scale (NPS) at six weeks post-treatment, in participants that received GMI compared to ongoing medical management. Moseley 2004 reported a NNT to obtain a 50% reduction in the NPS (total score) of three (95% CI 1.4 to 10.1). Moseley 2006 reported statistically significant improvements in pain, as measured by a 0 to 100 VAS, and function, as measured by an 11-point NRS, immediately postintervention and at six months post-treatment for the combined cohort of participants with CRPS I and phantom limb pain. At six weeks post-treatment Schreuders 2014 found no statistically significant differences between groups on any measure of pain intensity or function. None of these trials reported any data about adverse events and did not measure other outcomes of interest, such as composite scoring of symptoms, HRQoL and PGIC.

Moseley 2004, Moseley 2006 and Schreuders 2014 presented data for changes in pain and function in participants specifically with

CRPS I graphically only and did not report numerical data (i.e. group means and SD values at each time-point) for measures of pain intensity or function, or both. However, 0 to 100 VAS pain and function data were available from Moseley 2004 and the CRPS I participants in Moseley 2006 from a previous overview of systematic reviews of interventions for CRPS (O'Connell 2013). We used these data in this Cochrane review with the authors' permission. Pooling of these results gave an effect size (weighted mean difference) of −14.45 (95% CI −23.02 to −5.87, P = 0.001, 49 participants, two trials; Analysis 1.1) with no significant heterogeneity. We expressed this data as a percentage of the mean baseline pain levels in the larger trial (58 out of 100), which equated to a 25% (95% CI 10 to 40) reduction in pain intensity at the end of the treatment period. Moseley 2004 presented outcomes at medium-term follow-up (six weeks post-treatment, N = 13, MD −20.00, 95% CI −7.97 to −32.13, P = 0.001). This equated to an improvement of 34% (95% CI 14 to 55) of the baseline VAS pain level in the Moseley 2006 trial (average baseline data for pain VAS was not available from the Moseley 2004 trial report). At long-term follow-up (six months post-treatment (N = 36)) in Moseley 2006, the MD was −21.00, 95% CI −10.83 to −31.17, P < 0.001, which equates to an improvement of 36% (95% CI 19% to 54%). The immediate post-treatment effect was below the threshold for a moderately clinically important difference but exceeded the threshold for a minimally clinically important difference. The medium- and long-term effects met the threshold for a moderately important benefit. We were unable to obtain numerical data from Schreuders 2014.

We pooled the data on function from two trials (Moseley 2004 and Moseley 2006; data on CRPS I participants only), which returned a MD of: 1.87 (95% CI 1.03 to 2.71, 49 participants, two trials; P < 0.001; Analysis 1.2) at the end of treatment; 2.26 (95% CI 1.42 to 3.10, P < 0.001) at medium-term follow-up (Moseley 2004, N = 13); and 2.30 (95% CI 1.12 to 3.48, P < 0.001) at long-term follow-up (Moseley 2006, N = 36). This represented a large improvement in function from the baseline function score (0.5) in the control group of the larger trial (Moseley 2006).

In a three-arm trial, Moseley 2005 (N = 20) compared a six-week GMI programme with its three components delivered in the 'correct' order (i.e. two weeks of laterality recognition followed by two weeks of imagined movements followed by two weeks of mirror-box therapy) to two other GMI programmes with selected components delivered in different orders at odds with its hypothesised mechanism of action, in participants with longstanding CRPS I of the upper limb post wrist fracture. We found statistically significant improvements in pain and function in the correctly ordered GMI group compared to both comparison groups, as measured by the NPS and an 11-point NRS respectively at 12 weeks post-treatment. Moseley 2005 reported that at 12-week follow-up, the mean reduction in NPS score for the correctly ordered GMI group was approximately seven and 18 points greater than the mean reductions in the other two groups respectively. The trial did not report numerical data for measures of pain intensity and function, and we have been unable to obtain these data from the trial author. Consequently we were unable to perform any further analyses of these measures and we could not determine the effect sizes. The trial did not report any data concerning adverse events and did not measure other outcomes of interest, such as composite scoring of symptoms, HRQoL and PGIC.

### Quality of the evidence

There is very low quality evidence (RCT evidence: high, downgraded once for methodological limitations, once for imprecision and once for inconsistency) that GMI plus medical management may be more effective at reducing pain and improving function than conventional physiotherapy plus medical management in the treatment of CRPS I of the upper limb. There is very low quality evidence (RCT evidence: high, downgraded once for methodological limitations, once for imprecision and once for inconsistency) that appropriately ordered GMI was more effective at reducing pain and improving function than inappropriately ordered GMI.

### Mirror therapy

We included two trials of mirror therapy (Cacchio 2009a; Cacchio 2009b). Cacchio 2009a (N = 48) compared four weeks of mirror therapy plus conventional stroke rehabilitation to placebo mirror therapy (covered mirror) plus conventional stroke rehabilitation in participants with CRPS I of the upper limb post-stroke. In a trial judged to be at 'unclear' risk of bias, Cacchio 2009a reported statistically significant improvements in pain and function, at all post-treatment time-points, in the mirror therapy group compared to the placebo group. Specifically, Cacchio 2009a 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, P < 0.001) and in pain on movement (shoulder flexion) of −3.10 (95% CI −4.28 to −1.92, P < 0.001). At six-month follow-up the differences were still present, −3.4 (95% CI −4.71 to −2.09, P < 0.001) for pain at rest, and −3.8 (95% CI −4.96 to −2.64, P < 0.001) for pain on movement. The post-treatment and six-months follow-up mean differences for pain at rest equated to a 38% (95% CI 21 to 56%) and 45% (95% CI 28 to 62%) reduction in the average baseline pain level respectively, whist the post-treatment and six-months follow-up mean differences for pain on movement equated to a 36% (95% CI 23 to 50%) and 45% (95% CI 31 to 58%) reduction in the average baseline pain level respectively, consistent with a moderately important benefit.

Regarding disability, Cacchio 2009a also reported significant mean between-group differences in functional limitation, as measured by the functional ability subscale of the Wolf Motor Function Test (WMFT, zero to five score range) of −1.9 (95% CI −2.36 to −1.44, P < 0.001) at the end of treatment and of −2.3 (95% CI −2.88 to −1.72, P < 0.001) at six-months follow-up.

In a separate three-arm trial, judged to be at 'high' risk of bias, Cacchio 2009b (N = 24) compared four weeks of mirror therapy to either placebo mirror therapy (covered mirror) or mental imagery training in participants with CRPS I of the upper limb post stroke. Cacchio 2009b reported that seven out of eight participants in the mirror therapy group reported reduced pain (median change in zero to 100 VAS of −51 mm, range −70 to −18) compared with one of eight participants in the covered mirror therapy group and two of eight participants 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, the trial authors did not report any further between-group data and we have been unable to obtain these data from the trial authors. Consequently we were unable to perform any further analyses of these measures and we could not determine the effect size. The trial authors did not report data from other outcomes of interest, including measures of function and adverse events, while they did not measure outcomes, such as composite scoring of symptoms, HRQoL and PGIC.

#### Quality of the evidence

There was very low quality evidence (RCT evidence: high, downgraded once for methodological limitations, once for imprecision, once for indirectness) that mirror therapy reduced pain and improved upper limb function in participants with post stroke CRPS I of the upper limb compared with covered mirror therapy.

### Virtual body swapping

We included one trial of virtual body swapping with mental rehearsal compared to virtual body swapping alone (Jeon 2014) (N = 10) in participants with CRPS I of either the upper or lower limbs, multiple limbs or the whole body, the aetiology of which was not reported. Participants underwent a single session of their allocated intervention with follow-up immediately post-treatment only. Jeon 2014 reported that there was no difference between the groups regarding pain intensity, as measured by an 11-point Likert rating scale ranging from zero (no pain) to 10 (severe pain) immediately post-treatment. The trial authors did not report numerical data for measures of pain intensity, and we have been unable to obtain these data from the trial authors. As a result, we could not conduct any further analyses and we could not determine the effect size. We rated the trial as at 'unclear' risk of bias for random sequence generation and allocation concealment, and at 'high' risk of bias for selective outcome reporting. The trial authors did not report any data concerning adverse events and did not measure other outcomes of interest, such as measures of function, composite scoring of symptoms, HRQoL and PGIC.

#### Quality of the evidence

There was very low quality evidence (RCT evidence: high, downgraded once for methodological limitations, once for imprecision and once for inconsistency) that virtual body swapping with mental rehearsal does not reduce pain in people with CRPS I in the short-term.

### Tactile discrimination training

We included one trial, Moseley 2009, that compared four tactile discrimination training (TDT) protocols with one another (N = 10) in participants with CRPS I of the upper limb from mixed aetiologies. Moseley 2009 reported no significant differences in self-reported pain intensity (0 to 100 VAS) at two day follow-up. The trial authors did not report numerical data for measures of pain intensity, and they have not supplied us with these data. Thus we were unable to perform any further analyses and we could not determine the effect size. We rated the trial at 'high' risk of bias for selective outcome reporting, sample size and duration of follow-up. Regarding adverse events, three participants reported that the pressure stimuli associated with the TDT occasionally hurt but that this was not enough to necessitate modification or cessation of the TDT training. The trial authors did not measure other outcomes of interest, such as function, composite scoring of symptoms, HRQoL and PGIC.

#### Quality of the evidence

There was very low quality evidence (RCT evidence: high, downgraded once for methodological limitations, once for imprecision and once for inconsistency) that TDT does not reduce the pain associated with CRPS I at short-term follow-up.

## Electrotherapy interventions

### Ultrasound of the stellate ganglion versus placebo

Two trials, Askin 2014 and Aydemir 2006, investigated the effectiveness of applying ultrasound directed to the stellate ganglion versus placebo. Both trials were small, with fewer than 50 participants, and were at 'high' or 'unclear' risk of bias based on a number of criteria. Askin 2014 (N = 45) compared two doses (3.0 watts and 0.5 watts intensity) of high frequency ultrasound to placebo ultrasound. All trial groups also received multimodal conventional treatment that included a course of medication (including vitamin C, gabapentin and prednisolone) and physiotherapy (including TENS, contrast baths, active and passive range of motion exercises and stretching, resistance and mirror box exercises). The participants received treatments daily for 20 days. Aydemir 2006 (N = 25) compared stellate ganglion block with ultrasound to blocks with lidocaine and placebo conditions for both interventions. All

trial groups received exercises, TENS, contrast baths, compression and oral paracetamol. While only one trial, Aydemir 2006, provided data in an extractable format for meta-analysis, both trials demonstrated no statistically significant difference of ultrasound over placebo for pain. Regarding assessment of function, Askin 2014 used the DASH score to measure function. While Askin 2014 did not present data in a format extractable for meta-analysis, they reported no statistically significant effect of ultrasound. Aydemir 2006 measured hand function using a Functional Hand Scale (0 to 19 scale, with lower scores indicating better function) and reported statistically significant improvements in all three trial groups post-treatment and at one month follow-up. According to our analyses there were significantly greater improvements in the placebo group post-treatment (MD 7.86, 95% CI 1.93 to 13.79, P = 0.009) and at one month follow-up (MD 6.79, 95% CI 0.85 to 12.73, P = 0.02). The trial authors did not present any data concerning adverse events and did not measure other outcomes of interest, such as composite scoring of symptoms, HRQoL and PGIC.

**Quality of the evidence**

There is low quality evidence (RCT evidence: downgrade once for methodological limitations and once for imprecision) that stellate ganglion block via ultrasound is not effective for the treatment of pain or loss of hand function in people with CRPS I.

#### Ultrasound of the stellate ganglion versus TENS.

One trial with 30 participants compared ultrasound of the stellate ganglion to TENS in military recruits with acute (mean duration of symptoms: 44 days) CRPS I of the upper limb secondary to mixed aetiologies (Hazneci 2005). Both groups also received contrast baths and physiotherapist prescribed exercises. In this trial the ultrasound group demonstrated inferior post-treatment pain scores (0 to 10 VAS; MD 2.13, 95% CI 1.47 to 2.79, P < 0.001) which equates to a potentially clinically important difference of 27% (95% CI 19 to 36) of the average baseline pain score. The trial authors measured pain severity at the end of the three-week intervention period only without longer-term follow-up. We rated the trial at 'unclear' risk of bias for random sequence generation and allocation concealment. They did not report any data concerning adverse events and did not measure other outcomes of interest, such as function, composite scoring of symptoms, HRQoL and PGIC.

**Quality of the evidence**

There is low quality evidence (RCT evidence: high, downgraded once for imprecision and once for inconsistency) that ultrasound to the stellate ganglion is inferior to TENS for the treatment of pain in people with CRPS I in the short-term.

#### Pulsed electromagnetic field therapy

One trial with 40 participants, Durmus 2004, compared pulsed electromagnetic field (PEMF) treatment (100 Gauss, 50 Hz, five times weekly for six weeks) plus calcitonin and a stretching exercise routine to placebo EMF plus calcitonin and stretching in participants with acute (mean duration of symptoms: 52 days) CRPS I of the upper limb following Colles fracture. At the end of treatment, Durmus 2004 found no statistically significant between-group difference in pain at rest (VAS), pain on activity, or range of motion. We rated the trial at 'high' risk of bias for study size and duration of follow-up and at 'unclear' risk of bias for allocation concealment. The trial authors did not report any data concerning adverse events and did not measure other outcomes of interest, such as function, composite scoring of symptoms, HRQoL and PGIC.

**Quality of the evidence**

There is low quality evidence (RCT evidence: high, downgraded once for imprecision and once for inconsistency) that PEMF is not superior to placebo for the treatment of pain or range of motion in people with CRPS I.

#### Laser therapy versus Interferential therapy

One trial with 50 participants compared 20 sessions of low-level laser therapy with interferential current therapy in participants with post-traumatic CRPS I of the upper or lower limb (Dimitrijevic 2014). Both trial groups also received kinesitherapy that consisted of individualised active and active assisted exercises, strictly dosed up to pain threshold. We rated the trial at 'high' risk of bias for incomplete outcome data, trial size and duration of follow-up. Post-therapy the results demonstrated a statistically significant between-group mean difference for pain at rest (0 to 100 VAS) of −8.6 (95% CI −16.27 to −0.93, P = 0.03) in favour of laser therapy. This equates to a difference of 14% (95% CI 1.5 to 26) from the mean baseline pain score of the two groups, which falls below our criteria for a minimal clinically important difference. There was no statistically significant post-treatment between-group difference with respect to pain with movement of the affected wrist or ankle according to our analysis (P = 0.07). The trial authors reported that there were no negative effects of therapy recorded. The trial authors did not measure other outcomes of interest, such as function, composite scoring of symptoms, HRQoL and PGIC.

**Quality of the evidence**

There is very low quality evidence (RCT evidence: high, downgraded once for methodological limitations, once for imprecision and once for inconsistency) that low level laser therapy does not result in a clinically important reduction in pain when compared to interferential therapy when added to exercise therapy.

#### $CO_2$ Bath therapy

One trial, Mucha 1992, with 40 participants compared carbon dioxide ($CO_2$) baths in addition to exercise therapy with exercise therapy alone in participants with post-traumatic CRPS I of the hand. Neither intervention is clearly described in the paper though the baths were administered in 12-minute sessions five times a week for four weeks. Mucha 1992 reported that there was a statistically significant between-group difference in pain at rest, pain with movement and night pain in favour of the $CO_2$ bath group. The trial authors did not report numerical data, and we have been unable to obtain these data from the trial authors. Consequently, we were unable to perform any further analyses of these measures and could not determine an effect size. We rated the study at 'high' risk of bias on five separate criteria. The trial authors did not report any data concerning adverse events and did not measure other outcomes of interest, such as function, composite scoring of symptoms, HRQoL and PGIC.

#### Quality of the evidence

There is very low quality evidence (RCT evidence: high, downgraded once for methodological limitations, once for imprecision and once for inconsistency) that $CO_2$ baths combined with exercise therapy are more effective for relieving the pain associated with CRPS I than exercise alone.

#### Electro-acupuncture and massage versus rehabilitation

One trial, Li 2012, with 120 participants compared 30 sessions of electro-acupuncture combined with upper limb massage therapy to 30 sessions of rehabilitation in participants with post stroke shoulder-hand syndrome. Rehabilitation consisted of active-assisted scapular movements, Bobath exercises to clench the fist, functional transfer training and proprioceptive neuromuscular facilitation (PNF) exercise. It is unclear if the primary aim of the rehabilitation offered was to manage the shoulder-hand syndrome explicitly or if it was a general rehabilitation programme aimed at addressing the motor impairments related to the stroke. This trial measured pain in the shoulder when it was taken passively to 90° of elevation but did not include any other measure of upper limb or hand pain. We rated the trial at 'high' risk of bias for blinding of participants and at 'unclear' risk of bias for sample size. Li 2012 reported greater reductions on the outcome pain (in the shoulder when taken passively to 90°) in favour of the electro-acupuncture and massage group at the end of the six-week treatment period (MD −1.70, 95% CI −2.09 to −1.31, P = 0.01) which were sustained at 12-weeks follow-up (MD −1.40, 95% CI −1.78 to −1.02, P < 0.001). The post-treatment and 12-week follow-up MD values equated to a 21% (95% CI 16 to 26%) and 18% (95% CI 13 to 22%) reduction in the average baseline pain level respectively. These were below the threshold for a moderately clinically important difference but exceeded the IMMPACT threshold (15%) for a minimally important benefit. Li 2012 reported no statistically significant difference in hand function between the two trial groups, but a statistically significant difference in upper limb function in favour of the electro-acupuncture and massage group at the end of treatment (MD 4.5, 95% CI 0.85 to 8.15, P = 0.05) which was no longer significant at 12-weeks follow-up. The trial authors reported that there were no adverse reactions to intervention in either trial group. They did not measure other outcomes of interest, such as composite scoring of symptoms, HRQoL and PGIC. Notably, we also have some concerns regarding the diagnostic equivalence of 'shoulder-hand syndrome' and CRPS I and whether the control intervention was directed towards the management of the shoulder-hand syndrome or the upper limb functional stroke problem, both of which may have implications for the generalisability of this trial's findings.

#### Quality of the evidence

There is very low quality evidence (RCT evidence: high, downgraded once for methodological limitations, once for imprecision and once for indirectness) that a course of electro-acupuncture and massage is superior to rehabilitation therapy for pain on passive shoulder elevation in participants with post stroke shoulder-hand syndrome, but not hand-specific function. Also, the magnitude of effect on pain severity was clinically minimal.

### Other interventions

#### Manual Lymphatic Drainage therapy

Two included trials, Duman 2009 and Uher 2000, investigated the effectiveness of adding MLD therapy to rehabilitation. Duman 2009 (N = 34) compared the addition of MLD massage to conventional care (nonsteroidal anti-inflammatory drugs and physical therapy) to conventional care alone in participants with CRPS I of the upper limb of mixed aetiology. Uher 2000 (N = 40) compared the addition of MLD in addition to exercise therapy to exercise therapy alone in participants with CRPS I of the lower limb of mixed aetiology. We rated both trials as being at 'high' risk of bias on multiple criteria. We were only able to extract data on relevant outcomes from Duman 2009, but both trials demonstrated no statistically significant effect of the addition of MLD on pain. The trial authors did not report any data on adverse events and did not measure other outcomes of interest, such as function, composite scoring of symptoms, HRQoL and PGIC.

#### Quality of the evidence

There is low quality evidence (RCT evidence: high, downgraded once for methodological limitations and once for imprecision) that the addition of MLD to rehabilitation does not improve pain in people with CRPS I.

# DISCUSSION

## Summary of main results

Given the paucity of high quality of evidence derived from our analyses of the 18 included randomised controlled trials (RCTs) (739 participants), we cannot draw any firm conclusions regarding the effectiveness or harmfulness of a broad range of physiotherapy-based interventions for treating the pain and disability associated with complex regional pain syndrome (CRPS) I in adults.

The results of one included trial, Oerlemans 1999, provided very low quality evidence that a multimodal physiotherapy programme may provide a small, long-term improvement in impairment, as measured by a composite scoring method, compared to a minimal intervention of 'social work', but the magnitude of this effect is of questionable clinical significance. We could not determine its effect on a range of pain-related outcomes.

Evidence that supports the use of cortically-directed sensory-motor rehabilitation strategies was mixed. Our findings suggest that graded motor imagery (GMI) may provide clinically meaningful medium- and long-term improvements in both pain and disability in people with CRPS I, although the results from these trials were from very low quality studies and were inconsistent. While our meta-analysis of two trials, Moseley 2004 and Moseley 2006, provided evidence of such benefits, we were unable to obtain and include data from one, as yet unpublished, clinical trial with contradictory results (Schreuders 2014); these results should therefore be treated with caution.

Based on two included trials we found very low quality evidence that mirror therapy provides long-term clinically meaningful improvements in pain and function in people with CRPS I following stroke (Cacchio 2009a; Cacchio 2009b). The effectiveness of mirror therapy in broader participant populations with CRPS I (e.g. post-trauma) is unknown. We also found very low quality evidence that the more novel interventions of virtual body swapping ± mental rehearsal (Jeon 2014) and tactile discrimination training (TDT) (Moseley 2009) do not provide any short-term benefits for pain in people with CRPS I.

Evidence that supported the use of electrotherapy-based interventions was mixed. There was low to very low quality evidence that:

1. stellate ganglion block via ultrasound combined with a conventional treatment programme was not superior to placebo ultrasound for pain and hand function at medium-term follow-up (Askin 2014; Aydemir 2006);
2. stellate ganglion block via ultrasound combined with contrast baths and exercise was inferior to TENS combined with contrast baths and exercise for pain and short-term follow-up (Hazneci 2005);
3. PEMF therapy was not superior to placebo PEMF for pain at short-term follow-up (Durmus 2004);
4. laser therapy combined with exercise may provide a small, probably clinically insignificant, benefit in pain compared to interferential current therapy and exercise at short-term follow-up (Dimitrijevic 2014); and
5. $CO_2$ bath therapy combined with exercise may improve pain compared to exercise therapy alone although the effect size could not be determined (Mucha 1992) and the interventions were inadequately described.

Two RCTs provided low quality evidence that manual lymphatic drainage (MLD) combined with and compared to either non-steroidal anti-inflammatories and physical therapy (Duman 2009) or exercise therapy (Uher 2000) is not beneficial for pain in people with CRPS I.

We found very low quality evidence from one trial, Li 2012, that electro-acupuncture and massage were superior to a stroke rehabilitation programme for pain on passive shoulder movement in shoulder-hand syndrome post stroke at longer-term follow-up. However, the magnitude of this effect was unlikely to be clinically important and both the reliability and validity of the outcome measure used are questionable.

Only two trial reports, one related to laser and interferential therapies, Dimitrijevic 2014, and one to TDT, Moseley 2009, commented on the presence or absence of adverse events and reported no serious events.

We did not find any clinical trials that included participants with CRPS II that met the inclusion criteria of this Cochrane review.

Overall, we identified a lack of high or moderate quality evidence with which to inform or guide rehabilitation practice in people with CRPS I or II. Based on the current body of evidence, we cannot draw any accurate or firm conclusions regarding the effectiveness or safety of any of the specific physiotherapy-based interventions we identified in this Cochrane review.

## Overall completeness and applicability of evidence

The evidence base for the use of physiotherapy interventions in CRPS is incomplete, although this reflects a broader problem for all intervention research in CRPS (O'Connell 2013). Most included trials (16/18) used established diagnostic criteria to identify participants with CRPS I. However, as might be expected given the development history of such criteria in CRPS, there was some variation in the criteria used between included trials. Beyond various issues relating to risk of bias and study size (see Quality of the evidence) there are very few instances where more than one included trial tested a specific intervention. Two trials, Duman 2009 and Hazneci 2005, specifically recruited participants from military populations. As such, it is possible that contextual factors specific to that participant group and environment may limit the applicability of those results to civilian clinical practice. Eight trials only measured outcomes immediately at the end of treatment with no longer-term follow-up. Such trials offer limited information about the genuine clinical utility of interventions for a condition that is commonly persistent. The broad heterogeneity

of interventions assessed in the included trials afforded us limited opportunities to pool data. However, it is possible that advances in meta-analytical statistics may permit such analyses in the future (Melendez-Torres 2015).

The aim of this Cochrane review was to investIgate the effectiveness of physiotherapy interventions for people with CRPS I or II. We used a deliberately inclusive definition to attempt to include evidence on any intervention that might reasonably be delivered within a physiotherapy context for people with CRPS. As a result the included trials varied considerably but most were designed to test the specific effectiveness of individual modalities either alone, when added to other treatments or compared to other treatments. While these trials offered information about the specific or additional clinical benefits of those modalities, they are less informative about the effectiveness of physiotherapy programmes that incorporate multiple treatment modalities, but are more likely to reflect physiotherapy as it is delivered in clinical practice. Only one included trial, Oerlemans 1999, took the pragmatic approach of testing a multimodal physiotherapy programme against a minimal treatment control group. Notably, this trial pre-dates substantial developments in the pathophysiological models of CRPS and it is possible that a modern multimodal physiotherapy programme might differ substantially. In addition, the included trials rarely reported on adverse events (two out of 18 trials) and it is unclear whether or not this represents an absence of adverse events or a failure to report them.

While we categorised these interventions under the label "physiotherapy" in this Cochrane review, we recognise that rehabilitation therapies may be delivered by a range of different professionals, including occupational therapists and nurses.

## Quality of the evidence

As reflected by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) ratings, the overall quality of the evidence in this Cochrane review was low or very low. This reflects the fact that most included trials were at unclear or high risk of bias for criteria included under the standard domains of the Cochrane 'Risk of bias' tool, and under the additional 'Risk of bias' criteria of study size and duration included in this review. The included trials studied a broad heterogeneity of interventions, which afforded us limited opportunity to pool data and that, coupled with study size, led to issues of imprecision and inconsistency. It is likely that small study effects, wherein there is a propensity for negative studies to not be published, might lead to an overly positive picture for some interventions, particularly in a field with such a limited evidence base. Evidence from the wider literature indicates that this might lead to an overly positive picture for some interventions (Dechartres 2013; Moore 2012; Nüesch 2010). In a review of meta-analyses, Dechartres 2013 demonstrated that trials with fewer than 50 participants, which reflects most trials (17/18) included in this Cochrane review, returned effect estimates that were on average 48% larger than the largest trials and 23% larger than estimates from studies with sample sizes of more than 50 participants. We did not downgrade any of the GRADE judgements on the basis of publication bias, as there can be no direct evidence with so few trials for any given intervention. Moreover, it is accepted that existing approaches to detecting publication bias are unsatisfactory. To an extent our GRADE judgements reflect this risk through the assessment of imprecision and the limitations of included trials. Conversely, the issue of small study size with few included trials available for any single comparison raises the possibility of false negatives through lack of statistical power (Button 2013). Many of the comparisons we included in this review did not demonstrate a statistically significant difference. However, it is possible that we may have missed real effects on this basis.

The quality of reporting in many included trials was problematic. There was a lack of detailed descriptions of some interventions and a number of included trials did not present key numerical outcome data for all time-points (9/18 trials) or insufficiently reported the scoring properties of their outcome measures for pain intensity (7/18 trials). The quality of reporting of pain-related outcomes measures in clinical trials and observational studies is frequently insufficient (Smith 2015). In a systematic review of the quality of pain intensity reporting in three prominent pain journals, Smith 2015 found that nearly one quarter of published studies inadequately reported the type of pain intensity measure employed.

## Potential biases in the review process

We conducted extensive and sensitive literature searches and included trials regardless of the language of publication. As such this Cochrane review probably represents the totality of currently available evidence. The choice to use the IMMPACT thresholds to determine the clinical importance of effect sizes is potentially controversial. What exactly constitutes an important difference on any given outcome measure remains contentious as the construct of a generic importance thresholds for a variety of interventions fails to reflect that patient satisfaction might differ substantially between interventions given their risks, costs and inconvenience, the point in the care pathway at which the participant arrives, and a range of other possible factors. Moreover, the IMMPACT thresholds are based on estimates of the degree of within-person change from baseline that participants might consider to be clinically important, whereas the effect sizes focused on in this review reflect the average change between intervention-groups following the interventions. For some pharmacological interventions the distribution of participant outcomes is bimodal (Moore 2013; Moore 2014a; Moore 2014b). That is, some participants experience a substantial reduction in symptoms, some minimal to no improvement and very few experience intermediate (moderate) improvements. In this instance, and if the distribution of participant outcomes reflects the distribution of treatment effects, then the average effect may be the effect that the fewest participants actu-

ally demonstrate (Moore 2013). It is therefore possible that a small average between-group effect size might reflect that a proportion of participants responded very well to the intervention tested. The common solution to this problem is to conduct a 'responder analysis', which compares the proportion of participants achieving a clinically important improvement from baseline in the treatment and control groups. However responder analysis is very rare in rehabilitation therapies and there is no evidence to date to establish whether outcomes are commonly bimodal in rehabilitation trials. It therefore remains equally possible that a very small average between-group effect might accurately represent the generally very small effects of an intervention for most or all individuals.

As such, the between-group change is our sole available estimate of the specific effectiveness of the interventions in the included trials. Since the publication of our protocol for this review, Smart 2013, the OMERACT 12 group reported recommendations for minimally important difference for pain outcomes (Busse 2015). The group recommends a threshold of 10 mm on a 0 to 100 VAS as the threshold for minimal importance for average between-group change, though stress that this should be interpreted with caution as it remains possible that estimates which fall closely below this point may still reflect a treatment that benefits an appreciable number of participants. Using this largely more lenient threshold would not alter our conclusions regarding clinical importance. The OMERACT thresholds present similar problems to those associated with all generic thresholds and it seems likely that the discussion around what constitutes clinical importance will continue. Arguably, the thresholds used in this Cochrane review of a 15% or 30% improvement in baseline levels of pain that are specifically attributable to the interventions do not represent unreasonably high thresholds.

### Agreements and disagreements with other studies or reviews

The results of this systematic review are largely consistent with the conclusions drawn in our recent overview of systematic reviews of all interventions for CRPS (O'Connell 2013). In O'Connell 2013 we drew our conclusions mainly based on two non-Cochrane reviews of physiotherapy interventions for CRPS (Daly 2009; Smith 2005) and we based the analysis of the evidence at the level of those included reviews. Our current review is more up-to-date, includes a number of additional studies and our conclusions are drawn from direct analysis of the original trials. Daly 2009 concluded that there was good to very good quality evidence to support the use of GMI for CRPS; and a review by Bowering 2013 (of which review author NEO was a co-author) concluded that there was limited evidence to suggest that GMI may be effective for CRPS. In O'Connell 2013 we concluded that there was low quality evidence for the effectiveness of GMI. In this Cochrane review we downgraded the GRADE rating for the evidence related to GMI to very low, largely due to the inconsistency introduced by the inclusion of Schreuders 2014. In Schreuders 2014 the trial authors adjusted the treatment schedule compared to the schedules delivered by Moseley 2004 and Moseley 2006, though it was based on the same theoretical model. Smith 2005 concluded that there was some evidence that exercise, acupuncture, TENS, relaxation techniques, mirror therapy, GMI and combined treatment programmes may be helpful and that it was not possible to determine the effectiveness of individual treatments for CRPS-I. Ten years on, that picture has not changed substantially. It is possible that future systematic reviews may provide further evaluations of the effectiveness of cortically-directed sensory-motor rehabilitation strategies (Plumbe 2013).

Recent clinical guidelines from the USA (Harden 2013) and the UK (Goebel 2012) have placed rehabilitation therapies as first-line treatments for people with CRPS. Both guidelines describe and recommend an extensive range of possible physiotherapy modalities that might be employed. In making their recommendations, these guidelines (unlike this Cochrane review) draw on evidence from non-randomised studies, expert consensus and studies of neuropathic pain generally. This Cochrane review highlights the fragility of the evidence underpinning these recommendations. The optimal approach to physiotherapy for people with CRPS and the true extent of potential benefits and risks remain uncertain. Also, there may be substantial redundancy within the broad range of therapies described or recommended in the guidelines.

## AUTHORS' CONCLUSIONS

### Implications for practice

It is likely that, in line with contemporary clinical guidelines, physiotherapy and rehabilitation based interventions will continue to be first-line treatments for people with complex regional pain syndrome (CRPS). In this Cochrane review we have been unable to find compelling evidence of the effectiveness, or lack thereof, of physiotherapy interventions, or to inform an optimal approach to therapy, although very low quality evidence suggests a possible benefit of multimodal physiotherapy, graded motor imagery (GMI) and mirror therapy. The available evidence suggests that applying ultrasound to the stellate ganglion or manual lymphatic drainage (MLD) to the affected limb are unlikely to offer clinical benefit to people with CRPS type I.

### Implications for research

Overall, given the existing limitations within the current body of evidence, there is a clear need for further research into physiotherapy interventions in people with CRPS but many challenges remain in addressing this problem. Given the relatively low incidence of CRPS, it is likely to be difficult to recruit adequate numbers of participants to clinical trials. It seems likely that the best

chance of addressing this challenge is through multicentre, collaborative research projects aimed at recruiting participants from potentially larger pools of clinical populations. It seems unlikely that it will be possible to generate sufficient evidence to support the many individual modalities currently applied to people with CRPS. In this instance there is a case for taking a pragmatic approach to developing contemporary multi-modal, individually tailored "best practice" models of physiotherapy care and prioritising trials of these programmes against usual or minimal care. Such trials might provide pragmatic estimates of effectiveness which best reflect the value of guideline recommended practice. Larger replication trials of GMI and mirror therapy would also be useful in order to provide more accurate estimates of treatment effect for these interventions, which current evidence suggests may offer meaningful clinical benefit. Future trials should use established diagnostic criteria, clearly report the type of CRPS under investigation and their design should consider recent recommendations (Busse 2015; Dworkin 2008; Dworkin 2009; Dworkin 2010; Turk 2008a; Turk 2008b) for the design and reporting of trials in chronic pain. This will help to ensure that outcomes, thresholds for clinical importance and study design are optimal and we also highlight the need to measure patient-focused outcomes over clinically relevant periods of time. Furthermore, future trials should adhere to CONSORT guidance, including that related to the reporting of the development and evaluation of complex interventions (Möhler 2015).

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* *Indicates the major publication for the study*

# CHARACTERISTICS OF STUDIES

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

**Askin 2014**

| | |
|---|---|
| Methods | **Design:** parallel group, 3-arm, single-blind RCT (Turkey; dates not reported)<br>**Setting:** outpatient hospital clinic.<br>**Interventions:** conventional care plus low dose high frequency ultrasound therapy (0.5 watts/cm²) for stellate ganglion blockade or conventional care plus low dose high frequency ultrasound therapy (3.0 watts/cm²) for stellate ganglion blockade or conventional care plus placebo ultrasound therapy<br>**Sample size calculation:** not reported. |
| Participants | **Number of participants:** 45 (15 per group).<br>**Type of noxious initiating event:** mixed (fracture of the distal radius (n = 17), tendon injury (n = 10), hand contusion (n = 5), postsurgery for carpal tunnel syndrome (n = 4), fracture of the elbow (n = 2), fracture of the humerus (n = 1), fracture of the finger (n = 1)) (upper limb)<br>**Diagnostic criteria:** Bruehl 1999 (CRPS I).<br>**Baseline characteristics:**<br>1. conventional care plus low dose high frequency ultrasound therapy (0.5 watts/cm²) for stellate ganglion blockade:<br>i) Mean (range) age = 45 (23 to 69) years; female:male = 7:6;<br>ii) Mean (range) duration of CRPS I 57 (38 to 156) days;<br>2. conventional care plus low dose high frequency ultrasound therapy (3.0 watts/cm²) for stellate ganglion blockade:<br>i) Mean (range) age = 46 (23 to 69) years; female:male = 7:6;<br>ii) Mean (range) duration of CRPS I 62 (26 to 161) days;<br>3. conventional care plus placebo ultrasound therapy<br>i) Mean (range) age = 44 (22 to 69) years; female:male = 5:9;<br>ii) Mean (range) duration of CRPS I 70.5 (15 to 162) days.<br>**Inclusion criteria:**<br>1. upper limb CRPS I.<br>**Exclusion criteria:**<br>1. peripheral or central nerve lesions;<br>2. diabetes mellitus;<br>3. severe heart failure;<br>4. severe hypertension;<br>5. cardiac conduct disorders;<br>6. chronic obstructive pulmonary disease;<br>7. chronic alcoholism;<br>8. rheumatologic disease;<br>9. malignancy;<br>10. thyroid disease;<br>11. participants using anticholinergic or antihypertensive medication. |
| Interventions | Participants in all 3 groups received conventional care including:<br>1. pharmacotherapy (including 500 mg/day vitamin C, Gabapentin (dose: 1800 mg/day) and Prednisolone (dose: 30 mg/day-2 weeks, stopped within next 2 weeks)); |

| | |
|---|---|
| | 2. 20 sessions of transcutaneous electrical nerve stimulation ((Enraf Nonius brand Endomed 582ID) 100 hertz (Hz) frequency to the painful area of the affected extremity once a day, 20 minutes);<br>3. contrast bath applications ((Ewac brand device) by immersing the affected upper extremity into hot (38°C) water for 4 minutes and then cold water (4°C) for 1 minute for a total 20 minutes); and<br>4. exercise (active, active assistive and passive range of motion exercises to the wrist and fingers, stretching exercises, progressive resistance exercises, performed as 2 sets of 15 repetitions for each exercise, once per day, plus mirror box exercises (details not reported) for 30 minutes).<br>**Conventional care plus low dose high frequency ultrasound therapy (0.5 watts/cm$^2$) (N = 15)**<br>Components of intervention: using a Enraf Nonius Sonopuls (590 model) therapeutic ultrasound of the stellate ganglion was applied by placing the 1 cm$^2$ ultrasound head at the level of transverse process of the 7th vertebra and 3 cm to 4 cm above the sternoclavicular joint, using a 1 MHz frequency and pulsed pattern of 1:4<br>Dosage: 0.5 watts/cm$^2$, for 5 minutes.<br>Frequency of administration: not reported (5 times per week for 4 weeks (20 sessions)) (Askin, personal communication)<br>Provider: not reported.<br>**Conventional care plus low dose high frequency ultrasound therapy (3.0 watts/cm$^2$) (N = 15)**<br>Components of intervention: ultrasound procedure as described above<br>Dosage: 3.0 watts/cm$^2$, for 5 minutes.<br>Frequency of administration: 5 times per week for 4 weeks (20 sessions)<br>Provider: not reported.<br>**Conventional care plus placebo ultrasound therapy (N = 15)**<br>Components of intervention: ultrasound procedure as described above, with the machine turned off |
| Outcomes | Time points at which outcomes were measured were not explicitly specified in the trial report. Outcomes were assessed at baseline and on completion of the intervention period (4 weeks post recruitment) (Askin, personal communication). The trial authors did not state any primary outcome<br>1. Self-rated pain intensity at rest using a 10 cm VAS (0 = no pain, 10 = severe pain);<br>2. limitation of total finger flexion was assessed by measuring finger pulp-distal crease distance using a ruler;<br>3. grip strength was assessed using a hand dynamometer (average of 3 measurements in kg);<br>4. self-reported upper extremity disability was assessed using the Disability of the Arm, Shoulder and Hand (DASH) questionnaire (Turkish version), with lower scores indicating better function (score range not reported). |
| Notes | **Source of funding:** not reported.<br>**Statement regarding declarations of interest:** none declared. |

| *Risk of bias* | | | *Risk of bias* |
|---|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** | |

**Askin 2014** (*Continued*)

| | | |
|---|---|---|
| Random sequence generation (selection bias) | High risk | Quote: "Patients were randomly divided into 3 groups by picking cards in different colours. First, three groups of cards (each group consisted of 15 cards) in 3 different colours (blue for 3 watts/cm2, pink for 0.5 watts/cm2, yellow for placebo) were prepared. Participants were asked to choose a card before starting the treatment. The US dose was determined according to the colour of the selected card and it was recorded. The randomisation process was performed by another physician"<br>Comment: the trial authors used a non-random sequence generation process |
| Allocation concealment (selection bias) | Low risk | Quote: "The randomisation process was performed by another physician"<br>Comment: the trial authors probably used an acceptable method to conceal the allocation sequence |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "No information was given to patients and to the physician who will make assessments and US application about the randomisation process until the end of the study"<br>Comment: the participants were blinded to treatment allocation |
| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | Low risk | Quote: "No information was given to patients and to the physician who will make assessments and US application about the randomisation process until the end of the study" |
| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Low risk | Quote: "No information was given to patients and to the physician who will make assessments and US application about the randomisation process until the end of the study" |
| Incomplete outcome data (attrition bias)<br>Drop-out rate described and acceptable | Low risk | Quote: "Thirteen patients from group I, 13 patients from group II and 14 patients from group III, a total of 40 patients completed the study"<br>Comment: an overall drop-out rate of 11% is unlikely to have biased the results |

**Askin 2014** (*Continued*)

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated | High risk | Quote: "Two patients from group I, 2 patients from group II and 1 patient from group III who did not come to therapy sessions regularly were excluded"<br>Comment: the trial authors excluded 5 participants in violation of the ITT principle |
| Selective reporting (reporting bias) | Low risk | Comment: outcome data were fully reported for all outcomes reported in the methods section of the publication |
| Sample size | High risk | Quote: "Fourty-five patients with CRPS type I were randomly allocated into three groups"<br>Comment: the small sample size may have introduced bias in estimates of treatment effect |
| Duration of follow-up | High risk | Quote: "Before and after the treatment the severity of the pain experienced at rest was assessed"<br>Comment: outcomes were re-measured on completion of the intervention period only and were not measured over a clinically relevant length of time |
| Other bias | Low risk | Comment: we did not identify any other sources of bias were identified |

**Aydemir 2006**

| | |
|---|---|
| Methods | **Design:** parallel group, 3-arm double RCT (Turkey; dates not reported)<br>**Setting:** Department of Physical Medicine and Rehabilitation Clinic, Gulhane Military Medical Academy<br>**Interventions:** stellate ganglion block (SGB) with lidocaine and sham SGB with ultrasound (US) or SGB with US and sham SGB with lidocaine or sham SGB with lidocaine and sham SGB with US<br>**Sample size calculation:** not reported. |
| Participants | **Number of participants:** 25 (SGB with lidocaine (N = 9); SGB with US (N = 9); sham SGB with lidocaine and sham SGB with US (N = 7))<br>**Type of noxious initiating event:** mixed (trauma n = 12, fracture n = 11, idiopathic n = 2) (upper limb)<br>**Diagnostic criteria:** Bruehl 1999 (CRPS I).<br>**Baseline characteristics:**<br>1. SGB with lidocaine:<br>i) Mean (±) age = 21.9 (1.05) years; female:male = not reported (assumed to be all males as setting identical to (Hazneci 2005); |

| | |
|---|---|
| | ii) Mean (SD) duration of CRPS I = not reported;<br>2. Group receiving SGB with US:<br>i) Mean (±) age = 21.4 (0.73) years; female:male = not reported (assumed to be all males);<br>ii) Mean (SD) duration of CRPS I = not reported;<br>3. Group receiving sham SGB with lidocaine and US:<br>i) Mean (±) age = 21.1 (0.38) years; female:male = not reported (assumed to be all males);<br>ii) Mean (SD) duration of CRPS I = not reported.<br>**Inclusion criteria:**<br>1. CRPS I.<br>**Exclusion criteria:**<br>1. peripheral or central nervous system lesion affecting the upper limb;<br>2. participants using anti-hypertensive or anti-cholinergic medications;<br>3. lidocaine allergy;<br>4. cardiac arrhthymias;<br>5. history of stellate ganglion blockade within the last month. |
| Interventions | Participants in all 3 groups received 21 sessions of exercise (active, active assisted, passive exercises for the wrist and fingers, twice daily supervised by the same physiotherapist), contrast baths (extremities were put in 38 °C hot water, 4 °C cold water for 4 minutes hot and 1 minute cold, 4 minutes cold and 1 minute hot and 4 minutes cold (total time 14 minutes)), transcutaneous electrical nerve stimulation (Enraf Nonius Endomed 582 instrument; for a period of 20 minutes with a frequency of 100 Hz), external pneumatic compression (involved extremity was compressed by a pressure of 50 mmHg for a period of 60 seconds and then pressure was released for 20 seconds and this compression and release procedure was repeated for 15 minutes, for participants who could not tolerate the 50 mmHg pressure a lower level pressure was used) and paracetamol (500 mg orally every 4 hours, maximum dosage of 3 g/daily was given if it is needed)<br>**Stellate ganglion block with lidocaine (N = 9)**<br>Components of intervention:<br>1. 10 mL of 1% lidocaine was injected slowly into the stellate ganglion (on the line of 6th vertebra, 1.5 cm lateral of the median line, 4 cm to 5 cm under the skin);<br>2. (sham SGB with US) using a Enraf Nonius Sonopuls 590 and with the machine turned off the instrument was put on the ganglion for 5 minutes.<br>Dosage: 10 mL of 1% lidocaine.<br>Frequency of administration: not reported.<br>Provider: anaesthetist (other providers not reported).<br>**Stellate ganglion block with ultrasound (N = 9)**<br>Components of intervention:<br>1. (sham SGB with lidocaine) 10 mL saline solution was used as placebo and injected slowly into the stellate ganglion;<br>2. SGB with US was applied by using Enraf Nonius Sonopuls 590 (further details regarding method of application not reported).<br>Dosage: 3 watt/cm² for 5 minutes.<br>Frequency of administration: not reported.<br>Provider: anaesthetist (other providers not reported).<br>**Sham stellate ganglion block with lidocaine and ultrasound (N = 7)**<br>Components of intervention: |

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|---|---|
| | 1. (sham SGB with lidocaine) 10 mL saline solution was used as placebo and injected slowly into the stellate ganglion;<br>2. (sham SGB with US) using a Enraf Nonius Sonopuls 590 and with the machine turned off the instrument was put on the ganglion for 5 minutes.<br>Dosage: n/a.<br>Frequency of administration: not reported.<br>Provider: anaesthetist (other providers not reported). |
| Outcomes | Outcomes assessed at baseline, after treatment and 1 month post-treatment:<br>1. self-reported spontaneous pain measured using a 10 cm VAS (0 to 10) (anchor points not reported);<br>2. self-reported provocative pain measured using a Likert-type scale (0 = no pain, 1 = mild pain with deep palpation, 2 = serious pain with deep palpation, 3 = serious pain with superficial palpation, 4 = hyperaesthesia) (further details not reported);<br>3. oedema measured using a standard forearm volumeter (measured in mL, further details not reported);<br>4. finger pulp-distal palmer crease distance (measured in cm, further details not reported);<br>5. grip strength measured using a Jamar dynamometer, in a sitting position (measured in kg);<br>6. functional hand scale (score range 0 to 19 with lower scores indicating better function);<br>7. Keitel index score (score range 4 to 42; interpretation of scores not reported). |
| Notes | **Source of funding:** not reported.<br>**Statement regarding declarations of interest:** not reported. |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Patients were randomised by envelope method and 3 groups were established"<br>Comment: "Treatment orders were made online..."<br>Comment: it is likely that the trial authors used an acceptable method to generate the sequence allocation |
| Allocation concealment (selection bias) | Low risk | Quote: "Patients were randomised by envelope method and 3 groups were established"<br>Comment: the trial authors probably used an acceptable method to conceal the allocation sequence |

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "The study was designed as a double blind study. Treatment orders were made online and except the personnel who were involved in the therapy nobody even the doctor was aware of the selected method"<br>Comment: participants were likely to have been adequately blinded |
| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | Low risk | Quote: "The study was designed as a double blind study. Treatment orders were made online and except the personnel who were involved in the therapy nobody even the doctor was aware of the selected method"<br>Comment: participants who completed self-reported outcome measures were blinded to treatment allocation |
| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Low risk | Quote: "Treatment orders were made online and except the personnel who were involved in the therapy nobody even the doctor was aware of the selected method"<br>Comment: the outcome assessor was blinded to the treatment allocation |
| Incomplete outcome data (attrition bias)<br>Drop-out rate described and acceptable | Unclear risk | Comment: the drop-out rate was not reported. |
| Incomplete outcome data (attrition bias)<br>Participants analysed in the group to which they were allocated | Unclear risk | Comment: the method of analysis (ITT versus per protocol) was not reported |
| Selective reporting (reporting bias) | Low risk | Comment: the trial authors fully reported outcome data for all outcomes reported in the methods section of the publication |
| Sample size | High risk | Quote: "Twenty-five patients were divided into three groups"<br>Comment: the small sample size may have introduced bias in estimates of treatment effect |
| Duration of follow-up | Unclear risk | Quote: "These evaluations were performed before and after treatment and one month later"<br>Comment: the clinical relevance of a 1 month follow-up of outcomes is uncertain |

**Aydemir 2006** (*Continued*)

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| Other bias | Low risk | Comment: we did not identify any other sources of bias. |

**Cacchio 2009a**

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|---|---|
| Methods | **Design:** parallel group, 2-arm, single-blind RCT (Italy; October 2000 to December 2006)<br>**Setting:** inpatient and outpatient rehabilitation centre.<br>**Interventions:** mirror therapy or placebo control (covered mirror).<br>**Sample size calculation:** 24 participants per group required to detect a 2 cm reduction in pain on a 10 cm VAS (SD 1.5) with 0 cm labelled as "no pain" and 10 cm as "worst pain i have ever had" at 1 week after treatment at 1% level of statistical significance with 90% power, including a 30% rate of loss at follow-up |
| Participants | **Number of participants:** 48 (24 per group).<br>**Type of noxious initiating event:** stroke (upper limb).<br>**Diagnostic criteria:** Bruehl 1999 (CRPS I).<br>**Baseline characteristics:**<br>1. conventional stroke rehabilitation plus mirror therapy:<br>i) mean (SD) age = 57.9 (9.9) years; female:male = 13:11;<br>ii) mean (SD) duration of CRPS I 2.8 (1.3) months;<br>2. conventional stroke rehabilitation plus placebo control:<br>i) mean (SD) age = 58.8 (9.4) years; female:male = 13:11;<br>ii) mean (SD) duration of CRPS I 2.6 (1.5) months.<br>**Inclusion criteria:**<br>1. first episode of unilateral stroke with hemiparesis during the previous 6 months;<br>2. VAS, 0 to 10 cm) pain score > 4 cm.<br>**Exclusion criteria:**<br>1. ipsilateral intra-articular shoulder injection within the last 6 months or use of systemic corticosteroids with the previous 4 months;<br>2. presence of another obvious explanation for the pain;<br>3. prior surgery to either shoulder or neck region;<br>4. serious uncontrolled medical conditions;<br>5. global aphasia, cognitive or visual impairments interfering with testing or treatment;<br>6. visual impairment that might interfere with the trial aims;<br>7. evidence of recent drug or alcohol abuse or severe depression. |
| Interventions | Participants in both groups received 4 weeks of conventional stroke rehabilitation comprising neuro-rehabilitation techniques, occupational therapy (OT) and speech therapy (if required), consisting of 5 1-hour sessions per week<br>**Conventional stroke rehabilitation plus mirror therapy (N = 24)**<br>Components of intervention: mirror therapy programme: Whilst seated with a mirror board positioned between the upper limbs, perpendicular to the midline and with the unaffected limb facing the reflective surface and with their affected upper limb hidden from view, participants observed the reflection of their unaffected upper limb while performing flexion and extension at the shoulder, elbow and wrist and pronation and supination of the forearm |

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| | Dosage: 30 minutes per session (for the first 2 weeks), 1 hour per session (for the second 2 weeks)<br>Frequency of administration: 5 times per week for 4 weeks (20 sessions)<br>Provider: physiotherapist.<br>**Conventional stroke rehabilitation plus placebo control (N = 24)**<br>Components of intervention: participants performed the same exercises, according to the same dosage and frequency, with the reflective mirror surface covered |
| Outcomes | Outcomes assessed at baseline and at 1 week and 6 months post-treatment<br>**Primary outcomes:**<br>1. self-rated pain intensity at rest using a 10 cm horizontal VAS labelled "no pain" to "worst pain I have ever had" (pain location not reported);<br>2. self-rated pain intensity on shoulder movement (forward flexion) using a 10 cm VAS labelled "no pain" to "worst pain I have ever had";<br>3. brush evoked tactile allodynia, assessed by means of 3 brush movements within the area of maximum pain, using a 10 cm VAS labelled "no pain" to "worst pain I have ever had".<br>**Secondary outcomes:**<br>1. functional ability value of the Wolf Motor Function Test (WMFT), to assess upper limb functional limitation (score range 0 to 5, higher scores indicate poorer performance);<br>2. performance time value of the WMFT, to assesses upper limb functional performance speed (measured in seconds, longer times indicate poorer performance);<br>3. Quality of Movement (QOM) item in the Motor Activity Log (MAL), to assess how well participants can use their affected upper limb in 30 activities of daily living (score range 0 to 5, lower scores indicate poorer performance). |
| Notes | **Source of funding:** not reported<br>**Statement regarding declarations of interest:** not reported |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "...we undertook a randomized placebo-controlled study in which stroke patients with CRPSt I were randomly allocated..."<br>Comment: the trial authors did not report the method of sequence generation |
| Allocation concealment (selection bias) | Unclear risk | Comment: the trial authors did not report the method of concealment allocation |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Comment: given the nature of the intervention, participants were not blinded to treatment allocation but the extent to which the lack of blinding may have introduced bias is uncertain |

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| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | Unclear risk | Comment: unblinded participants self-reported some outcomes (e.g. pain intensity) but the extent to which the lack of blinding may have introduced bias is uncertain |
| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Low risk | Quote: "All the patients were examined 3 times by an investigator who was blinded to the nature of treatment performed"<br>Comment: the outcome assessor was blinded to treatment allocation |
| Incomplete outcome data (attrition bias)<br>Drop-out rate described and acceptable | Unclear risk | Quote: "Two patients (8%) in the mirror group and 7 patients (29%) in the control group dropped out of the study"<br>Quote: "One of the 2 patients in the mirror group dropped out because he moved to another city, while the other decided to perform corticosteroid injection therapy in another center. Three of the 7 patients in the control group refused to complete the study, while 4 decided to perform corticosteroid injection therapy in another center"<br>Comment: the extent to which an overall drop-out rate of 19% and an unequal drop-out rate between groups may have introduced biased estimates of treatment effect is uncertain |
| Incomplete outcome data (attrition bias)<br>Participants analysed in the group to which they were allocated | Low risk | Quote: "Both the primary and secondary outcome analyses were performed according to the intention-to-treat (ITT) principle. In this study, subjects that provided baseline and at least 1 post-treatment measurement constituted the ITT population, whereas those who completed all tests from baseline to the 6-month follow-up constituted the per protocol population<br>Comment: the trial authors reported analyses according to the ITT principle |
| Selective reporting (reporting bias) | Low risk | Comment: the trial authors fully reported outcome data for all outcomes reported in the methods section of the publication |
| Sample size | High risk | Quote: "48 patients with CRPSt1 of the affected upper limb were enrolled"<br>Comment: the small sample size may have introduced bias in estimates of treatment effect |

**Cacchio 2009a** (*Continued*)

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| Duration of follow-up | Low risk | Quote: "The decision to set the follow-up at 6 months is based on the hypothesis that pain improves spontaneously over a long period of time"<br>Comment: the trial authors measured outcomes over a clinically relevant length of time |
| Other bias | High risk | Quote: "For the ITT population, outcome measurements were analyzed using the last observation carried forward method"<br>Comment: the use of 'last observation carried forward' when accounting for missing data may have introduced bias in estimates of treatment effect |

**Cacchio 2009b**

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|---|---|
| Methods | **Design:** parallel group, single-blind, 3-arm, sham-controlled RCT (Italy, dates not reported). (Whilst the trial authors reported that a number of participants from the 2 comparator groups crossed over into the experimental group, this was not undertaken in a randomised way and therefore we deemed that this trial did not employ a true crossover design. We analysed it as a 3-arm parallel group trial up to the endpoint just prior to crossover)<br>**Setting:** not reported.<br>**Interventions:** mirror therapy or placebo control (covered mirror) or mental imagery<br>**Sample size calculation:** not reported. |
| Participants | **Number of participants:** 24 (8 per group).<br>**Type of noxious initiating event:** stroke (upper limb).<br>**Diagnostic criteria:** Bruehl 1999 (CRPS I).<br>**Baseline characteristics:** not adequately reported.<br>**Inclusion criteria:** not explicitly reported.<br>**Exclusion criteria:** not reported. |
| Interventions | **Mirror therapy (N = 8)**<br>Components of intervention: whilst viewing a reflected image of the unaffected arm in a mirror, participants performed all of the cardinal (proximal to distal) movements of the affected arm (reported as the 'affected' arm but assumed to be the 'unaffected' arm)<br>Dosage: 30 minutes per session.<br>Frequency of administration: daily for 4 weeks (28 sessions)<br>Provider: not reported.<br>**Placebo control (N = 8)**<br>Components of intervention: participants performed the same movements, according to the same dosage and frequency, with the reflective mirror surface covered<br>Provider: not reported.<br>**Mental imagery (N = 8)**<br>Components of intervention: not reported. |

**Cacchio 2009b** (*Continued*)

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| | Dosage: not reported.<br>Frequency of administration: not reported.<br>Provider: not reported. |
| Outcomes | The trial authors assessed outcomes at baseline and on completion of the intervention period (4 weeks post recruitment)<br>**Primary outcomes:**<br>1. self-rated pain intensity on movement using a 100 mm VAS (anchor point labels not reported) but with higher scores indicating more severe pain.<br>**Secondary outcomes:**<br>1. motor function as assessed by the Wolf Motor Function Test (WMFT) (scoring properties not reported);<br>2. brush-induced allodynia (method of assessment not reported);<br>3. oedema (method of assessment not reported). |
| Notes | **Source of funding:** not reported.<br>**Statement regarding declarations of interest:** not reported. |

***Risk of bias*** ***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "We conducted a randomised, sham-controlled study involving 24 patients with stroke"<br>Comment: the trial authors did not report the method of sequence |
| Allocation concealment (selection bias) | Unclear risk | Quote: "We randomly assigned the 24 patients to one of three groups"<br>Comment: the trial authors did not report the method of concealment allocation |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Comment: given the nature of the intervention, participants were not blinded to treatment allocation but the extent to which the lack of blinding may have introduced bias is uncertain |
| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | Unclear risk | Comment: unblinded participants self-reported some outcomes (e.g. pain intensity) but the extent to which the lack of blinding may have introduced bias is uncertain |
| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Low risk | Quote: "The investigators were unaware of the study-group assignments"<br>Comment: outcome assessors were blinded to participants group allocation |

**Cacchio 2009b** (*Continued*)

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|---|---|---|
| Incomplete outcome data (attrition bias) Drop-out rate described and acceptable | Low risk | Quote: "In the active-mirror group, seven of eight patients (88%) reported reduced pain"<br>Quote: "In the covered-mirror group, only one of eight patients (12%) reported reduced pain"<br>Quote: "In the mental-imagery group, two of eight patients (25%) reported reduced pain"<br>Comment: there were no apparent drop-outs. |
| Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated | Low risk | Comment: the trial authors analysed participants in the group to which they were allocated but did not report the method of analysis (ITT versus per protocol) |
| Selective reporting (reporting bias) | High risk | Quote: "After 4 weeks of active mirror therapy, the pain intensity decreased (Fig. 1), and motor function, brush-induced allodynia, and edema improved (data not shown) "<br>Comment: the trial authors presented mean values for the primary outcome of pain severity in graphical format only; they did not report raw data in numerical form with measures of variation<br>Comment: the trial authors did not report any outcome data for the 3 secondary outcome measures (motor function, brush-induced allodynia, oedema) |
| Sample size | High risk | Quote: "We conducted a randomised, sham-controlled study involving 24 patients..."<br>Comment: the small sample size may have introduced bias in estimates of treatment effect |
| Duration of follow-up | High risk | Quote: "The primary end point was the score for the severity of pain after 4 weeks of therapy"<br>Comment: the trial authors re-measured outcomes on completion of the intervention period only and did not measure them over a clinically relevant length of time |

**Cacchio 2009b** (*Continued*)

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|---|---|---|
| Other bias | Unclear risk | Comment: the trial was reported and published as a 'Letter to the Editor'. Full trial methodology and results have not been published elsewhere (Cacchio, personal communication)<br>Comment: the trial authors presented limited group-specific baseline data<br>Comment: the trial authors did not report any inclusion/exclusion data |

**Dimitrijevic 2014**

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| Methods | **Design:** parallel group, 2-arm, single-blind RCT (Serbia; December 2004 to January 2007)<br>**Setting:** outpatient clinic.<br>**Interventions:** low-level laser therapy and kinesitherapy or interferential current therapy and kinesitherapy<br>**Sample size calculation:** not reported. |
| Participants | **Number of participants:** 50 (25 per group).<br>**Type of noxious initiating event:** trauma (no further details reported) (upper and lower limb)<br>**Diagnostic criteria:** Harden 2005 (CRPS I).<br>**Baseline characteristics:**<br>1. laser therapy and kinesitherapy:<br>i) Mean (±) age = 53.9 (13.36) years; female:male = 12:8;<br>ii) Mean (±) duration of CRPS I 33.75 (8.44) days.<br>2. interferential current therapy and kinesitherapy:<br>i) Mean (±) age = 57.8 (10.75) years; female:male = 17:8;<br>ii) Mean (±) duration of CRPS I = 31.64 (7.79) days.<br>**Inclusion criteria:**<br>1. CRPS I.<br>**Exclusion criteria:**<br>1. acute and subacute thrombophlebitis;<br>2. thrombosis;<br>3. neoplastic disease;<br>4. fever;<br>5. pregnancy. |
| Interventions | Participants were instructed not to take any specific CRPS medication (corticosteroids, bisphosphonates, calcitonin, nifedipine, antiepileptic drugs, etc.) or analgesic medication. Participants in both groups received individual kinesitherapy (active and active assisted exercises, strictly dosed up to pain threshold) for 30 minutes, twice a day<br>**Low-level laser therapy and kinesitherapy (N = 20)**<br>Components of intervention: using a GaAs laser diode, 8 points along the joint line and painful points in the affected area were treated using the following parameters: a low power of 70 mW, 810 nm wavelength, and 70 Hz, 640 Hz, and 5000 Hz frequency, depending on the dominant findings |

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| | Dosage: 1.5 J/cm$^2$.<br>Frequency of administration: 5 days a week for 2 weeks (10 sessions), and then every other day (10 sessions) (20 sessions)<br>Provider: not reported.<br>**Interferential current therapy and kinesitherapy (N = 25)**<br>Components of intervention: bipolar IFC therapy was applied with electrodes positioned locally on the painful and swollen part using the following parameters: 90 Hz frequency<br>Dosage: 15 minutes.<br>Frequency of administration: 5 days a week for 2 weeks (10 sessions), and then every other day (10 sessions) (20 sessions)<br>Provider: not reported. |
| Outcomes | The trial authors did not explicitly specify the time points at which outcomes were measured in the trial report. Outcomes assessed at baseline and on completion of the intervention period (6 weeks post recruitment) (Dimitrijevic, personal communication) . The trial authors did not state any primary outcome<br>1. Self-rated pain intensity at rest using a 100 mm horizontal VAS (0 = no pain, 100 = worst pain possible) with responses based on the average pain intensity over last few days;<br>2. self-rated pain intensity during active movements of the wrist/ankle using a 100 mm horizontal VAS (0 = no pain, 100 = worst pain possible) with responses based on the average pain intensity over last few days;<br>3. oedema of the hand/foot using a figure-of-8 measurement (measurement tool and method not reported). Hand/foot oedema was expressed as the difference between hand/foot circumference of the affected and unaffected sides;<br>4. total active range of motion of the wrist/ankle joint in the sagittal plane using a standard full-circle goniometer and recorded in degrees with the final value derived from mean of 3 measurements. |
| Notes | **Source of funding:** the trial authors declared that this study received no financial support<br>**Statement regarding declarations of interest:** none declared. |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "...patients were randomly selected and classified into two groups using sequentially numbered, closed, opaque envelopes that had been prepared earlier using a computer-generated list of random numbers, and balanced to ensure equal numbers in each group"<br>Comment: the trial authors used an acceptable method to generate the sequence allocation |
| Allocation concealment (selection bias) | Low risk | Quote: "...patients were randomly selected and classified into two groups, using se- |

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| | | quentially numbered, closed, opaque envelopes that had been prepared earlier"<br>Comment: the trial authors used an acceptable method to conceal the allocation sequence |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Comment: the participants were not blinded to treatment allocation but lack of blinding unlikely to have biased the results given that participants received interventions judged to have been of relatively equal credibility |
| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | Low risk | Comment: the participants were not blinded to treatment allocation and self-reported some outcomes but lack of blinding unlikely to have biased the results given that participants received interventions judged to have been of relatively credibility |
| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Unclear risk | Comment: the trial authors did not provide a statement of procedures regarding blinding of the outcome assessor |
| Incomplete outcome data (attrition bias)<br>Drop-out rate described and acceptable | Unclear risk | Quote: "During the study, 5 out of 50 patients dropped out. A total of 45 patients completed the study"<br>Comment: all 5 drop-outs came from the laser therapy group (lost to follow-up, n = 2; discontinued intervention, n = 3). Whilst the overall drop-out rate was 10%, the extent to which an unequal drop-out rate between groups may have biased the results is uncertain |
| Incomplete outcome data (attrition bias)<br>Participants analysed in the group to which they were allocated | High risk | Comment: the trial authors excluded 3 participants from the laser therapy group from the analysis because they discontinued the intervention, in violation of the ITT principle |
| Selective reporting (reporting bias) | Low risk | Comment: the trial authors fully reported outcome data for all outcomes reported in the methods section of the publication |
| Sample size | High risk | Quote: "The prospective randomized study included 50 patients with unilateral posttraumatic CRPS I"<br>Comment: the small sample size may have |

**Dimitrijevic 2014** (*Continued*)

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| | | introduced bias in estimates of treatment effect |
| Duration of follow-up | High risk | Quote: "All patients underwent evaluation of each separate parameter before treatment and after applying 20 therapeutic procedures"<br>Comment: outcomes were re-measured on completion of the intervention period only and were not measured over a clinically relevant length of time |
| Other bias | Low risk | Comment: we did not identify any other sources of bias. |

**Duman 2009**

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|---|---|
| Methods | **Design:** parallel group, 2-arm RCT (Turkey; dates not reported).<br>**Setting:** not reported.<br>**Interventions:** conventional care plus manual lymphatic drainage (MLD) or conventional care<br>**Sample size calculation:** not reported. |
| Participants | **Number of participants:** 34 (experimental group N = 18, control group N = 16).<br>**Type of noxious initiating event:** mixed (fracture n = 23, soft-tissue trauma n = 7, incisive injury n = 3, non-traumatic n = 1) (upper limb)<br>**Diagnostic criteria:** Bruehl 1999 (RSD i.e. CRPS I).<br>**Baseline characteristics:**<br>Total sample (separate intervention and control group data not reported but no statistically significant between-group differences)<br>Mean (±) age = 20.6 (0.8) years; female:male = not reported.<br>Mean (±) duration of Reflex sympathetic dystrophy (RSD) 5.1 (1.3) months<br>**Inclusion criteria:**<br>1. fulfilled IASP criteria for RSD;<br>2. minimum 50 cc volumetric difference between 2 upper limbs.<br>**Exclusion criteria:**<br>1. infection;<br>2. thrombosis;<br>3. cardiac, pulmonary or renal problems. |
| Interventions | Participants in both groups received conventional care including non-steroidal anti-inflammatory drugs (NSAIDs) (type, dosage, frequency of administration not reported) and physical therapy (once per day, 5 days per week for 3 weeks), comprising therapeutic ultrasound of the affected limb and stellate ganglions (treatment parameters not reported) and therapeutic exercises for all joints of the affected limb (10 repetitions, twice per day; type of exercises performed not reported) followed by a 2-month programme of home maintenance therapeutic exercises<br>**MLD (N = 18)**<br>Components of intervention: MLD. Light massage for superficial abdominal, axillary |

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| | and upper limb lymphatic stimulation of the affected upper limb followed by light upper limb massage in a distal to proximal direction up to the axillary region<br>Dosage: 1 session per day for approximately 45 minutes administered by a therapist plus 1 session per day of participant self-administered MLD (duration not reported)<br>Frequency of administration: 5 times per week for 3 weeks (15 sessions), followed by a home maintenance. programme of self-administered MLD for 2 months<br>Provider: not reported.<br>**Conventional care (N = 16).** |
| Outcomes | Outcomes assessed at baseline, at the end of the 3-week treatment period and 2 months post-treatment. The trial authors did not state any primary outcome<br>1. Self-rated pain intensity during gentle passive finger flexion using a 10-cm VAS labelled "no pain" to "worst possible pain";<br>2. upper limb oedema using volumetric measurements of water displacement;<br>3. functional range of motion measuring the third finger pulp-distal palmer crease distance. |
| Notes | **Source of funding:** not reported<br>**Statement regarding declarations of interest:** not reported. |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "The patients were allocated randomly into two groups"<br>Comment: the trial authors did not report the method of sequence generation |
| Allocation concealment (selection bias) | Unclear risk | Comment: the trial authors did not report the method of concealment allocation |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention |
| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | High risk | Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. pain intensity) |
| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Unclear risk | Quote: "All of the parameters were obtained before the treatment (baseline), after treatment and 2 months after treatment (follow-up) by a different physician"<br>Comment: the trial authors did not report a |

**Duman 2009** (*Continued*)

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| | | statement of procedures regarding blinding of the outcome assessor |
| Incomplete outcome data (attrition bias) Drop-out rate described and acceptable | Low risk | Quote: "After 2 months, all of the patients were re-evaluated"<br>Comment: there were no apparent drop-outs. |
| Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated | Low risk | Quote: "After 2 months, all of the patients were re-evaluated"<br>Comment: trial authors analysed participants analysed in the group to which they were allocated but did not report the method of analysis (ITT versus per protocol) |
| Selective reporting (reporting bias) | Low risk | Comment: the trial authors fully reported outcome data for all outcomes reported in the methods section of the publication |
| Sample size | High risk | Quote: "A total of 34 patients who fulfilled the modified International Association for the Study of Pain (IASP) criteria and diagnosed as RSD were enrolled"<br>Comment: the small sample size may have introduced bias in estimates of treatment effect |
| Duration of follow-up | Low risk | Quote: "After 2 months, all of the patients were re-evaluated"<br>Comment: the trial authors measured outcomes over a clinically relevant length of time |
| Other bias | Low risk | Comment: we did not identify any other other sources of bias |

**Durmus 2004**

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| Methods | **Design:** parallel group, 2-arm, double-blind placebo-controlled RCT (Turkey; 1999 to 2001)<br>**Setting:** out-patient rehabilitation clinic.<br>**Interventions:** usual care plus pulsed electromagnetic field treatment or usual care plus placebo pulsed electromagnetic field treatment<br>**Sample size calculation:** not reported. |
| Participants | **Number of participants:** 40 (number of participants per group not reported).<br>**Type of noxious initiating event:** Colles fracture (upper limb).<br>**Diagnostic criteria:** Merskey 1994 (CRPS I). |

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| | **Baseline characteristics:**<br>1. pulsed electromagnetic field treatment:<br>i) mean (SD) age = 37.65 (12.33) years; female:male = 50%:50%;<br>ii) mean (SD) duration of CRPS I: 48.80 (28.63) days;<br>2. placebo:<br>i) mean (SD) age = 40.60 (11.05) years; female:male = 45%:55%;<br>ii) mean (SD) duration of CRPS I: 54.55 (36.24) days.<br>**Inclusion criteria:**<br>1. aged 18 to 55 years;<br>2. development of pathology after trauma;<br>3. presence of phase I CRPS I based on 3 phase bone scintigraphy;<br>4. absence of any known hypersensitivities to calcitonin.<br>**Exclusion criteria:**<br>1. previous treatment for CRPS I;<br>2. pacemaker;<br>3. presence of an infectious or malignant disease;<br>4. being either pregnant or in a menopausal state. |
| Interventions | Participants in both groups received 100 units of calcitonin via intramuscular injection for 6 weeks; once per day for the first 3 weeks then once every other day for the second 3 weeks, and performed active and active assisted range of motion exercises and a stretching programme for 30 minutes, 3 times per day<br>**Electromagnetic field treatment (N = not reported)**<br>Components of intervention: pulsed electric magnetic field treatment. Treatment was administered using a Magnetic-Therapy Mg Port Cosgamma® device. The trial authors did not report participant and equipment positioning<br>Dosage: 100 Gauss intensity and 50 Hz frequency for 60 minutes per session<br>Frequency of administration: 5 times per week for 6 weeks (30 sessions)<br>Provider: not reported.<br>**Placebo (N = not reported)**<br>Components of intervention: participants were placed in the same device without it being switched on |
| Outcomes | The trial authors assessed outcomes at baseline and on completion of the intervention period (6 weeks post recruitment). The trial authors did not state any primary outcome<br>1. Self-rated pain at rest using a 10 cm VAS graded between 0 and 10 (anchor point descriptors not reported);<br>2. self-rated pain with activity (details not reported) using a 10 cm VAS graded between 0 and 10 (anchor point descriptors not reported);<br>3. 4-point verbal pain scale (measurement properties not described);<br>4. pain on palpation using 5-point grading scale (0 = no pain, 4 = hyperesthesia) (further measurement properties not reported);<br>5. ratings of stiffness and change of colour (measurement properties not reported);<br>6. change in oedema using volumetric displacement;<br>7. range of motion using a goniometer (joints not specified);<br>8. 3-phase bone scintigraphy (bone to soft-tissue ratios) (measurement properties not reported);<br>9. biochemical markers of bone formation (bone alkaline phosphatase, osteocalcin, procollagen 1) and bone resorption (pyridinoline, deoxypyridinoline, hydroxyproline) |

**Durmus 2004** (*Continued*)

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| | (measurement properties not reported). |
| Notes | **Source of funding:** not reported.<br>**Statement regarding declarations of interest:** not reported. |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The patients were divided into two groups with the random numbers table"<br>Comment: the trial authors used an acceptable method was used to generate the sequence allocation |
| Allocation concealment (selection bias) | Unclear risk | Comment: the trial authors did not report the method of concealment allocation |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "In this randomized double-blind, placebo-controlled study"<br>Quote: "the second group of patients received placebo treatment by being placed in the same device without it being switched on"<br>Comment: participants were likely to have been adequately blinded but the trial authors did not explicitly report the extent to which the placebo intervention controls for the auditory and sensory characteristics of the intervention<br>Comment: the trial authors did not report the procedure for blinding of care providers |
| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | Low risk | Quote: "the second group of patients received placebo treatment by being placed in the same device without it being switched on"<br>Comment: the participants who completed self-reported outcome measures were blinded to treatment allocation |
| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Low risk | Quote: "The patients were assessed at the beginning of a 6 week course of treatment and on the final week of treatment by a physician who did not know which group received the applied magnetic field treatment"<br>Comment: the outcome assessor was blinded to treatment allocation |

**Durmus 2004** (*Continued*)

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| Incomplete outcome data (attrition bias) Drop-out rate described and acceptable | Low risk | Quote: "There were no refusals or drop-outs from the study".<br>Comment: all randomly assigned participants completed the study |
| Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated | Low risk | Quote: "There were no refusals or drop-outs from the study".<br>Comment: the trial authors did not report the method of analysis (ITT versus per protocol) |
| Selective reporting (reporting bias) | Low risk | Comment: the trial authors fully reported outcome data for the 2 main pain outcomes but did not report any outcome data for the 4-point verbal pain scale or any other outcomes (pain on palpation, ratings of stiffness and change of colour, range of motion and 3-phase bone scintigraphy), as reported in the methods section of the publication |
| Sample size | High risk | Quote: "Forty patients diagnosed as having Type I CRPS subsequent to trauma (Colles Fracture), who consulted the Physical Medicine and Rehabilitation Department of Istanbul University, Istanbul Medical Faculty between 1999 and 2001 were included in the study"<br>Comment: the small sample size may have introduced bias in estimates of treatment effect |
| Duration of follow-up | High risk | Quote: "Patients were assessed at the beginning of a 6 week course of treatment and on the final week of treatment"<br>Comment: the trial authors re-evaluated participants at the end of the treatment period only |
| Other bias | Low risk | Comment: we did not identify any other sources of bias. |

**Hazneci 2005**

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| Methods | **Design:** parallel group, 2-arm RCT (Turkey; 2001 to 2002).<br>**Setting:** Department of Physical Medicine and Rehabilitation Clinic, Gulhane Military Medical Academy<br>**Interventions:** transcutaneous electrical nerve stimulation (TENS) or pulsed ultrasound of the stellate ganglion<br>**Sample size calculation:** not reported |
| Participants | **Number of participants:** 30 (TENS N = 16; pulsed ultrasound N = 14).<br>**Type of noxious initiating event:** mixed (trauma n = 20, sports injury n = 5, post finger amputation n = 1, post injection n = 1, idiopathic n = 3) (upper limb)<br>**Diagnostic criteria:** Kozin 1992 (stage I and II) (Reflex sympathetic dystrophy syndrome).<br>**Baseline characteristics**<br>1. TENS:<br>i) mean (SD) age = 20.75 (0.58) years; female:male = 0:16;<br>ii) mean (SD) duration of CRPS I 45.31 (26.68) days;<br>2. pulsed ultrasound of the stellate ganglion:<br>i) mean (SD) age = 20.6 (0.76) years; female:male = 0:14;<br>ii) mean (SD) duration of CRPS I 43.21 (17.72) days.<br>**Inclusion criteria:** CRPS I.<br>**Exclusion criteria:** not reported. |
| Interventions | Participants in both groups received contrast bathing (the upper extremity was put in hot water for 4 minutes and then in cold water for 1 minute and this procedure was repeated for 20 minutes) and an exercise programme (undertaken with the assistance of a physiotherapist and comprising active, assisted active and passive exercise within the pain limits; including extension, flexion, ulnar and radial deviation for the wrist, abduction and flexion for the thumb, flexion and extension for the metacarpophalangeal, proximal and distal interphalangeal joints)<br>**TENS (N = 16)**<br>Components of intervention: TENS was applied, using a Myomed 932 Enraf model, to the painful area of the involved upper extremity<br>Dosage: frequency 100 Hz, mono-rec wave module.<br>Frequency of administration: once per day, for 20 minutes, for 3 weeks (total number of sessions not reported)<br>Provider: not reported.<br>**Pulsed ultrasound of the stellate ganglion (N = 14)**<br>Components of intervention: using a BTL 07p model ultrasound device pulsed ultrasound was applied with a 1 $cm^2$ probe to the stellate ganglion on the involved side of the upper extremity<br>Dosage: 3 watt/$cm^2$ (pulsed).<br>Frequency of administration: once per day, for 5 minutes, for 3 weeks (total number of sessions not reported)<br>Provider: not reported. |
| Outcomes | The trial authors assessed outcomes at baseline and on completion of the intervention period (3 weeks post recruitment):<br>1. self-reported spontaneous pain measured using a VAS (0 = no pain to 10 = worst pain);<br>2. self-reported provocative pain (pain on palpation) measured using a Likert-type |

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| | scale (0 = no pain, 1 = mild pain with deep palpation, 2 = severe pain with deep palpation, 3 = severe pain with superficial palpation, 4 = hyperaesthesia);<br>3. grip strength measured using a hand dynamometer device with the score (in kg) determined by the mean of 3 attempts;<br>4. joint mobility (extension, flexion, ulnar and radial deviation of the wrist; flexion and extension for the fingers). Active joint movement distance was measured by standard goniometer. Mobility loss was calculated by the formula: 100 − (measured value/normal joint movement distance) x 100. The mean value for the joint movement distance for all directions was calculated and compared with the values of the normal extremity. The scale was as follows: 0 = total mobility; 1 = 1% to 25% mobility loss; 2 = 26% to 50% mobility loss; 4 = mobility loss of more than 76%;<br>5. oedema measured using standard volumetric measurements. Firstly the participant's uninvolved upper extremity was placed in a container filled with water. The volume (in mL) of displaced water was measured and compared to the volume displaced when he involved upper extremity was placed in the same container with the value taken as the difference between the volumes displaced by the affected and normal extremities. |
| Notes | **Source of funding:** not reported.<br>**Statement regarding declarations of interest:** not reported. |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Patients were divided into two groups randomly".<br>Comment: the trial authors did not report the method of sequence generation |
| Allocation concealment (selection bias) | Unclear risk | Comment: the trial authors did not report the method of concealment allocation |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Comment: the participants appear not to have been blinded to treatment allocation but lack of blinding is unlikely to have biased the results given that participants received interventions judged to have been of relatively equal credibility |
| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | Low risk | Comment: participants appear not to have been blinded to treatment allocation and self-reported some outcomes, but lack of blinding is unlikely to have biased the results given that participants received interventions judged to have been of relatively equal credibility |

**Hazneci 2005** (*Continued*)

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| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Unclear risk | Comment: the trial authors did not give a statement of procedures regarding blinding of the outcome assessor |
| Incomplete outcome data (attrition bias)<br>Drop-out rate described and acceptable | Unclear risk | Comment: the trial authors did not report the drop-out rate. |
| Incomplete outcome data (attrition bias)<br>Participants analysed in the group to which they were allocated | Unclear risk | Comment: the trial authors did not report the method of analysis (ITT versus per protocol) |
| Selective reporting (reporting bias) | Low risk | Comment: the trial authors fully reported outcome data for all outcomes reported in the methods section of the publication |
| Sample size | High risk | Quote: "30 patients diagnosed with Reflex Sympathetic Dystrophy Syndrome at the upper extremities were included into the study"<br>Comment: the small sample size may have introduced bias in estimates of treatment effect |
| Duration of follow-up | High risk | Quote: "All patients evaluated before treatment and 3rd week following the treatment"<br>Comment: the trial authors re-measured outcomes on completion of the intervention period only and were not measured over a clinically relevant length of time |
| Other bias | Low risk | Comment: we did not identify any other sources of bias. |

**Jeon 2014**

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| Methods | **Design:** parallel group, 2-arm, placebo-controlled pilot RCT (South Korea; dates not reported)<br>**Setting:** tertiary university pain centre.<br>**Interventions:** virtual body swapping with mental rehearsal or virtual body swapping alone<br>**Sample size calculation:** pilot RCT with bootstrapping method to increase the robustness of small-sample analyses |
| Participants | **Number of participants:** 10 (number per group not reported).<br>**Type of noxious initiating event:** not reported (upper limb only n = 1, lower limb only n = 1, multiple limbs n = 4, and whole body n = 4)<br>**Diagnostic criteria:** Harden 2007 (CRPS I). |

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| | **Baseline characteristics:**<br>Total sample (separate intervention and control group data not reported but no statistically significant between-group differences)<br>Mean (SD) age: 39.30 (10.99) years; female:male = 0:10.<br>Median (range) duration of CRPS I: 52 (33 to 120) months.<br>**Inclusion criteria:** CRPS I<br>**Exclusion criteria:** not reported |
| Interventions | The trial authors did not report any co-interventions.<br>**Virtual body swapping with mental rehearsal (N = not reported)**<br>Components of intervention:<br>1. whilst lying down and wearing a head mounted display (VR2000; Virtual Realities, Ltd.) participants watched a virtual body swapping training video in order to evoke a virtual body swapping illusion. The 3 minute 20 second long video clip was filmed from the first person perspective and consisted of 4 physical movements (making fists and opening up the fingers, bending and unbending the elbows, bending the ankles forward and backward, and bending and unbending the legs). The first person perspective would help participants to feel as if they observed their body when they watch the video;<br>2. participants were additionally asked to assume a posture similar to that of the body on the screen and rehearse the movements mentally, as if the body presented on the display was their own body.<br>Dosage: 1 training session.<br>Frequency of administration: the experimental video clip was played twice with a 1-minute break given between viewing's<br>Provider: 1 specialist in pain and 2 assistants (trained graduate students); professional discipline not reported<br>**Virtual body swapping alone (N = not reported)**<br>Components of intervention: participants watched the same video but did not perform mental rehearsal of the 4 physical movements<br>Dosage: 1 training session.<br>Frequency of administration: the experimental video clip was played twice with a 1-minute break given between viewings<br>Provider: 1 specialist in pain and 2 assistants (trained graduate students); professional discipline not reported |
| Outcomes | The trial authors did not explicitly specify the time points at which they measured outcomes in the trial report. The outcomes were assessed immediately pre-intervention and postintervention. The trial authors did not state any primary outcome<br>1. Self-rated pain intensity measured on an 11-point Likert scale ranging from 0 (no pain) to 10 (severe pain);<br>2. the modified Body Perception Disturbance Questionnaire (BPDQ) consisting of 9 items with each item rated on an 11-point scale ranging from 0 (not at all) to 10 (very likely). Scores range from 0 to 90 with higher scores indicating greater body perception disturbance. |
| Notes | **Source of funding:** Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2012R1A1A2008624) and the Chung-Ang University Excellent Student Schol- |

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| | arship in 2014<br>**Statement regarding declarations of interest:** none declared. |

***Risk of bias*** ***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
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| Random sequence generation (selection bias) | Unclear risk | "Ten patients who met the diagnostic criterion for CRPS type 1 were randomly assigned to either the treatment or control group"<br>Comment: the trial authors did not report the method of sequence generation |
| Allocation concealment (selection bias) | Unclear risk | Comment: the trial authors did not report the method of concealment allocation |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Comment: given the nature of the intervention, participants were not blinded to treatment allocation but the extent to which the lack of blinding may have introduced bias is uncertain |
| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | Unclear risk | Comment: given the nature of the intervention, participants were not blinded to treatment allocation but the extent to which the lack of blinding may have introduced bias is uncertain |
| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Low risk | Not applicable. |
| Incomplete outcome data (attrition bias)<br>Drop-out rate described and acceptable | Low risk | Comment: the trial authors did not report the drop-out rate but, given the methodology, it is likely there were no drop-outs |
| Incomplete outcome data (attrition bias)<br>Participants analysed in the group to which they were allocated | Low risk | Comment: the trial authors did not report the method of analysis but, given the methodology, it is likely that they analysed all participants in the group to which they were allocated |
| Selective reporting (reporting bias) | High risk | Quote: "There was no significant difference between the groups in pain intensity, $F(1, 7) = 0.05$, $p = 0.81$"<br>Comment: the trial authors did not report any pre-intervention or postintervention outcome data for self-reported pain in- |

**Jeon 2014** (*Continued*)

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| | | tensity |
| Sample size | High risk | "Ten patients with CRPS type 1 were recruited from a tertiary university pain center in Seoul, Korea"<br>Comment: the small sample size may have introduced bias in estimates of treatment effect |
| Duration of follow-up | High risk | Quote: "The experimental video clip was played twice with a 1-minute break given between viewing's. The participants were then asked to respond to the pain intensity question...and to complete the BPDQ"<br>Comment: the trial authors re-measured outcomes on immediate completion of the intervention period only and did not measure them over a clinically relevant length of time |
| Other bias | Unclear risk | Comment: the trial authors did not report baseline pain data |

**Li 2012**

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| Methods | **Design:** parallel group, 2-arm RCT (China; July 2008 to July 2010).<br>**Setting:** hospital.<br>**Interventions:** acupuncture and massage or rehabilitation therapy.<br>**Sample size calculation:** not reported. |
| Participants | **Number of participants:** 120 (60 per group).<br>**Type of noxious initiating event:** stroke (upper limb).<br>**Diagnostic criteria:** Steinbrocker 1948 (stage 1).<br>**Baseline characteristics:**<br>1. acupuncture and massage:<br>i) mean (±) age = 62 (12) years; female:male = 20:40;<br>ii) mean (±) duration of shoulder-hand syndrome = 28 (6) days.<br>2. rehabilitation:<br>i) mean (±) age = 61 (13) years; female:male = 19:41;<br>ii) mean (±) duration of shoulder-hand syndrome 27 (5) days.<br>**Inclusion criteria:**<br>1. ischemic stroke;<br>2. age 18 to 75 years;<br>3. clinical symptoms of shoulder-hand syndrome conforming to stage I of the Steinbrocker criteria;<br>4. fixed address and agreement to long-term follow-up visits;<br>5. sufficient cognitive ability to consent.<br>**Exclusion criteria:**<br>1. shoulder-hand syndrome caused by a second stroke, cerebral haemorrhage, |

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| | cerebral tumour or trauma;<br>2. shoulder-hand syndrome at stage II or III;<br>3. pain or restricted shoulder motion secondary to dislocation or subluxation, fracture or brachial plexus injury;<br>4. severe heart, liver or kidney disease;<br>5. severe cognitive dysfunction, mental disorder, malnutrition or poor general condition;<br>6. unable to consent. |
| Interventions | **Acupuncture and massage (N = 60)**<br>Components of intervention:<br>1. acupuncture: electric and non-electric acupuncture involving the following points: Sanjian (LI 3), Houxi (SI 3), Zhongzhu (SJ 3), Jianzhongshu (SI 15), Jianliao (SJ 14), Shousanli (LI 10), Waiguan (SJ 5) and Tianzong (SI 11);<br>2. massage: massage of the affected upper limb, passive shoulder movements without pain.<br>Dosage: acupuncture = 25 minutes, massage = 25 minutes.<br>Frequency of administration: once per day for 6 therapeutic courses; each course comprised 5 sessions, with a 2-day interval between courses (30 sessions)<br>Provider: doctors.<br>**Rehabilitation therapy (n = 60)**<br>Components of intervention: active-assisted scapular movements; Bobath exercises to clench the fist, functional transfers (e.g. changing position from prone to sitting, sitting to standing); proprioceptive neuromuscular facilitation (PNF)<br>Dosage: active-assisted scapular movements = 15 minutes, Bobath exercises and functional transfers = 15 minutes, PNF = 10 minutes<br>Frequency of administration: once per day for 6 therapeutic courses; each course comprised 5 sessions, with a 2-day interval between courses (30 sessions)<br>Provider: doctors. |
| Outcomes | The trial authors assessed outcomes at baseline, at the end of the 6-week treatment period and at 12 weeks post-treatment<br>**Primary outcomes:**<br>1. self-rated pain on passive shoulder motion [direction of motion not described] to 90° with the participant in a seated position using a numeric pain rating scale (scale characteristics not reported);<br>2. number of participants with shoulder-hand syndrome at Steinbrocker stage II or III after treatment.<br>**Secondary outcomes**<br>1. Fugl-Meyer evaluation of functional movement of the upper limb (33 items, maximum possible score = 66; higher scores indicating more normal movement);<br>2. Fugl-Meyer evaluation of functional movement of the hand (7 items, maximum possible score = 14; higher scores indicating more normal movement);<br>3. Modified Rankin scale (scale properties and scoring method not reported);<br>4. adverse events (incidence of shoulder dislocation, fainting during acupuncture, haematoma, other). |
| Notes | **Source of funding:** not reported.<br>**Statement regarding declarations of interest:** not reported. |

| *Risk of bias* | | *Risk of bias* |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | Quote: "A random encoding plan was designed using SPSS software"<br>Comment: the trial authors used an acceptable method to generate the sequence allocation |
| Allocation concealment (selection bias) | Low risk | Quote: "A random encoding plan was designed using SPSS software and concealed in an envelope<br>Comment: the trial authors used an adequate method to conceal the allocation sequence |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention |
| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | High risk | Comment: unblinded participants who may have had different expectations about the benefits of the intervention they received self-reported some outcomes (e.g. pain intensity) |
| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Unclear risk | Comment: the trial authors did not give a statement of procedures regarding blinding of the outcome assessor |
| Incomplete outcome data (attrition bias)<br>Drop-out rate described and acceptable | Low risk | Quote: "All patients finished the treatment and had a follow-up visit"<br>Comment: all randomly assigned participants completed the study |
| Incomplete outcome data (attrition bias)<br>Participants analysed in the group to which they were allocated | Low risk | Quote: "All patients finished the treatment and had a follow-up visit"<br>Comment: the trial authors did not report the method of analysis (ITT versus per protocol) |
| Selective reporting (reporting bias) | Low risk | Comment: the trial authors fully reported outcome data for all outcomes reported in the methods section of the publication |

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| Sample size | Unclear risk | Quote: "The 120 subjects in this series. ..were selected from 202 stroke patients. ..They were randomly divided into an acupuncture-massage group and a rehabilitation group, with 60 cases in each"<br>Comment: the extent to which the small to moderate sample size may have introduced bias into estimates of treatment effect is uncertain |
| Duration of follow-up | Low risk | Quote: "Each of the above indices was recorded before treatment, at the end of the 6-week treatment period and at the 12th-week follow-up visit"<br>Comment: the trial authors measured outcomes over a clinically relevant length of time |
| Other bias | Low risk | Comment: we did not identify any other sources of bias. |

**Moseley 2004**

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| Methods | **Design:** single-blind, 2-arm RCT (Australia; dates not reported). (The trial author reported that participants in the control group crossed over into the experimental group. However, we deemed that this trial had not employed a true crossover design and we analysed it as a 2-arm parallel group trial up to the endpoint just prior to crossover)<br>**Setting:** hospital physiotherapy department.<br>**Interventions:** graded motor imagery (GMI) or ongoing medical management.<br>**Sample size calculation:** not reported. |
| Participants | **Number of participants:** 13 (experimental group n = 7; control group n = 6).<br>**Type of noxious initiating event:** wrist fracture (upper limb).<br>**Diagnostic criteria:** Bruehl 1999 (CRPS I).<br>**Baseline characteristics:**<br>1. GMI:<br>i) Mean (SD) age = 35 (15) years; female:male = 5:2;<br>ii) Mean (SD) duration of CRPS I: 51 (18) weeks;<br>2. ongoing medical management:<br>i) Mean (SD) age = 38 (14) years; female:male = 4:2;<br>ii) Mean (SD) duration of CRPS I : 65 (19) weeks.<br>**Inclusion criteria:** > 6 months post non-complicated wrist fracture.<br>**Exclusion criteria:**<br>1. previously benefited from an intravenous regional sympathetic blockade;<br>2. any other upper limb pathology or pain;<br>3. any neurological or motor disorder including dyslexia or difficulty performing a rapid naming task;<br>4. visually impaired; |

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| | 5. a diagnosed psychopathology;<br>6. any invasive analgesic strategy (e.g. spinal cord stimulator);<br>7. lived beyond the immediate metropolitan area of the host department. |
| Interventions | **GMI (N = 7)**<br>Components of intervention:<br>1. recognition of hand laterality stage (2 weeks): whilst seated at a computer monitor, participants viewed a random sequence of 56 photographic images of either a right or left hand in a variety of postures. Participants were instructed to identify whether the displayed image was of a right or left hand by pressing an appropriate button on the computer keyboard. participants borrowed a notebook computer to repeat the task at home;<br>2. imagined hand movements stage (2 weeks): whilst viewing a random sequence of 28 images of the affected hand participants were advised to deliberately imagine moving their hand to adopt the posture shown in the picture, 3 times<br>3. Mirror therapy stage (2 weeks): using a mirror box which concealed the affected limb from view but allowed participants to view a mirror image of their unaffected limb, participants viewed a sequence of 20 pictures of the unaffected hand and were instructed to slowly and smoothly adopt the posture shown in each picture with both hands. Emphasis was placed on watching the reflection of their unaffected hand in the mirror.<br>Dosage: hand laterality and imagined movements tasks - 3 times; mirror therapy task - 10 times<br>Frequency of administration: each waking hour, daily for 2 weeks (6 weeks in total)<br>Provider: not reported.<br>**Ongoing medical management (N = 6)**<br>Components of intervention:<br>1. no limitations placed on treatment;<br>2. participants were requested not to change medication type or dosage and to record any new treatments received;<br>3. predominantly physical therapy (2 to 3 sessions per week) comprising active and passive limb mobilisation, systemic desensitisation and hydrotherapy;<br>4. chiropractic manipulation and acupuncture (1 participant); psychological counselling (1 participant). |
| Outcomes | Trial authors assessed outcomes at baseline, at 2 and 4 weeks after commencement of treatment, at the end of the 6-week treatment period (week 6) and 6 weeks post-treatment (week 12). The trial authors did not state a primary outcome<br>1. Neuropathic pain scale (NPS), with responses regarding the 2 previous days (scoring properties not reported);<br>2. swelling, using the average of measure of the circumference of the base of the 2nd and 3rd digits, as measured with a hand measuring tape. |
| Notes | **Source of funding:** Clinical Research Fellowship from the National Health and Medical Research Council of Australia ID 210348<br>**Statement regarding declarations of interest:** not reported. |
| ***Risk of bias*** | ***Risk of bias*** |

**Moseley 2004** (*Continued*)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Patients were randomised by an independent investigator to the 6-week MIP treatment group or to ongoing medical management (control) using a random number table"<br>Comment: the trial authors used an acceptable method to generate the sequence allocation |
| Allocation concealment (selection bias) | Low risk | Quote: "Patients were randomised by an independent investigator..."<br>Comment: the trial authors used an acceptable method to conceal the allocation sequence |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention |
| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | High risk | Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. NPS) |
| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Low risk | Quote: "All assessments were made by a separate investigator who was blind to experimental group and measurement occasion"<br>Comment: the outcome assessor of objective outcomes was blinded to treatment allocation |
| Incomplete outcome data (attrition bias)<br>Drop-out rate described and acceptable | Low risk | Comment: all randomly assigned participants completed the study (as displayed in the published report's 'Experimental plan') |
| Incomplete outcome data (attrition bias)<br>Participants analysed in the group to which they were allocated | Low risk | Comment: the trial authors analysed participants in the group to which they were allocated |
| Selective reporting (reporting bias) | High risk | Comment: the trial authors fully reported outcome data graphically for all outcomes; but did not report raw data in numerical form with measures of variation |

**Moseley 2004** (*Continued*)

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| Sample size | High risk | Quote: "Written informed consent was obtained from the remaining 13 subjects"<br>Comment: the small sample size may have introduced bias in estimates of treatment effect |
| Duration of follow-up | Unclear risk | Quote: "Post hoc analyses showed...a significant reduction in all three variables during the MIP with the effect maintained for at least 6 weeks after the completion of treatment"<br>Comment: the clinical relevance of a 6-week follow-up of outcomes is uncertain |
| Other bias | Unclear risk | Comment: we did not identify any other sources of bias. |

**Moseley 2005**

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| Methods | **Design:** parallel group, 3-arm, single-blind RCT (Australia; dates not reported)<br>**Setting:** not reported.<br>**Interventions:** hand laterality recognition followed by imagined movements followed by mirror movements (RecImMir, MIP) or imagined movements followed by laterality recognition followed by imagined movements (ImRecIm) or laterality recognition followed by mirror movements followed by recognition (RecMirRec)<br>**Sample size calculation:** not reported. |
| Participants | **Number of participants:** 20 (RecImMir, MIP group (1) N = 7; ImRecIm group (2) N = 6; RecMirRec group (3) N = 7)<br>**Type of noxious initiating event:** wrist fracture (upper limb).<br>**Diagnostic criteria:** Bruehl 1999 (CRPS I)<br>**Baseline characteristics:**<br>1. RecImMir, MIP:<br>i) mean (SD) age = 36 (8) years; female:male = 5:2;<br>ii) mean (SD) duration of CRPS I: 12 (6) months;<br>2. ImRecIm:<br>i) mean (SD) age = 27 (7) years; female:male = 4:2;<br>ii) mean (SD) duration of CRPS I : 16 (5) months;<br>3. RecMirRec:<br>i) mean (SD) age = 39 (8) years; female:male = 5:2;<br>ii) mean (SD) duration of CRPS I : 14 (5) months.<br>**Inclusion criteria:** onset of CRPS I post non-complicated wrist fracture > 6 months prior to enrolment<br>**Exclusion criteria:**<br>1. previously obtained relief from an intravenous regional sympathetic blockade;<br>2. any invasive analgesic strategy (e.g. spinal cord stimulator, sympathectomy);<br>3. any other neurological, psychopathology or motor disorder or dyslexia;<br>4. difficulty performing a rapid naming task; |

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| | 5. visually impaired;<br>6. any other upper limb pathology or pain;<br>7. lived outside the immediate metropolitan area of the host department. |
| Interventions | Participants were advised to avoid changing medication or seeking alternative treatment during the course of the trial up to and including the 12-week follow-up. Participants were permitted to attend physiotherapy during the 12-week follow-up, but no criteria about physiotherapy were set<br>**RecImMir, group 1 (N = 7)**<br>Components of intervention:<br>1. hand laterality recognition (2 weeks): whilst seated at a computer monitor, participants viewed a random sequence of 56 photographic images of either a right or left hand in a variety of postures. Participants were instructed to identify whether the displayed image was of a right or left hand by pressing an appropriate button on the computer keyboard. Participants borrowed a notebook computer to repeat the task at home;<br>2. imagined hand movements (2 weeks): whilst viewing a random sequence of 28 images of the affected hand participants were advised to imagine moving their own hand to adopt the posture shown in the picture then returning it to its resting position, and to repeat the process twice for each picture;<br>3. mirror therapy (2 weeks): using a mirror box which concealed the affected limb from view but allowed participants to view a mirror image of their unaffected limb, participants viewed a sequence of 20 pictures of the unaffected hand and were instructed to slowly and smoothly adopt the posture shown in each picture with both hands. Emphasis was placed on watching the reflection of their unaffected hand in the mirror.<br>Dosage: hand laterality task - 3 times, imagined movements task - twice; mirror therapy task - 5 times<br>Frequency of administration: each waking hour, daily for 2 weeks (6 weeks in total)<br>Provider: not reported.<br>**ImRecIm, group 2 (N = 6)**<br>Components of intervention: 2 weeks imagined movements, 2 weeks hand laterality recognition, 2 weeks imagined movements (components described above)<br>Dosage and frequency of administration: as described above.<br>**RecMirRec, group 3 (N = 7)**<br>Components of intervention: 2 weeks hand laterality recognition, 2 weeks mirror therapy, 2 weeks hand laterality recognition (components described above)<br>Dosage and frequency of administration: as described above. |
| Outcomes | The trial authors assessed outcomes at baseline, at 2 and 4 weeks after commencement of treatment, at the end of the 6-week treatment period (week 6) and 12 weeks post-treatment (week 18). The trial authors did not state a primary outcome<br>1. NPS, with responses regarding the 2 previous days (possible range 0 to 100);<br>2. self-rated function with respect to 5 self-selected activities or tasks using an 11-point numerical rating scale (NRS) anchored with "0, completely unable to perform" and "10, able to perform normally" (final score average of 5 tasks, possible range 0 to 10 higher number indicates less severe limitation). |

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| Notes | **Source of funding:** Australian Clinical Research Fellowship from the National Health and Medical Research Council of Australia ID 210348<br>**Statement regarding declarations of interest:** not reported. |

***Risk of bias*** ***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Using a random numbers table, an independent investigator allocated consenting patients into one of three treatment groups"<br>Comment: the trial authors used an acceptable method to generate the sequence allocation |
| Allocation concealment (selection bias) | Low risk | Quote: "Using a random numbers table, an independent investigator allocated consenting patients..."<br>Comment: the trial authors used an acceptable method to conceal the allocation sequence |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Comment: participants were not blinded to treatment allocation but a lack of blinding is unlikely to have biased the results given that participants received interventions judged to have been of relatively equal credibility |
| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | Low risk | Comment: participants were not blinded to treatment allocation and self-reported their outcomes but lack of blinding unlikely to have biased the results given that participants received interventions judged to have been of relatively equal credibility |
| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Unclear risk | Not applicable. |
| Incomplete outcome data (attrition bias)<br>Drop-out rate described and acceptable | Low risk | Comment: all but 1 randomly assigned participant completed the study, and the 1 participant appeared to have dropped out from group 3 (as displayed in the published report's 'Treatment plan') |

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| Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated | High risk | Comment: the trial author did not report the method of analysis (ITT versus per protocol). The trial authors appear to have excluded 1 participant from group 3 from the analysis in an apparent violation of the principle of ITT |
| Selective reporting (reporting bias) | High risk | Comment: the trial authors fully reported outcome data graphically for all outcomes; but did not report raw data in numerical form with measures of variation |
| Sample size | High risk | Quote: "Twenty subjects with chronic CRPS1 initiated by wrist fracture and who satisfied stringent inclusion criteria, were randomly allocated to one of three groups"<br>Comment: the small sample size may have introduced bias in estimates of treatment effect |
| Duration of follow-up | Low risk | Quote: "Single blind randomised trial with 12-week follow-up"<br>Comment: the trial authors measured outcomes over a clinically relevant length of time |
| Other bias | Unclear risk | Comment: we did not identify any other sources of bias. |

**Moseley 2006**

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| Methods | **Design:** parallel group, 2-arm, single-blind RCT (Australia; dates not reported). NB: this trial recruited participants with CRPS I and phantom limb pain. However we only included information and data from participants with CRPS for the purpose of this systematic review<br>**Setting:** not reported.<br>**Interventions:** GMI or physiotherapy and ongoing medical care.<br>**Sample size calculation:** a total sample size of 51 participants would detect an effect size of 0.80 (equivalent to a reduction in pain of 29 mm on a 100 mm VAS), with a probability of 80%, assuming an alpha level of 0.05 |
| Participants | **Number of participants:** 37 (experimental group N = 17; control group N = 20).<br>**Type of noxious initiating event:** mixed (fractures n = 14, soft-tissue injury n = 15, post carpal tunnel release n = 2, venepuncture site n = 2, post finger/toe amputation n = 2, carpal tunnel syndrome n = 1, nail infection n = 1) (upper and lower limb)<br>**Diagnostic criteria:** Bruehl 1999 (CRPS I).<br>**Baseline characteristics:**<br>1. GMI: |

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| | i) mean (SD) age = 45 (14) years; female:male = 11:6;<br>ii) mean (SD) duration of CRPS I: 14 (10) months;<br>2. physical therapy and ongoing medical care:<br>i) mean (SD) age = 41 (14) years; female:male = 15:5;<br>ii) mean (SD) duration of CRPS I: 12 (8) months.<br>**Inclusion criteria:** CRPS I of an upper or lower limb.<br>**Exclusion criteria:**<br>1. any other neurologic, psychopathology or motor disorder;<br>2. dyslexia;<br>3. difficulty performing a rapid naming task;<br>4. visually impaired;<br>5. any other limb pathology or pain;<br>6. lived outside the immediate metropolitan area of the host department. |
| Interventions | **GMI (N = 17)**<br>Components of intervention<br>1. limb laterality recognition phase (2 weeks): whilst seated at a computer, participants viewed a random sequence of photographic images (matched to gender) of either a right or left hand (participants with an affected upper limb) or foot (participants with an affected lower limb) in a variety of positions and alignments. Participants indicated whether the displayed image was of a right or left limb by pressing an appropriate key on the computer keyboard;<br>2. imagined movements phase (2 weeks): whilst viewing a random sequence of images of both limbs participants were required to imagine twice adopting the posture shown with a smooth and pain-free movement;<br>3. mirror movements phase (2 weeks): using a mirror box which concealed the affected limb from view but allowed participants to view a mirror image of their unaffected limb, participants viewed a sequence of images and were instructed to twice adopt the posture shown with both limbs, using smooth and pain-free movements.<br>Dosage: participants were prescribed a training protocol of gradually increased training load according to task difficulty during each of the 3 GMI phases, as detailed by the trial authors<br>Frequency of administration: hourly training (further details not reported)<br>Provider: physiotherapist.<br>**Physiotherapy and ongoing medical care (N = 20)**<br>Components of intervention: not reported.<br>Dosage: not reported.<br>Frequency of administration: minimum of once per week together with a hourly home programme<br>Provider: physiotherapists. |
| Outcomes | Outcomes assessed at baseline, at the end of the 6-week treatment period and 6 months post-treatment<br>**Primary outcomes:**<br>1. self-rated function with respect to 5 self-selected activities or tasks using an 11-point NRS anchored with "0, completely unable to perform" and "10, able to perform normally";<br>2. self-rated pain severity using a 0 to 100mm VAS (anchor points not described) to rate average level of pain over the last 2 days; |

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| | 3. McGill Pain Questionnaire (MPQ). |
| Notes | Original trial publication reported data for participants with CRPS I and phantom limb pain (N = 51). Details reported above refer to only those participants with CRPS I (N = 37)<br>**Source of funding:** not reported<br>**Statement regarding declarations of interest:** the authors declared no conflicts of interest. |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Patients were randomized via random number generation by an independent investigator...using a random numbers table"<br>Comment: the trial authors used an acceptable method to generate the sequence allocation |
| Allocation concealment (selection bias) | Low risk | Quote: "Patients were randomized via random number generation by an independent investigator..."<br>Comment: the trial authors used an acceptable method to conceal the allocation sequence |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention |
| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | High risk | Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. pain intensity) |
| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Low risk | Not applicable. |
| Incomplete outcome data (attrition bias)<br>Drop-out rate described and acceptable | Low risk | Quote: "One female subject in the control group withdrew from the study because she sustained an unrelated injury. There were no other dropouts or withdrawals"<br>Comment: the minimal drop-out rate (5% |

**Moseley 2006** (*Continued*)

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| | | from 1 trial arm) is unlikely to have biased the results |
| Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated | Low risk | Comment: the trial authors performed an available case analysis |
| Selective reporting (reporting bias) | Low risk | Comment: the trial authors fully reported outcome data for self-reported function and pain severity outcomes for participants with CRPS and phantom limb pain combined as conceived in the original trial design. They presented outcome data for participants with CRPS graphically only |
| Sample size | High risk | Quote: "Fifty-one patients [37 with CRPS] with phantom limb pain or CRPS1 were randomly allocated"<br>Comment: the small sample size may have introduced bias in estimates of treatment effect. (We acknowledge that our judgement regarding the risk of bias linked to sample size for this study is based on the purposeful exclusion of a number of participants with phantom limb pain (N = 14) that the original design did not intend) |
| Duration of follow-up | Low risk | Quote: "All assessments were undertaken at prerandomization and at 6 weeks (completion of the treatment period). Pain VAS and function NRS were also undertaken at 6 months follow-up"<br>Comment: the trial authors measured outcomes over a clinically relevant length of time |
| Other bias | Unclear risk | Comment: we did not identify any other sources of bias. |

**Moseley 2009**

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| Methods | **Design:** within-subject randomised crossover design (Australia; dates not reported)<br>**Setting:** not reported.<br>**Interventions:** tactile discrimination training (TDT) under 4 separate conditions<br>**Sample size calculation:** not reported. |
| Participants | **Number of participants:** 10.<br>**Type of noxious initiating event:** mixed (fractures of the hand or wrist n = 4, sprains n = 2, carpal tunnel syndrome n = 2, post hand cannulation n = 1, thumb dislocation n |

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| | = 1) (upper limb)<br>**Diagnostic criteria:** Bruehl 1999 (CRPS I).<br>**Baseline characteristics:**<br>1. mean (SD) age = 43 (11) years; female:male = 6:4;<br>2. mean (SD) duration of CRPS I: 20 (5) months.<br>**Inclusion criteria:** CRPS of 1 wrist of hand.<br>**Exclusion criteria:** not reported. |
| Interventions | **TDT (N = 10)**<br>Components of intervention:<br>1. two probes (2 mm and 12 mm in diameter) were applied to 1 of 5 stimulation sites on the affected limb in a random order, with an interstimulus interval of 15 seconds;<br>2. TDT was performed under 4 different conditions:<br>i) facing + skin: involved participants watching the reflected image of their unaffected, non-stimulated arm in a mirror placed between the upper limbs while facing the stimulated arm;<br>ii) skin only: involved participants watching their unaffected, non-stimulated arm directly<br>iii) facing only: involved participants looking in the direction of their affected, stimulated arm but with no mirror and the unaffected limb hidden;<br>iv) control condition: involved participants looking away from their stimulated limb with the unaffected limb hidden.<br>Dosage: three 6-minute blocks of 24 stimuli were undertaken with a 3-minute rest period between blocks. Each treatment session involved 72 stimuli and lasted for 24 minutes<br>Frequency of administration: each participant received 4 sessions of each experimental condition in varying order (total of 16 sessions), with 3 to 4 days between sessions<br>Provider: not reported. |
| Outcomes | The trial authors assessed outcomes at baseline, immediately and 2 days post-treatment<br>**Primary outcomes:** 2-point discrimination threshold, measured in mm, using a mechanical calliper<br>**Secondary outcomes:** self-rated current pain (at rest) severity using a 100 mm VAS anchored with "no pain" and "worst possible pain" |
| Notes | **Source of funding:** Nuffield Oxford Medical Fellowship, NHMRC Senior Research Fellowship, Templeton Foundation<br>**Statement regarding declarations of interest:** the authors declared no conflicts of interest. |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "The conditions were randomised and counterbalanced so that each participant had four sessions of each condition, but in varying order"<br>Comment: the trial authors did not report the method of sequence generation |

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| Allocation concealment (selection bias) | Low risk | Comment: this was not applicable (when crossover design employed) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Comment: given the nature of the intervention, participants were not blinded to treatment allocation but the extent to which the lack of blinding may have introduced bias is uncertain |
| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | Unclear risk | Comment: unblinded participants self-reported some outcomes (e.g. pain intensity) but the extent to which the lack of blinding may have introduced bias is uncertain |
| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Unclear risk | Comment: we do not known whether or not the outcome assessors were blinded to the treatment condition |
| Incomplete outcome data (attrition bias)<br>Drop-out rate described and acceptable | Low risk | Comment: the trial authors did not report any drop-outs; they presented results based on the total number of included participants |
| Incomplete outcome data (attrition bias)<br>Participants analysed in the group to which they were allocated | Low risk | Comment: not applicable (when crossover design employed). |
| Selective reporting (reporting bias) | High risk | Comment: the trial authors fully reported outcome data graphically for all outcomes; they did not report raw data in numerical form with measures of variation |
| Sample size | High risk | Quote: "Ten patients with chronic CRPS of one hand or wrist (diagnosed according to Bruehl et al.) were recruited"<br>Comment: the small sample size may have introduced bias in estimates of treatment effect |
| Duration of follow-up | High risk | Quote: "The TPD for the three sites was averaged to provide a measure at pre-training, post-training and 2 days later"<br>Comment: the trial authors did not measure outcomes over a clinically relevant length of time |
| Other bias | Unclear risk | Quote: "...there were 1-2 days between the follow-up assessment and the next training session. Participants were advised not |

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| | | to undertake tactile training in between sessions"<br>Comment: the extent to which an interval of 1 to 2 days between outcome assessment and training sessions represented an adequate wash-out period, and therefore the extent to which a carry-over effect may have introduced bias in estimates of treatment effect, is not known |

**Mucha 1992**

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| Methods | **Design:** parallel group, 2-arm RCT (Germany; dates not reported). (The trial authors reported that participants in the control group crossed over into the experimental group. However, we deemed that this trial did not employ a true crossover design and we analysed it as a 2-arm parallel group trial up to the endpoint just prior to crossover)<br>**Setting:** not reported.<br>**Interventions:** $CO_2$ baths plus exercise therapy or exercise therapy alone.<br>**Sample size calculation:** not reported. |
| Participants | **Number of participants:** 40 (20 per group).<br>**Type of noxious initiating event:** post-trauma (no further details reported) (upper limb)<br>.<br>**Diagnostic criteria:** acute algodystrophy of the hand (diagnostic criteria not reported)<br>**Baseline characteristics:**<br>Total sample (separate intervention and control group data not reported)<br>Age range 47 to 56 years (group data not reported).<br>Duration of CRPS (range) 2 to 6 weeks (group data not reported)<br>1. $CO_2$ baths plus exercise therapy<br>i) Female:male = 13:7<br>2. exercise alone<br>i) Female:male = 11:9<br>**Inclusion criteria:**<br>1. CRPS I of the hand;<br>2. post-traumatic onset;<br>3. 'high active stage of condition';<br>4. minimum of 2 weeks duration of symptoms.<br>**Exclusion criteria:** more than 6 weeks duration of symptoms. |
| Interventions | Those participants on medication prior to the trial were instructed to cease their medication at the start of the trial<br>**$CO_2$ baths plus exercise (N = 20)**<br>Components of intervention<br>1. $CO_2$ bath;<br>2. after the bath, 30 to 45 minutes rest in an anti-swelling functional position;<br>3. exercise therapy (as below).<br>Dosage: 12 minute $CO_2$ bath with water temperature of 32 to 33 °C and a $CO_2$ concentration of 800 to 1000 mg/L.<br>Frequency of administration: 5 times a week for 4 weeks (20 sessions) |

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| | Provider: not reported.<br>**Exercise (N = 20)**<br>Components of intervention: progressive exercise therapy. The intensity was dependent on pain level and symptom behaviour<br>Dosage: not reported.<br>Frequency of administration: 5 times a week for 4 weeks (20 sessions)<br>Provider: not reported. |
| Outcomes | The trial authors assessed outcomes at baseline and twice weekly until completion of the intervention period (4 weeks post recruitment). The trial authors did not state any primary outcomes<br>1. self-rated pain intensity at rest; measured using a graphic analogue scale (no scale reported);<br>2. self-rated pain intensity at night; measured using a graphic analogue scale (no scale reported);<br>3. self-rated pain intensity with movement; measured using a graphic analogue scale (no scale points reported);<br>4. hand circumference: measured over the wrist, MCPs and DIPs, recorded in cm. Probably difference between sides. Only MCP data provided;<br>5. range of motion: neutral 0 method of forearm, hand and fingers, recorded in degrees, only wrist data reported;<br>6. grip strength: hand held dynamometer, relative to other side;<br>7. temperature: difference between sides; more than 0.8 degrees difference was recorded as positive. |
| Notes | **Source of funding:** not reported<br>**Statement regarding declarations of interest:** not reported |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: " Patients were randomised into two groups".<br>Comment: the trial authors did not report the method of sequence generation |
| Allocation concealment (selection bias) | Unclear risk | Comment: the trial authors did not report the method of concealment allocation |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention |
| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | High risk | Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they re- |

**Mucha 1992** (*Continued*)

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| | | ceived, self-reported some outcomes (e.g. pain intensity) |
| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Unclear risk | Comment: the trial authors did not report the statement of procedures regarding blinding of the outcome assessor |
| Incomplete outcome data (attrition bias)<br>Drop-out rate described and acceptable | Low risk | Comment: there were no apparent drop-outs. |
| Incomplete outcome data (attrition bias)<br>Participants analysed in the group to which they were allocated | Low risk | Comment: the trial authors analysed participants in the group to which they were allocated but did not report the method of analysis (ITT versus per protocol) |
| Selective reporting (reporting bias) | High risk | Comment: the trial authors fully reported outcome data graphically for all outcomes; but did not report raw data in numerical form with measures of variation |
| Sample size | High risk | Quote: "20 participants per group".<br>Comment: the small sample size may have introduced bias in estimates of treatment effect |
| Duration of follow-up | High risk | Comment: comparison was only possible immediately at the end of the 4-week therapy session as the control group crossed over to the treatment arm at this point |
| Other bias | Low risk | Quote: "Statistical testing showed homogeneity across both groups"<br>Comment: there were no apparent baseline differences between groups<br>Comment: we did not identify any other sources of bias. |

**Oerlemans 1999**

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| Methods | **Design:** parallel group, 3-arm, single-blind RCT (The Netherlands; June 1994 to February 1998)<br>**Setting:** outpatient clinics of 2 university hospitals.<br>**Interventions:** physical therapy (PT) plus medical treatment or occupational therapy (OT) plus medical treatment or social work (SW) plus medical treatment (control)<br>**Sample size calculation:** the study planned to recruit 150 participants (50 per group) in order to be able to detect between-group differences of 6 to 7 points in the impairment level sumscore (ISS) with 80% power |
| Participants | **Number of participants:** 135 (physical therapy group N = 44; OT group N = 44; SW (control) group N = 47)<br>**Type of noxious initiating event:** mixed (fracture (53%), spontaneous onset (13%) , contusion (11%), mallet finger, carpal tunnel syndrome, postoperative interventions, sprains (proportions not reported) (upper limb)<br>**Diagnostic criteria:** Veldman 1993 (CRPS I).<br>**Baseline characteristics:**<br>1. PT:<br>i) mean (SD) age = 50.4 (15.6) years; female:male = 29:15;<br>ii) mean (SD) duration of CRPS I: 3.1 (3.4) months;<br>2. OT:<br>i) mean (SD) age = 56.3 (17) years; female:male = 31:13;<br>ii) mean (SD) duration of CRPS I: 2.9 (2.5) months;<br>3. SW:<br>i) mean (SD) age = 51.5 (16.9) years; female:male = 35:12;<br>ii) mean (SD) duration of CRPS I: 2.9 (3.1) months.<br>**Inclusion criteria:**<br>1. CRPS I of 1 upper limb of less than 1 year duration;<br>2. participants could complete treatment at 1 of 2 study sites;<br>3. aged 18 years or older.<br>**Exclusion criteria:**<br>1. impairment of contralateral extremity;<br>2. relapse of CRPS I;<br>3. pregnancy or lactation;<br>4. prior sympathectomy of the affected extremity. |
| Interventions | All participants received medical treatment according to a fixed pre-established protocol, consisting of free-radical scavengers (dimethylsulfoxide (DMSO) 50% applied locally 5 times a day at the affected location or if DMSO-intolerant, N-acetylcysteine (600 mg 3 times a day), peripheral vasodilators in the case of primarily cold CRPS I (calcium entry blocker verapamil, sustained-release 240 mg once per day or ketanserine 20 mg twice per day eventually increased to 40 mg or pentoxifylline 400 mg twice per day) and treatment of trigger points. Participants also received general information regarding CRPS I; including advice to rest the extremity and not provoke pain<br>**PT (N = 44)**<br>Components of intervention:<br>1. intensity and form of treatment adjusted to the needs of each individual participant;<br>2. pain management advice/counselling directed towards helping participants gain control of the pain and optimise coping by offering insight, practical advice, and |

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| | support and/or by relaxation exercises;<br>3. connective tissue massage, transcutaneous electric nerve stimulation (TENS), exercises for reducing the pain (details not reported);<br>4. instruction, training and practicing of skills by addressing compensatory activities and body positioning (details not reported).<br>Dosage: 30 minutes per session (details for individual components not reported)<br>Frequency of administration: adjusted to the needs of each individual participant (details not reported)<br>Provider: physical therapists.<br>**OT (N = 44)**<br>Components of intervention:<br>1. intensity and form of treatment adjusted to the needs of each individual participant;<br>2. splinting;<br>3. desensitisation (tactile and proprioceptive) programme (details not reported);<br>4. improving functional abilities of the arm/hand by executing various activities, while moving as normally as possible;<br>5. training to improve performance of activities of daily living (e.g. learning how to perform activities differently, advice regarding assistive devices).<br>Dosage: 30 minutes per session (details for individual components not reported)<br>Frequency of administration: adjusted to the needs of each individual participant (details not reported)<br>Provider: occupational therapists.<br>**SW (N = 47)**<br>Components of intervention:<br>1. participants were given attention in the form of listening and insight into the social problems accompanying CRPS I;<br>2. advice regarding how not to evoke pain, rest and asking for help with performing activities perceived as excessively demanding.<br>Dosage: 45 minutes per session.<br>Frequency of administration: adjusted to needs of each individual participant (details not reported)<br>Provider: social workers. |
| Outcomes | Outcomes, as reported across trial reports, variously assessed at baseline and at 6 weeks, 3 months, 6 months and 12 months post recruitment. The primary endpoint was the difference in impairment level sum score between baseline and 12 months post recruitment<br>1. Self-rated pain intensity (present) using a VAS (0 to 100 scale, anchor points not reported);<br>2. self-rated pain intensity (resulting from effort with the affected extremity) using a VAS (0 to 100 scale, anchor points not reported);<br>3. self-rated pain intensity (least pain experienced in the preceding week) using a VAS (0 to 100 scale, anchor points not reported);<br>4. self-rated pain intensity (worst pain experienced in the preceding week) using a VAS (0 to 100 scale, anchor points not reported);<br>5. McGill Pain Questionnaire (Dutch language version), including the: a. total pain rating index (PRI-T), b. total number of words chosen (NWC-T), c. number of 'sensory' words chosen (NWT-S), d. number of 'affective' words chosen (NWT-A), e. |

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| | number of 'evaluative' words chosen (NWT-E);<br>6. percentage of reduced normal mobility, measured by dividing the difference in active range of motion, as measured with a plastic transparent goniometer, between the joints (shoulder, elbow, wrist, digits) of the affected and unaffected upper limbs;<br>7. impairment rating (according to the Guides to the Evaluation of Permanent Impairment (GEPI): a composite score derived from a. measures of loss of active range of motion assessed using goniometry, b. sensory loss in the fingers and thumb assessed via 2-point discrimination testing and c. grip strength assessed by a dynamometer; with a maximum possible score of 60%, with higher scores indicating greater impairment (only measured at 12 months post-treatment; not measured at baseline);<br>8. impairment level sumscore (ISS): constructed to map alterations in impairment in RSD participants; formed by outcomes obtained with 4 measurement parameters and 5 instruments. The outcomes for each instrument are converted into a score, from which the compounded ISS is derived, including a. VAS pain/effort; b. McGill Pain Qr (NWC-T); c. active ROM (from 5 joints (wrist/fingers); d. temperature difference between hands; e. volume difference between hands. Score range was from 5 to50, with higher scores indicating more severe impairment;<br>9. the Radboud Skills Questionnaire; used to determine the perceived degree of deviation from normal use of both hands in activities of daily living (details regarding scoring and interpretation not reported);<br>10. the modified Greentest; used to measure differences in the degree to which both hands could move light objects (e.g. small pins, discs) within 15 seconds using different grips (details regarding scoring and interpretation not reported);<br>11. the Radboud Dexterity Test; used to make qualitative assessments of 7 skills associated with daily activities (e.g. closing a zip fastener, washing hands) (details regarding scoring and interpretation not reported);<br>12. Sickness Impact Profile (SIP) 36. The total score was computed (score range of 0 to 100) as well as the sub-scores for the degree of physical dysfunction and the degree of psychosocial dysfunction (details regarding scoring and interpretation not reported). |
| Notes | **Source of funding:** research grant from the National Health Insurance Board (Ziekenfondsraad), The Netherlands<br>**Statement regarding declarations of interest:** not reported. |

***Risk of bias*** ***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Patients were randomly assigned to one of three groups"<br>Quote: "Randomisation was restricted to blocks of six".<br>Quote: "Assigmnent to groups was performed according to allocation lists established by the Department of Medical Statistics of the University of Nijmegen"<br>Comment: the trial authors used an acceptable method to generate the sequence allocation |

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| Allocation concealment (selection bias) | Unclear risk | Quote: "Assigmnent to groups was performed according to allocation lists established by the Department of Medical Statistics of the University of Nijmegen"<br>Comment: the trial authors did not adequately report the method of concealment allocation |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention |
| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | High risk | Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. pain intensity) |
| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Unclear risk | Comment: we do not know if outcome assessors were blinded to treatment allocation when measuring percentage loss of joint mobility, impairment ratings, impairment level sumscore and disability-based measures |
| Incomplete outcome data (attrition bias)<br>Drop-out rate described and acceptable | Unclear risk | Quote: "After inclusion in the study, 44 patients were assigned to PT, 44 patients to OT and 47 patients to CT. In the course of the 1-year study period, seven, four and four patients abandoned the trial, respectively"<br>Comment: whilst the overall drop-out rate was acceptable (11%), there was an unequal drop-out rate between groups (PT: 16%, OT: 9%, CT: 9%) and the trial authors did not report the reasons for dropping out |
| Incomplete outcome data (attrition bias)<br>Participants analysed in the group to which they were allocated | Low risk | Quote: "Two analyses were done: an intention-to-treat analysis (ITT) and a per-protocol analysis (PP). In the ITT analysis, outcomes of all the participants were used for the group they were originally assigned to. In the PP analysis, outcomes of protocol violators were ignored"<br>Quote: "Three patients from the PT group could not complete the treatment protocol (so were protocol violators) but had test |

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| | | continuity"<br>Comment: the trial authors presented limited data from both ITT and per protocol analyses for selected outcomes |
| Selective reporting (reporting bias) | High risk | Comment: the trial authors reported limited and incomplete outcome data across 4 separate trial reports for self-reported pain and disability outcomes and for investigator-administered outcomes<br>Comment: no numerical data presented for 3 out of the 4 measures of self-rated pain intensity or percentage of reduced normal mobility outcomes<br>Comment: no numerical data reported for impairment rating.<br>Comment: limited numerical data presented for ISS.<br>Comment: no numerical data presented for the Radboud Skills Questionnaire, modified Greentest or Radboud Dexterity Test |
| Sample size | High risk | Quote: "After inclusion in the study, 44 patients were assigned to PT, 44 patients to OT and 47 patients to CT"<br>Comment: the small sample size may have introduced bias in estimates of treatment effect |
| Duration of follow-up | Low risk | Quote: "Re-assessment was performed 6 weeks (t1), 3 months (t2), 6 months (t3) and 12 months (t4) after inclusion in the study"<br>Comment: the trial authors measured outcomes over a clinically relevant length of time |
| Other bias | High risk | Quote: "If, during the period of the trial, the patient explicitly indicated that he or she wanted to switch to another adjuvant therapy, this was allowed. Using a coin, with heads or tails it was decided which adjuvant therapy was next"<br>Quote: "Fourteen patients switched therapies: 12 from CT to PT (nine patients) or OT (three patients) and two from OT to PT"<br>Comment: violations of the random sequence generation were permitted |

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| | | Quote: "Thus, with the inclusion of 135 patients, the power to recognize significant differences was somewhat smaller: the power to detect a significant treatment effect within each group was 72%, whereas differences between the 3 groups could be established with a power of 79%"<br>Comment: the trial was slightly underpowered, which may have introduced bias in estimates of treatment effect and/or contributed to a lack of precision regarding estimates of treatment effect |

**Schreuders 2014**

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|---|---|
| Methods | **Design:** parallel group, 2-arm, single-blind RCT (The Netherlands; dates not reported)<br>**Setting:** not reported.<br>**Interventions:** GMI programme plus conventional treatment or conventional treatment alone<br>**Sample size calculation:** not reported. |
| Participants | **Number of participants:** 18 (experimental group N = 11, control group N = 7).<br>**Type of noxious initiating event:** not reported (upper limb).<br>**Diagnostic criteria:** Bruehl 1999 (CRPS I).<br>**Baseline characteristics:**<br>1. GMI programme (and included in the analysis N = 10):<br>i) mean (SD) age = 42.4 (16.8) years; female:male = 8:2;<br>ii) mean (SD) duration of CRPS I: 50.3 (53.7) months;<br>2. standard care (and included in the analysis N = 5):<br>i) mean (SD) age = 52.8 (12.7) years; female:male = 4:1;<br>ii) mean (SD) duration of CRPS I: 127.4 (87.5) months.<br>**Inclusion criteria:**<br>1. aged between 18 and 75 years;<br>2. symptoms > 6 months.<br>**Exclusion criteria:** not reported |
| Interventions | All participants received conventional treatment including a 6-week OT and physiotherapy programme, including training of grip function, muscle strengthening and joint mobility interventions, writing exercises and advice to reduce the use of splints. Participants were asked not to participate in other treatment programmes during the 12-week period and not to change the type or dosage medication of their medication unless instructed to do so by their physician<br>**GMI programme (N = 11)**<br>Components of intervention:<br>1. adapted from Moseley 2004;<br>2. hand laterality recognition (1 week);<br>3. visual movement imagery exercises (1 week);<br>4. mirror therapy (4 weeks).<br>Dosage: 10 minutes. |

| | |
|---|---|
| | Frequency of administration: every hour (3 times per day minimum) for a total of 6 weeks<br>Provider: therapists (distinction between physio- and occupational therapist not reported)<br>**Standard care (N = 7)**<br>Components of intervention:<br>1. supervised exercise (first 3 weeks);<br>2. feedback regarding home exercises (second 3 weeks);<br>3. training of grip functions (details not reported);<br>4. muscle strengthening exercises (details not reported);<br>5. joint mobility (details not reported);<br>6. housekeeping and other daily activities (details not reported);<br>7. writing exercises;<br>8. coaching to reduce the use of splints.<br>Dosage: 60 minutes per week (over 1 or 2 sessions).<br>Frequency of administration: 1 or 2 sessions per week, for 6 weeks<br>Provider: physical therapists and occupational therapists. |
| Outcomes | Outcomes were assessed at baseline and after 3, 6 (immediately post-treatment) and 12 weeks (6 weeks post-treatment) post enrolment<br>**Primary outcomes:**<br>1. self-rated current pain intensity using a VAS ranging from 0 (no pain) to 100 (unbearable pain);<br>2. self-rated minimum pain intensity (last 3 days) using a VAS ranging from 0 (no pain) to 100 (unbearable pain);<br>3. self-rated maximum pain intensity (last 3 days) using a VAS ranging from 0 (no pain) to 100 (unbearable pain);<br>4. activities of daily living using the Radboud Skills Questionnaire (RASQ) total score and 3 sub-scales:<br>i) clothing, washing, eating;<br>ii) household activities;<br>iii) recreation, social activities.<br>**Secondary outcomes:** fine hand coordination of both hands by using the Nine Hole Peg Test (recorded in seconds) |
| Notes | **Source of funding:** ErasmusMC Mrace Project Zorg 2004-20, grant number 2004-20.<br>**Statement regarding declarations of interest:** the trial authors declared no conflicts of interest. |

***Risk of bias*** ***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Based on a computerized random schedule..."<br>Comment: the trial authors used an acceptable method to generate the sequence allocation |

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | Quote: "Based on a computerized random schedule, a researcher not involved in the execution of the trial, made a sequence of numbered opaque envelopes. These envelopes were prepared with equality being achieved after every ten subjects (block size 10)"<br>Quote: "Envelopes were given in sequence of entry to the patient and were opened by the patient"<br>Comment: the trial authors used an acceptable method to conceal the allocation sequence |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "Patients were not blinded to the treatment as they were aware of the treatment content"<br>Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention |
| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | High risk | Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. pain intensity) |
| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Low risk | Quote: "The assessor was blinded for the allocation to the experimental or control group"<br>Quote: "The measurements were performed by trained blinded assessors"<br>Comment: the trial authors blinded outcome assessors to participant group allocation |
| Incomplete outcome data (attrition bias)<br>Drop-out rate described and acceptable | High risk | Comment: the trial authors did not adequately report drop-out rate in the 'Results' section of the manuscript<br>Comment: according to 'Figure 2' of the manuscript, 1 participant was lost to follow-up and 2 discontinued the intervention from the experimental group, 1 participant withdrew after randomisation, 1 participant was lost to follow-up and 3 discontinued the intervention from the conventional treatment group, giving drop-out |

| | | |
|---|---|---|
| | | rates of 27% and 71% respectively, and an overall drop-out rate of 44%<br>Comment: the high drop-out rate may have introduced bias in estimates of treatment effect |
| Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated | High risk | Comment: the trial authors reported analysis as ITT in Figure 2 of the unpublished manuscript<br>Quote: "Three patients (one in the experimental group, two in the control group) could not be included in the analysis due to insufficient compliance in filling out the VAS and RASQ questionnaires or because of immediate withdrawal from the control therapy because the participants only wanted the graded MIP"<br>Comment: violation of the principle of ITT analysis may have introduced bias in estimates of treatment effect<br>Quote: "From seven of the remaining fifteen patients (five in the experimental group and two in the control group) there were missing end-tests" (i.e. at 12 weeks post enrolment/6 weeks postintervention)<br>Quote: "Differences in changes in both groups over times were tested using a generalized estimating equations (GEE) approach. Under the assumption that missing data were random and not due to group allocation or treatment effect, this model estimates missing data values, thereby allowing the use of data from all participants, irrespective of whether they were measured at all time points"<br>Comment: use of GEE may have introduced bias in estimates of treatment effect |
| Selective reporting (reporting bias) | High risk | Comment: the trial authors reported outcome data graphically for all self-reported pain outcomes; and did not report raw data in numerical form with measures of variation. The trial authors presented effect sizes with measures of variation for the Radboud Skills Questionnaire and Nine Hole Peg Test; and did not report numerical data with measures of variation |

**Schreuders 2014** (*Continued*)

| | | |
|---|---|---|
| Sample size | High risk | Quote: "For this trial eighteen patients were included".<br>Quote: "For this study only 18 patients were assessed for eligibility and only 15 of them could be included in the analysis. The number of patients in the study was therefore too small to detect possible effects with the intended power for which 52 patients were needed"<br>Comment: the small sample size may have introduced bias in estimates of treatment effect |
| Duration of follow-up | Unclear risk | Quote: "Outcome was assessed at baseline, after 3, 6 and 12 [i.e. 6 weeks post-treatment] weeks"<br>Comment: the clinical relevance of a 6-week follow-up of outcomes is uncertain |
| Other bias | High risk | Comment: baseline data for 3 participants excluded from the analysis not reported<br>Comment: likely highly significant baseline imbalance in duration of symptoms between groups |

**Uher 2000**

| | |
|---|---|
| Methods | **Design:** parallel group, 2-arm, RCT (Germany, dates not reported).<br>**Setting:** not reported.<br>**Interventions:** manual lymph drainage (MLD) plus exercise or exercise alone<br>**Sample size calculation:** not reported. |
| Participants | **Number of participants:** 40 (15 in the manual lymph drainage group, 25 in the exercise alone group)<br>**Type of noxious initiating event:** mixed (postfracture n = 27, post dislocation n = 9, postsurgery n = 4) (lower limb)<br>**Diagnostic criteria:** CRPS I (diagnostic criteria not reported).<br>**Baseline characteristics:**<br>Total sample: female:male 31:4.<br>1. Group receiving manual lymph drainage plus exercise:<br>i) mean (SD) age = not reported; female:male = not reported;<br>ii) mean (SD) duration of CRPS I = not reported.<br>2. Group receiving exercise:<br>i) mean (SD) age = not reported; female:male = not reported;<br>ii) mean (SD) duration of CRPS I = not reported.<br>**Inclusion criteria:**<br>1. clinical, radiographic and scintigraphic signs of CRPS 1;<br>2. < 6 months post-trauma/surgery. |

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|---|---|
| | **Exclusion criteria:**<br>1. venous insufficiency;<br>2. recurrent thrombophlebitis;<br>3. peripheral vascular disease;<br>4. blood disorders;<br>5. currently receiving physical treatment. |
| Interventions | Participants were given a brochure providing general advice (details not reported), no analgesic or anti-inflammatory medication prescribed, participants were asked to inform the clinician if they took analgesia or anti-inflammatory medication for more than 3 days<br>**Manual lymph drainage plus exercise (N = 15)**<br>Components of intervention:<br>1. manual lymph drainage (further details not reported);<br>2. exercise (as below).<br>Dosage: 30 minutes<br>Frequency of administration: 3 times per week for 6 weeks (18 sessions)<br>Provider: physiotherapists<br>**Exercise (N = 25)**<br>Components of intervention:<br>1. goal to improve range of motion and reduce pain;<br>2. rhythmic stabilisation techniques of Klein Vogelbach and passive movements as tolerated of the affected ankle.<br>Dosage: 30 minutes.<br>Frequency of administration: 3 times per week for 6 weeks (18 sessions)<br>Provider: physiotherapists. |
| Outcomes | Outcomes assessed at baseline and immediately on completion of the intervention period (6 weeks post recruitment). The trial authors did not state any primary outcome<br>1. Self-rated pain intensity measured using a 6-point verbal rating scale (0 = no pain, 5 = maximum pain);<br>2. range of motion (dorsiflexion and plantarflexion) at the talocrural joint measured using a goniometer;<br>3. temperature measured using a surface thermometer, between the malleoli, with the value recorded as the difference between 2 sides;<br>4. swelling measured as the difference in ankle circumference (in cm), at level of malleoli, between 2 sides;<br>5. radiological assessment (details not reported);<br>6. scintigraphic assessment (details not reported). |
| Notes | **Source of funding:** not reported.<br>**Statement regarding declarations of interest:** not reported. |

***Risk of bias*** ***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Comment: the trial authors did not report the method of sequence generation |

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | Quote: "Randomisation was done using the sealed envelope method, by a doctor not involved in the study"<br>Comment: the trial authors used an acceptable method to conceal the allocation sequence |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention |
| Blinding of outcome assessment (detection bias)<br>Self-reported outcomes | High risk | Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. pain intensity) |
| Blinding of outcome assessment (detection bias)<br>Investigator-administered outcomes | Low risk | Quote: "Tested by a doctor who did not know group assignment"<br>Comment: the outcome assessor was blinded to treatment allocation |
| Incomplete outcome data (attrition bias)<br>Drop-out rate described and acceptable | Low risk | Comment: an overall, and balanced, drop-out rate of 12% is unlikely to have biased the results |
| Incomplete outcome data (attrition bias)<br>Participants analysed in the group to which they were allocated | High risk | Comment: the trial authors excluded 3 participants (2 from the MLD group and 1 from the exercise group) were excluded from the analysis because they did not regularly attend for therapy, in violation of the ITT principle. Two participants from the exercise group were excluded after randomisation secondary to wrongful inclusion despite fulfilment of exclusion criteria |
| Selective reporting (reporting bias) | High risk | Comment: the trial authors did not report outcome data for pain intensity |
| Sample size | High risk | Comment: the small sample size may have introduced bias in estimates of treatment effect |
| Duration of follow-up | High risk | Quote: "Assessment after six weeks of therapy".<br>Comment: outcomes were re-measured on immediate completion of the intervention |

**Uher 2000** (*Continued*)

| | | |
|---|---|---|
| | | period only and were not measured over a clinically relevant length of time |
| Other bias | Low risk | Comment: we did not identify any other sources of bias. |

Abbreviations: CRPS I: complex regional pain syndrome type 1; CT: control therapy; GMI: graded motor imagery; IFC: interferential current; ITT: intention to treat; MIP: motor imagery programme; MLD: manual lymphatic drainage; NRS: numerical rating scale; OT: occupational therapy; PT: physiotherapy/physical therapy; RCT: randomised controlled trial; RSD: reflex sympathetic dystrophy; SD: standard deviation; SGB: stellate ganglion block; SPSS: Statistical Package for the Social Sciences; SW: social work; TDT: tactile discrimination training; TENS: transcutaneous electrical nerve stimulation; TPD: two-point discrimination; US: ultrasound; VAS: visual analogue scale.

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

| Study | Reason for exclusion |
|---|---|
| Bolel 2006 | This study only evaluated the outcome measure of 'sympathetic skin response' and fell outside the inclusion criteria of this review |
| Fialka 1992 | Not a RCT. |
| Fialka 1996 | Autogenic training does not fall within the scope of practice of physiotherapy |
| Field 1993 | Not a RCT. |
| Gromo 1974 | Not a RCT. |
| Jasmina 2012 | Not a RCT. |
| Karabegović 2009 | Not a RCT. |
| Kocić 2010 | The study authors only evaluated 'infrared thermovision' as the only outcome measure and fell outside the inclusion criteria of this review |
| Perrigot 1982 | Not a RCT. |
| Toth 2014 | The trial included participants (N = 54) with mixed aetiologies but only 2 participants with complex regional pain syndrome (CRPS) with 1 randomised to each trial arm. We could not make any meaningful comparison |
| Tulgar 1991 | Not a RCT. |
| Wu 1999 | Qigong does not fall within the scope of practice of physiotherapy |

(*Continued*)

| | |
|---|---|
| Zyluk 1994 | Not a RCT. |

Abbreviations: RCT: randomised controlled trial.

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

**ISRCTN39729827**

| | |
|---|---|
| Methods | Unavailable. |
| Participants | Unavailable. |
| Interventions | Unavailable. |
| Outcomes | Unavailable. |
| Notes | We are awaiting submission for publication. |

**Mete-Topcuoglu 2010**

| | |
|---|---|
| Methods | Not yet assessed. |
| Participants | Not yet assessed. |
| Interventions | Not yet assessed. |
| Outcomes | Not yet assessed. |
| Notes | This is currently only available as a conference abstract. |

**NCT00625976**

| | |
|---|---|
| Methods | Unavailable. |
| Participants | Unavailable. |
| Interventions | Unavailable. |
| Outcomes | Unavailable. |
| Notes | We were unable to contact the study authors. |

## Characteristics of ongoing studies *[ordered by study ID]*

**Barnhoorn 2012**

| | |
|---|---|
| Trial name or title | The effectiveness and cost evaluation of pain exposure physical therapy and conventional therapy in patients with complex regional pain syndrome type 1. Rationale and design of randomized controlled trial |
| Methods | Parallel-group, 2-arm randomised controlled trial (RCT) (The Netherlands) |
| Participants | **Inclusion criteria:**<br>1. diagnosis of CRPS I; of upper or lower extremity; and of between 3 and 24 months duration;<br>2. age 18 to 80 years.<br>**Exclusion criteria:**<br>1. alternative diagnoses that may explain the pain syndrome;<br>2. impairments of the contra-lateral extremity;<br>3. relapse of CRPS I;<br>4. prior sympathectomy of the affected extremity;<br>5. pregnancy; lactation. |
| Interventions | **Experimental group:** 'pain exposure physical therapy', consisting of a progressive-loading exercise programme, de-sensitising massage and management of pain-avoidance behaviour<br>**Conventional group:** conventional treatment according to Dutch guidelines; comprising pharmacological and physical therapy exercise interventions |
| Outcomes | **Primary outcome measures:**<br>1. impairment level SumScore (ISS) (restricted version).<br>**Secondary outcome measures:**<br>1. Disability of Arm, Shoulder and Hand questionnaire;<br>2. Lower Limb Tasks Questionnaire;<br>3. Fear-Avoidance Beliefs Questionnaire;<br>4. SF-36;<br>5. muscle force measurements, as measured by a hand-held dynamometer;<br>6. 10 metre walking test;<br>7. Timed Up and Go test;<br>8. compliance and adherence, as measured by interview, questionnaires (the Seven Days Physical Activity Recall, International Physical Activity Questionnaire, Pain Catastrophising Scale, Pain Disability Index) and accelerometry. |
| Starting date | January 2009 |
| Contact information | Jan Paul Frölke MD, PhD; J.Frolke@chir.umcn.nl |
| Notes | http://clinicaltrials.gov/show/NCT00817128 |

**ISRCTN48768534**

| | |
|---|---|
| Trial name or title | Transcutaneous electrical nerve stimulation (TENS) for patients with upper limb complex regional pain syndrome: a feasibility study |
| Methods | Parallel-group, 2-arm RCT (UK) |
| Participants | **Inclusion criteria:**<br>1. 18 years of age or older;<br>2. have had CRPS for ≥ 6 months;<br>3. can speak English to a good standard;<br>4. no neurological conditions;<br>5. capable of making an informed decision to take part or not.<br>**Exclusion criteria:**<br>1. individuals with a pacemaker, heart disease or epilepsy;<br>2. individuals who are pregnant;<br>3. abnormal skin sensation in the area below the electrodes. |
| Interventions | **Intervention group:** transcutaneous electrical nerve stimulation<br>**Placebo group:** sham transcutaneous electrical nerve stimulation |
| Outcomes | **Primary outcome measures:**<br>1. pain intensity using a VAS;<br>2. medication use;<br>3. Disability of Arm, Shoulder and Hand questionnaire;<br>4. Hand Laterality Recognition Task;<br>5. Bath CRPS Body Perception Disturbances questionnaire.<br>**Secondary outcome measures:**<br>1. placebo blinding credibility;<br>2. adverse reactions;<br>3. qualitative interviews. |
| Starting date | November 2013 |
| Contact information | Dr Cormac Ryan PhD, c.ryan@tees.ac.uk |
| Notes | http://controlled-trials.com/ISRCTN48768534 |

**NCT01915329**

| | |
|---|---|
| Trial name or title | Effects of repetitive electrical sensory stimulation (RSS) as intervention in complex regional pain syndrome type I (CRPS) |
| Methods | Parallel-group, 2-arm RCT (Germany) |
| Participants | **Inclusion criteria:**<br>1. age 18 to 75 years;<br>2. diagnosed with CRPS.<br>**Exclusion criteria:**<br>1. intolerable hyperalgesia; |

**NCT01915329** (*Continued*)

| | |
|---|---|
| | 2. lesions at the finger tips;<br>3. high grade digit contracture;<br>4. central neurological disorders;<br>5. psychiatric disorders; |
| Interventions | **Experimental group:** repetitive electrical sensory stimulation<br>**Sham comparator:** sham repetitive electrical sensory stimulation |
| Outcomes | **Primary outcome measures:**<br>1. static tactile 2-point discrimination threshold.<br>**Secondary outcome measures:**<br>1. pain intensity using an 11-point NRS;<br>2. somatosensory evoked potentials. |
| Starting date | February 2012 |
| Contact information | Christoph Maier MD, PhD; christopp.maier@rub.de |
| Notes | http://clinicaltrials.gov/show/NCT01915329 |

**NCT01944150**

| | |
|---|---|
| Trial name or title | Association of transcutaneous electrical nerve stimulation and hypnosis (HYPTENS) |
| Methods | Parallel-group, 2-arm RCT (France) |
| Participants | **Inclusion criteria:**<br>1. age 18 to 80 years suffering from chronic non-cancer pain of mixed aetiologies (either nociceptive or neuropathic) including osteoarthritic limb arthralgia, chronic lumbo radiculalgia, chronic back pain, cervical radiculopathy, postherpetic neuralgia, postsurgical peripheral neuropathic pain, post-trauma neuropathic pain, CRPS I or II, tendinopathy;<br>2. uninjured skin;<br>3. ability to comply with requirements of the trial.<br>**Exclusion criteria:**<br>1. participants with fibromyalgia;<br>2. participants receiving relaxation therapy, acupuncture or cognitive/behavioural therapies;<br>3. participants with cognitive disorders, unaided hearing loss, a major hearing impairment, a pace maker, allodynia or complete anaesthesia of the painful territory or already been treated by TENS or hypnosis, or both;<br>4. pregnancy. |
| Interventions | **Experimental group:** transcutaneous electrical nerve stimulation and hypnosis.<br>**Active comparator group:** transcutaneous electrical nerve stimulation. |
| Outcomes | **Primary outcome measures:**<br>1. pain intensity using a VAS (0 to 100 mm).<br>**Secondary outcome measures:**<br>1. analgesic consumption; |

**NCT01944150** (*Continued*)

| | |
|---|---|
| | 2. SF36;<br>3. patient global impression of change (PGIC). |
| Starting date | September 2013 |
| Contact information | Louise Geoffroy, ide.emdsp@sat.aphp.fr |
| Notes | http://clinicaltrials.gov/show/NCT01944150 |

**UKCRN ID 12602**

| | |
|---|---|
| Trial name or title | Development of an Electrical Sensory Discrimination Therapies device (ESDT) for the relief of chronic pain in Complex Regional Pain Syndrome. A proof of concept study |
| Methods | Parallel-group, 2-arm RCT (UK) |
| Participants | **Inclusion criteria:**<br>1. diagnosed with CRPS type I.<br>**Exclusion criteria:**<br>1. diagnosed with any other neurological, psychopathologic, motor disorder or major nerve damage (CRPS II);<br>2. the presence of any other limb pathology or pain on the affected CRPS limb;<br>3. cutaneous damage on the area to be stimulated;<br>4. receiving intensive CRPS-specific MDT rehabilitation in an inpatient setting during the time course of the study or within the previous month;<br>5. unable to understand written or verbal English and give informed consent. |
| Interventions | **Intervention group:** ESDT and de-sensitisation tasks.<br>**Control group:** routine care, including de-sensitisation tasks. |
| Outcomes | 1. Short form McGill Pain Questionnaire;<br>2. Brief Pain Inventory questionnaire;<br>3. Disability of Arm, Shoulder and Hand questionnaire (upper limb CRPS);<br>4. Lower Extremity Functional Scale questionnaire (lower limb CRPS);<br>5. Hospital Anxiety and Depression Scale;<br>6. adverse events. |
| Starting date | 2012 |
| Contact information | Prof CS McCabe PhD, Candy; Mccabe@uwe.ac.uk |
| Notes | |

Abbreviations: ESDT: electrical sensory discrimination therapies; PGIC: patient global impression of change; RCT: randomised controlled trial; RSS: repetitive electrical sensory discrimination; TENS: transcutaneous electrical nerve stimulation; UK: United Kingdom; VAS: visual analogue scale.

## DATA AND ANALYSES

### Comparison 1. Graded motor imagery versus usual care

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Pain intensity (post-treatment) | 2 | 49 | Mean Difference (IV, Random, 95% CI) | -14.45 [-23.02, -5.87] |
| 2 Function (0 to 10 patient specific functional scale) (post-treatment) | 2 | 49 | Mean Difference (IV, Random, 95% CI) | 1.87 [1.03, 2.71] |

### Analysis 1.1. Comparison 1 Graded motor imagery versus usual care, Outcome 1 Pain intensity (post-treatment).

Review: Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II

Comparison: 1 Graded motor imagery versus usual care

Outcome: 1 Pain intensity (post-treatment)

| Study or subgroup | GMI N | GMI Mean(SD) | Usual care N | Usual care Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Moseley 2004 | 7 | 38 (10) | 6 | 58 (12) | | 38.3 % | -20.00 [ -32.13, -7.87 ] |
| Moseley 2006 | 19 | 36 (16) | 17 | 47 (10) | | 61.7 % | -11.00 [ -19.62, -2.38 ] |
| **Total (95% CI)** | **26** | | **23** | | | **100.0 %** | **-14.45 [ -23.02, -5.87 ]** |

Heterogeneity: $Tau^2$ = 11.68; $Chi^2$ = 1.41, df = 1 (P = 0.24); $I^2$ =29%

Test for overall effect: Z = 3.30 (P = 0.00096)

Test for subgroup differences: Not applicable

**Analysis 1.2. Comparison 1 Graded motor imagery versus usual care, Outcome 2 Function (0 to 10 patient specific functional scale) (post-treatment).**

Review: Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II

Comparison: 1 Graded motor imagery versus usual care

Outcome: 2 Function (0 to 10 patient specific functional scale) (post-treatment)

| Study or subgroup | GMI | | Usual care | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| Moseley 2004 | 7 | 4.42 (0.786) | 6 | 2.16 (0.752) | | 54.7 % | 2.26 [ 1.42, 3.10 ] |
| Moseley 2006 | 19 | 3.3 (1.7) | 17 | 1.9 (1.3) | | 45.3 % | 1.40 [ 0.42, 2.38 ] |
| **Total (95% CI)** | **26** | | **23** | | | **100.0 %** | **1.87 [ 1.03, 2.71 ]** |

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 1.70$, df = 1 (P = 0.19); $I^2 = 41\%$

Test for overall effect: Z = 4.37 (P = 0.000013)

Test for subgroup differences: Not applicable


# APPENDICES

## Appendix 1. Search strategies

### CENTRAL, DARE and HTA search strategies

#1 MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees
#2 "complex regional pain syndrome*":ti,ab,kw (Word variations have been searched)
#3 crps:ti,ab,kw (Word variations have been searched)
#4 (Post traumatic near/1 (algodystrophy or dystrophy or neurodystrophy or osteoporosis or pain syndrome)):ti,ab,kw (Word variations have been searched)
#5 "Minor causalgia":ti,ab,kw (Word variations have been searched)
#6 "Transient migratory osteoporosis":ti,ab,kw (Word variations have been searched)
#7 "Peripheral trophneurosis":ti,ab,kw (Word variations have been searched)
#8 ((Major or mitchell*) near/1 causalgia):ti,ab,kw (Word variations have been searched)
#9 "Neurovascular dystrophy":ti,ab,kw (Word variations have been searched)
#10 "Sudecks Osteodystrophy":ti,ab,kw (Word variations have been searched)
#11 Sympathalgia:ti,ab,kw (Word variations have been searched)
#12 Chronic traumatic oedema:ti,ab,kw (Word variations have been searched)
#13 Sympathetic dystrophy syndrome:ti,ab,kw (Word variations have been searched)
#14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#15 MeSH descriptor: [Physical Therapy Modalities] explode all trees

#16 physiotherap*:ti,ab,kw (Word variations have been searched)
#17 "physical therap*":ti,ab,kw (Word variations have been searched)
#18 manual therapy:ti,ab,kw (Word variations have been searched)
#19 manipulative therapy:ti,ab,kw (Word variations have been searched)
#20 ((therapeutic or therapy) near/2 exercise):ti,ab,kw (Word variations have been searched)
#21 MeSH descriptor: [Electric Stimulation Therapy] explode all trees
#22 (electrotherapy or TENS or "transcutaneous electrical nerve stimulation" or "therapeutic ultrasound" or interferential or "shortwave diathermy" or "laser therapy " or "heat therapy" or cryotherapy):ti,ab,kw (Word variations have been searched)
#23 graded motor imagery:ti,ab,kw (Word variations have been searched)
#24 mirror therapy:ti,ab,kw (Word variations have been searched)
#25 MeSH descriptor: [Musculoskeletal Manipulations] explode all trees
#26 tactile sensory discriminatory training:ti,ab,kw (Word variations have been searched)
#27 sensory-motor integration:ti,ab,kw (Word variations have been searched)
#28 sensory-motor re-tuning:ti,ab,kw (Word variations have been searched)
#29 hydrotherapy:ti,ab,kw (Word variations have been searched)
#30 (pain near/3 (advice or education)):ti,ab,kw (Word variations have been searched)
#31 (manipulation or massage or de-sensiti?ation or mobili?ation):ti,ab,kw (Word variations have been searched)
#32 #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31
#33 #14 and #32

### MEDLINE search strategy

1. exp Complex Regional Pain Syndromes/
2. "complex regional pain syndrome*".tw.
3. crps.tw.
4. (Post traumatic adj1 (algodystrophy or dystrophy or neurodystrophy or osteoporosis or pain syndrome)).tw.
5. "Minor causalgia".tw.
6. "Transient migratory osteoporosis".tw.
7. "Peripheral trophneurosis".tw.
8. "Sudeck's Osteodystrophy".tw.
9. "Neurovascular dystrophy".tw.
10. ((Major or mitchell*) adj1 causalgia).tw.
11. Sympathalgia.tw.
12. Chronic traumatic oedema.tw.
13. Sympathetic dystrophy syndrome.tw.
14. or/1-13
15. exp Physical Therapy Modalities/
16. physiotherap*.tw.
17. "physical therap*".tw.
18. manual therapy.tw.
19. manipulative therapy.tw.
20. ((therapeutic or therapy) adj2 exercise).tw.
21. exp Electric Stimulation Therapy/
22. (electrotherapy or TENS or "transcutaneous electrical nerve stimulation" or "therapeutic ultrasound" or interferential or "shortwave diathermy" or "laser therapy " or "heat therapy" or cryotherapy).tw.
23. graded motor imagery.tw.
24. mirror therapy.tw.
25. exp Musculoskeletal Manipulations/
26. tactile sensory discriminatory training.tw.
27. sensory-motor integration.tw.
28. sensory-motor re-tuning.tw.
29. hydrotherapy.tw.
30. (pain adj3 (advice or education)).tw.

31. (manipulation or massage or de-sensiti#ation or mobili#ation).tw.
32. or/15-31
33. 14 and 32
34. randomized controlled trial.pt.
35. controlled clinical trial.pt.
36. randomized.ab.
37. placebo.ab.
38. drug therapy.fs.
39. randomly.ab.
40. trial.ab.
41. or/34-40
42. exp animals/ not humans.sh.
43. 41 not 42
44. 33 and 43

### EMBASE search strategy

1. exp Complex Regional Pain Syndromes/
2. "complex regional pain syndrome*".tw.
3. crps.tw.
4. (Post traumatic adj1 (algodystrophy or dystrophy or neurodystrophy or osteoporosis or pain syndrome)).tw.
5. "Minor causalgia".tw.
6. "Transient migratory osteoporosis".tw.
7. "Peripheral trophneurosis".tw.
8. "Sudeck's Osteodystrophy".tw.
9. "Neurovascular dystrophy".tw.
10. ((Major or mitchell*) adj1 causalgia).tw.
11. Sympathalgia.tw.
12. Chronic traumatic oedema.tw.
13. Sympathetic dystrophy syndrome.tw.
14. or/1-13
15. exp Physical Therapy Modalities/
16. physiotherap*.tw.
17. "physical therap*".tw.
18. manual therapy.tw.
19. manipulative therapy.tw.
20. ((therapeutic or therapy) adj2 exercise).tw.
21. exp Electric Stimulation Therapy/
22. (electrotherapy or TENS or "transcutaneous electrical nerve stimulation" or "therapeutic ultrasound" or interferential or "shortwave diathermy" or "laser therapy " or "heat therapy" or cryotherapy).tw.
23. graded motor imagery.tw.
24. mirror therapy.tw.
25. exp Musculoskeletal Manipulations/
26. tactile sensory discriminatory training.tw.
27. sensory-motor integration.tw.
28. sensory-motor re-tuning.tw.
29. hydrotherapy.tw.
30. (pain adj3 (advice or education)).tw.
31. (manipulation or massage or de-sensiti#ation or mobili#ation).tw.
32. or/15-31
33. 14 and 32
34 random$.tw.
35 factorial$.tw.

36 crossover$.tw.
37 cross over$.tw.
38 cross-over$.tw.
39 placebo$.tw.
40 (doubl$ adj blind$).tw.
41 (singl$ adj blind$).tw.
42 assign$.tw.
43 allocat$.tw.
44 volunteer$.tw.
45 Crossover Procedure/
46 double-blind procedure.tw.
47 Randomized Controlled Trial/
48 Single Blind Procedure/
49 or/34-48 (1433702)
50 (animal/ or nonhuman/) not human/
51 49 not 50
52 33 and 51

### PsycINFO search strategy

1. exp "Complex Regional Pain Syndrome (Type I)"/
2. "complex regional pain syndrome*".tw.
3. crps.tw.
4. (Post traumatic adj1 (algodystrophy or dystrophy or neurodystrophy or osteoporosis or pain syndrome)).tw.
5. "Minor causalgia".tw.
6. "Transient migratory osteoporosis".tw.
7. "Peripheral trophneurosis".tw.
8. "Sudeck's Osteodystrophy".tw.
9. "Neurovascular dystrophy".tw.
10. ((Major or mitchell*) adj1 causalgia).tw.
11. Sympathalgia.tw.
12. Chronic traumatic oedema.tw.
13. Sympathetic dystrophy syndrome.tw.
14. or/1-13
15. exp Physical Therapy/
16. physiotherap*.tw.
17. "physical therap*".tw.
18. manual therapy.tw.
19. manipulative therapy.tw.
20. ((therapeutic or therapy) adj2 exercise).tw.
21. exp Electrical Stimulation/
22. (electrotherapy or TENS or "transcutaneous electrical nerve stimulation" or "therapeutic ultrasound" or interferential or "shortwave diathermy" or "laser therapy " or "heat therapy" or cryotherapy).tw.
23. graded motor imagery.tw.
24. mirror therapy.tw.
25. tactile sensory discriminatory training.tw.
26. sensory-motor integration.tw.
27. sensory-motor re-tuning.tw.
28. hydrotherapy.tw.
29. (pain adj3 (advice or education)).tw.
30. (manipulation or massage or de-sensiti#ation or mobili#ation).tw.
31. or/15-30
32. 14 and 31

33. clinical trials/
34. (randomis* or randomiz*).tw.
35. (random$ adj3 (allocat$ or assign$)).tw.
36. ((clinic$ or control$) adj trial$).tw.
37. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
38. (crossover$ or "cross over$").tw.
39. random sampling/
40. Experiment Controls/
41. Placebo/
42. placebo$.tw.
43. exp program evaluation/
44. treatment effectiveness evaluation/
45. ((effectiveness or evaluat$) adj3 (stud$ or research$)).tw.
46. or/33-45
47. 32 and 46

### CINAHL search strategy

S43 S33 AND S42
S42 S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41
S41 (allocat* random*)
S40 (MH "Quantitative Studies")
S39 (MH "Placebos")
S38 placebo*
S37 (random* allocat*)
S36 (MH "Random Assignment")
S35 (Randomi?ed control* trial*)
S34 (singl* blind* ) or (doubl* blind* ) or (tripl* blind* ) or (trebl* blind* ) or (trebl* mask* ) or (tripl* mask* ) or (doubl* mask* ) or (singl* mask* )
S33 S14 AND S32
S32 S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31
S31 (manipulation or massage or de-sensiti?ation or mobili?ation)
S30 (pain N3 (advice or education))
S29 hydrotherapy
S28 sensory-motor re-tuning
S27 sensory-motor integration
S26 tactile sensory discriminatory training
S25 (MH "Manual Therapy+")
S24 mirror therapy
S23 graded motor imagery
S22 (electrotherapy or TENS or "transcutaneous electrical nerve stimulation" or "therapeutic ultrasound" or interferential or "shortwave diathermy" or "laser therapy " or "heat therapy" or cryotherapy)
S21 (MH "Transcutaneous Electrical Nerve Stimulation (Iowa NIC)")
S20 ((therapeutic or therapy) N2 exercise)
S19 manipulative therapy
S18 manual therapy
S17 "physical therap*"
S16 physiotherap*
S15 (MH "Physical Therapy+")
S14 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
S13 Sympathetic dystrophy syndrome
S12 Chronic traumatic oedema

S11 Sympathalgia
S10 ((Major or mitchell*) N1 causalgia)
S9 “Neurovascular dystrophy”
S8 “Sudeck’s Osteodystrophy”
S7 “Peripheral trophneurosis”
S6 “Transient migratory osteoporosis”
S5 “Minor causalgia”
S4 (Post traumatic N1 (algodystrophy or dystrophy or neurodystrophy or osteoporosis or pain syndrome))
S3 crps
S2 “complex regional pain syndrome*”
S1 (MH “Complex Regional Pain Syndromes+”)

### LILACS search strategy

1. “crps”
2. “physiotherapy”
3. “clinical trial”

### PEDro search strategy

1. “complex regional pain syndrome”
2. “reflex sympathetic dystrophy”
3. “causalgia”
4. “sudeks”’
5. “sympathetic pain”
6. “clinical trial”

### Web of Science search strategy

1. “crps”
2. “physiotherapy”
3. “orthopaedic rehabilitation”
4. “articles”

## WHAT’S NEW

Last assessed as up-to-date: 15 February 2015.

| Date | Event | Description |
|---|---|---|
| 11 March 2016 | Amended | Minor amendment to Analysis 1.2. |

## HISTORY

Protocol first published: Issue 11, 2013

Review first published: Issue 2, 2016

| Date | Event | Description |
|---|---|---|
| 1 March 2016 | Review declared as stable | See Published notes. |

## CONTRIBUTIONS OF AUTHORS

KMS conceived and designed the protocol, implemented the search strategy, applied eligibility criteria, assessed studies, extracted and analysed data, and led the write-up of the review. BMW informed the protocol design, applied eligibility criteria, assessed studies, extracted and analysed data, and assisted with the write-up of the review. NEO informed the protocol design, acted as the third review author, oversaw data synthesis, and assisted with the write-up of the review. KMS will be responsible for updating this Cochrane review.

## DECLARATIONS OF INTEREST

All review authors are qualified physiotherapists, although none currently practice in private health care or for a 'for profit' organisation.

KMS received honoraria from Pfizer (Ireland) to speak at public events, although we declare that Pfizer (Ireland) has no direct interest in this Cochrane review and did not provide any direct or indirect funding for this Cochrane review.

BMW and NEO have no known conflicts of interest.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

With respect to Types of interventions, after the publication of Smart 2013 we decided to exclude studies that evaluated non-physiotherapy based interventions (e.g. pharmacological) in which all study arms received the same physiotherapy intervention (differing only in the application of the non-physiotherapy component) as they are unlikely to offer any insight into the value of physiotherapy management. In Smart 2013 we stated our intention to search the SciVerse SCOPUS electronic database. However we did not search this database as the primary review author (KMS) did not have institutional access. The Trials Search Co-ordinator of the Cochrane PaPaS group advised that its omission was unlikely to adversely influence our search results. We have described, in additional detail, our operational definitions upon which we based our 'Risk of bias' judgements (see the 'Assessment of risk of bias in included studies' section). In this Cochrane review we have specified the criteria upon which we based our GRADE judgements for rating the quality of evidence (see the 'Data synthesis' section).

## NOTES

A new search within two years is not likely to identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in five years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

## INDEX TERMS

### Medical Subject Headings (MeSH)

*Physical Therapy Modalities; Complex Regional Pain Syndromes [classification; * therapy]; Pain Measurement [methods]; Randomized Controlled Trials as Topic

### MeSH check words

Adult; Humans

thebmj

STATE OF THE ART REVIEW

# Complex regional pain syndrome

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**ABSTRACT**

Complex regional pain syndrome is a chronic pain condition characterized by autonomic and inflammatory features. It occurs acutely in about 7% of patients who have limb fractures, limb surgery, or other injuries. Many cases resolve within the first year, with a smaller subset progressing to the chronic form. This transition is often paralleled by a change from "warm complex regional pain syndrome," with inflammatory characteristics dominant, to "cold complex regional pain syndrome" in which autonomic features dominate. Multiple peripheral and central mechanisms seem to be involved, the relative contributions of which may differ between individuals and over time. Possible contributors include peripheral and central sensitization, autonomic changes and sympatho-afferent coupling, inflammatory and immune alterations, brain changes, and genetic and psychological factors. The syndrome is diagnosed purely on the basis of clinical signs and symptoms. Effective management of the chronic form of the syndrome is often challenging. Few high quality randomized controlled trials are available to support the efficacy of the most commonly used interventions. Reviews of available randomized trials suggest that physical and occupational therapy (including graded motor imagery and mirror therapy), bisphosphonates, calcitonin, subanesthetic intravenous ketamine, free radical scavengers, oral corticosteroids, and spinal cord stimulation may be effective treatments. Multidisciplinary clinical care, which centers around functionally focused therapies is recommended. Other interventions are used to facilitate engagement in functional therapies and to improve quality of life.

## Introduction

Complex regional pain syndrome (CRPS) is a chronic pain condition characterized by spontaneous and evoked regional pain, usually beginning in a distal extremity, that is disproportionate in magnitude or duration to the typical course of pain after similar tissue trauma.[1]

CRPS is distinguished from other chronic pain conditions by the presence of signs indicating prominent autonomic and inflammatory changes in the region of pain. In its most severe form, patients present with a limb displaying extreme hyperalgesia and allodynia (normally non-painful stimuli such as touch or cold are experienced as painful); obvious changes to skin color, skin temperature, and sweating relative to the unaffected side; edema and altered patterns of hair, skin, or nail growth in the affected region; reduced strength; tremors; and dystonia.[2] Altered body perception and proprioception may also be present, reflected in reduced limb positioning accuracy, delays in recognizing limb laterality, abnormal referred sensations and tactile perception, and altered subjective mental representations of the affected limb.[3-8] The syndrome is often associated with serious impairments in activities of daily living and ability to function.[9-12]

First recognized as a distinct pain condition during the American civil war,[13] CRPS has been known since that time by various names, including reflex neurovascular dystrophy, neuroalgodystrophy, shoulder-hand syndrome, reflex sympathetic dystrophy, and causalgia.

The dramatic nature of its presentation, limited understanding of its mechanisms, and frequent lack of response to intervention has led to clinical confusion and misunderstanding in the past. Research into CRPS and consequently understanding of the condition have grown extensively in the past 20 years, although understanding remains incomplete. Even now, the simple question of whether complex regional pain syndrome should be classified as a neuropathic pain condition remains a subject of debate among experts in the area.[14 15]

As currently conceptualized, CRPS is subdivided into type I and type II on the basis of absence or presence, respectively, of clinical signs of major peripheral nerve injury (such as nerve conduction study abnormalities). Despite this clinical distinction, core diagnostic features are identical across both subtypes, which adds to the confusion about the role of neuropathic mechanisms.

This review summarizes the current state of knowledge about CRPS, including its epidemiology, pathophysiological mechanisms, diagnosis, natural course, prevention, and treatment. Although complete understanding of the syndrome remains a work in progress, this review aims

### HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

The perspective of patients with complex regional pain syndrome (CRPS) was incorporated into the final article on the basis of comments made on an initial draft by a patient with CRPS and James Broatch, executive vice president/director of the Reflex Sympathetic Dystrophy Syndrome Association (RSDSA). The RSDSA is the primary CRPS patient advocacy organization in the United States.

**Box 1 | Current International Association for the Study of Pain clinical diagnostic criteria for complex regional pain syndrome[1]**

- Continuing pain, which is disproportionate to any inciting event
- Must report at least one symptom in three of the four following categories*:
  - Sensory: Reports of hyperalgesia and/or allodynia
  - Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
  - Sudomotor/edema: Reports of edema 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, nails, skin)
- 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 or deep somatic pressure, or joint movement)
  - Vasomotor: Evidence of temperature asymmetry and/or skin color changes and/or asymmetry
  - Sudomotor/edema: Evidence of edema 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, nails, skin)
- There is no other diagnosis that better explains the signs and symptoms

*For research settings in which it is desirable to maximize specificity, a more stringent research diagnostic decision rule requires all four of the symptom categories and at least two of the sign categories to be positive for diagnostic criteria to be met.

to dispel some misunderstandings that have continued despite recent advances.

## Incidence

Two questions about the incidence of CRPS are of interest. The first is how commonly the condition occurs in the general population, and the second is how commonly it occurs after injuries that are known to trigger it.

### Incidence in the general population

Two retrospective population based studies have assessed the incidence of CRPS in the general population. Both found that it is three to four times more common in women than in men, more commonly affects the upper limbs, and peaks in incidence at 50-70 years of age.[16 17] Estimates from both studies reflect the 1994 International Association for the Study of Pain (IASP) diagnostic criteria for CRPS.[18] In a study conducted in the United States, incidence rates of CRPS type I and CRPS type II were reported as 5.46 per 100 000 person years and 0.82 per 100 000 person years, respectively.[16] A population study in the Netherlands reported an incidence of CRPS type I and type II combined (based on clinician diagnoses of CRPS confirmed against 1994 IASP criteria in 93% of cases) of 26.2 cases per 100 000 person years[17]—more than four times higher than that noted in the US sample.

More specific diagnostic criteria were adopted in 2012 as the new international standard for the diagnosis of CRPS by the IASP (box 1),[1] and these criteria have been shown to reduce CRPS diagnostic rates by about 50%.[17 19 20] The earlier estimates may therefore provide an upper limit of the incidence of CRPS as currently defined in the general population. The US Food and Drug Administration and the European Medicines Agency have granted CRPS an orphan disease designation on the basis of their determination that fewer than 200 000 people in the US and fewer than 154 000 people in the European Union are affected each year.[21 22]

### Incidence after injury

In the general population, CRPS seems to occur most often after fracture (>40% of CRPS cases in two population based studies[16 17]), although sprains, contusions, crush injuries, and surgery are also known triggers.[2] The best information on the incidence of CRPS after injury comes from two large prospective studies of fracture patients (n=596; n=1549).[23 24] Using the most restrictive research version of the 2012 IASP criteria,[25] the incidence of CRPS was 3.8-7.0% within four months of fracture.[23 24]

A slightly higher incidence (8.3%) was reported in a large (n=301) prospective study of patients undergoing carpal tunnel release.[26] In summary, only a minority of people develop CRPS even after the most common precipitating event—fracture. The fact that some people develop CRPS and others with similar injuries do not underlies the importance of understanding the pathophysiological mechanisms of CRPS.

## Sources and selection criteria

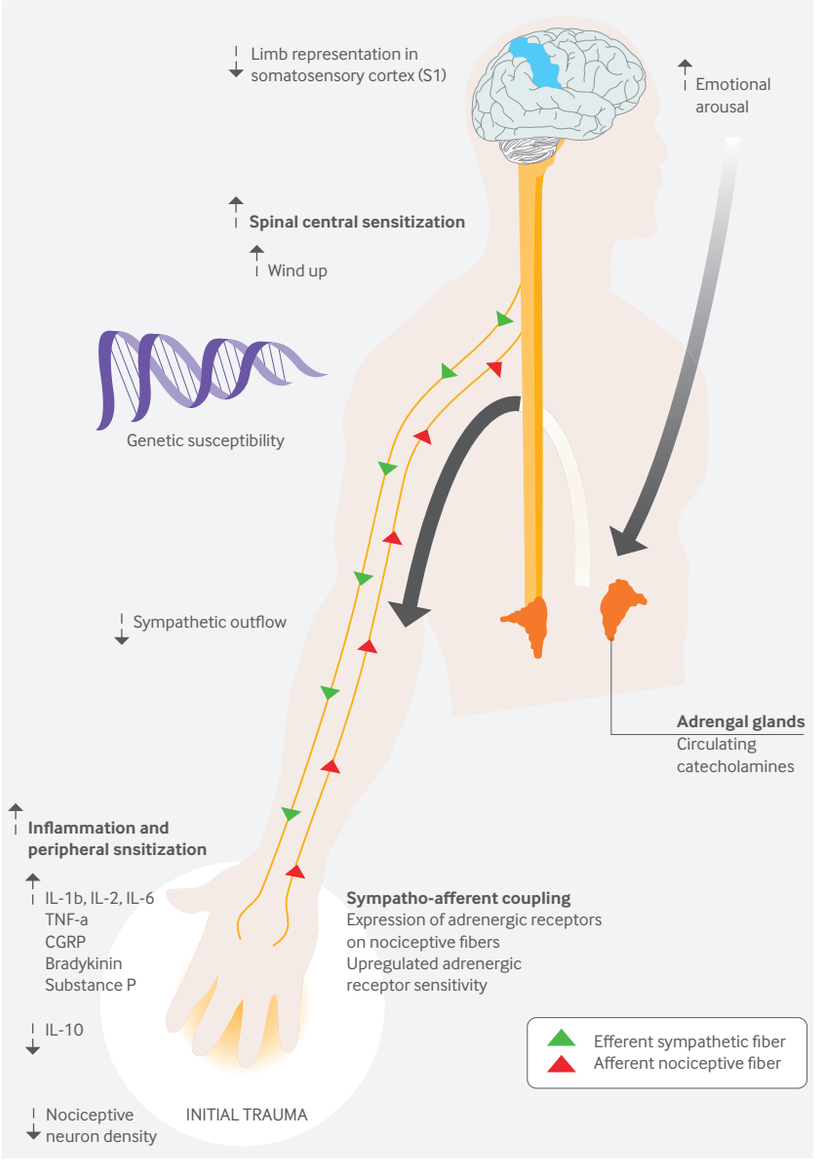
The PubMed database was searched from 1985 to 1 October 2014 using the terms "complex regional pain syndrome", "reflex sympathetic dystrophy", "causalgia", "CRPS", and "RSD". Bibliographies of articles were also searched for other relevant studies. A selective narrative review is provided below that does not incorporate a systematic quality assessment of the literature. Studies presented below are those that the author judged to be representative of the highest methodological quality (for example, prospective studies) or most relevant to the topics discussed.

## Pathophysiology

In contrast to past attempts to reduce CRPS to a single mechanism (such as sympathetically maintained pain),[27] it is now generally agreed that the syndrome is caused by a multifactorial process involving both peripheral and central mechanisms.[28 29] Although there is evidence for a role of each of the mechanisms below in the development or expression of CRPS (box 2), little is known experimentally about how these mechanisms might interact to produce CRPS. Given the diversity of presentations seen in CRPS, the relative contributions of different mechanisms probably differ across individual patients and even within patients over time. The figure provides a speculative model of interacting mechanisms involved in the development of CRPS.

**Box 2 | Possible mechanisms involved in complex regional pain syndrome**

- Nerve injury[31-34]
- Ischemic reperfusion injury or oxidative stress[35-40]
- Central sensitization[41-43]
- Peripheral sensitization[44 45]
- Altered sympathetic nervous system function or sympathoafferent coupling[46-52]
- Inflammatory and immune related factors[53-77]
- Brain changes[78-89]
- Genetic factors[90-92]
- Psychological factors and disuse[93-103]




**Speculative model of interacting mechanisms involved in the development of complex regional pain syndrome. CGRP=calcitonin gene related peptide; CRPS=complex regional pain syndrome; IL=interleukin; SNS=sympathetic nervous system; TNF=tumor necrosis factor. Adapted, with permission, from Bruehl[30]**

### Factors related to the initiating injury

Although CRPS is reported to occur without clear antecedent injury (or no specific injury that is recalled by the patient) in a small number of cases, most cases occur after known tissue injury. One key mechanistic question that is still debated is: what aspects of the initiating injury trigger the development of CRPS?

One important trigger seems to be the extent to which a proinflammatory and immunological response is elicited by the initiating injury. Evidence from animal fracture models of CRPS type I suggest that changes after injury, such as B cell activation and increased interleukin 1β (IL-1β) and substance P signaling, are crucial for the development of CRPS.[53-55]

A recent human study suggests that after injury persistently raised concentrations of osteoprotegerin, an osteoclastogenesis inhibitory factor, may also have a role in determining whether tissue injury resolves normally or evolves into CRPS.[104] On the basis of findings in a different animal model of CRPS type I,[35] ischemic reperfusion injury and related microvascular disease in deep tissues after injury have also been suggested as triggers for the onset of CRPS.[36] These processes have been shown to produce similar inflammatory responses and clinical characteristics (allodynia, hyperalgesia, edema, and altered vasoconstriction) to those seen in acute CRPS.[35 37]

It has also been suggested that nerve injury itself may trigger CRPS. A clinical distinction is made between CRPS type I and CRPS type II, with CRPS type II being distinguished by evidence of peripheral nerve injury. Nonetheless, similar injuries can trigger both CRPS subtypes, and the nature of these injuries (for example, fractures, crush injuries, and surgery) could all plausibly be associated with some degree of nerve injury. Some studies report decreased C-fiber and A-δ fiber density in the affected limbs of patients with CRPS type I,[31-33] although others report that such changes were seen in only a subset (20%) of these patients.[34] These last findings suggest that such changes may reflect an occasional consequence or correlate of CRPS type I rather than a consistent cause.

### Central and peripheral nociceptive sensitization

After tissue or nerve injury, the nervous system adapts in a manner that enhances responsiveness to pain and increases inflammation; this protects the injured area and leads to avoidance of activities that might cause further injury. These changes occur in both the peripheral and central nervous systems. Within the central nervous system, ongoing noxious input after tissue injury triggers central sensitization—an increase in the excitability of nociceptive neurons in the spinal cord that increase responsiveness to pain.[41] A role for central sensitization in CRPS is indicated by findings that the limb affected by CRPS (relative to unaffected limbs) exhibits increased temporal summation—a laboratory derived objective index believed to reflect central sensitization.[42 43] In the periphery, injury produces local changes to primary afferent fibers that increase background firing of nociceptors, increase firing in response to normally painful stimuli, and decrease the nociceptive firing threshold for thermal and mechanical stimuli.[44 45] Peripheral and central sensitization are mediated by the release of inflammatory mediators (such as bradykinin) and pronociceptive neuropeptides (such as substance P). In addition, proinflammatory cytokines also contribute to peripheral sensitization,[44] and the excitatory amino acid glutamate has a role in central sensitization through its activation of spinal N-methyl-D-aspartate (NMDA) receptors.[41 105] Both peripheral and central sensitization can contribute to some of the characteristic features of CRPS, including spontaneous pain, hyperalgesia, and allodynia.[41 44]

### Altered sympathetic nervous system function and sympatho-afferent coupling

Other nervous system changes after injury that may also contribute to CRPS are altered function of the sympathetic nervous system and possible sympatho-afferent coupling. It has long been assumed that the sympathetic nervous system plays a key role in CRPS—the most common older label for CRPS type I was "reflex sympathetic dystrophy." Because patients with chronic CRPS commonly present

with a cold and sweaty limb, it was assumed that excessive sympathetic nervous system outflow was involved, and this was the rationale for using sympathetic ganglion blocks to reduce the symptoms of CRPS. However, a prospective study in patients early after fracture indicates that patients with reduced sympathetic nervous system outflow after injury are the ones at greatest risk of developing subsequent CRPS symptoms, with these changes noted to be bilateral despite unilateral injury.[46]

Other relevant nervous system changes after injury are more localized. One study found that within days after nerve injury, nociceptive fibers in the affected area, even when not directly injured, displayed increased firing in the presence of sympathetic nervous system activity.[106] Similar injuries have been shown to result in the expression of catecholamine receptors on nociceptive fibers,[47 48] leading to a situation in which sympathetic nervous system outflow or circulating catecholamines (released in response to pain or stress) might directly trigger firing of nociceptors (thus producing pain). This phenomenon is referred to as sympatho-afferent coupling.

Although this phenomenon has been directly observed in humans (through single nerve fiber recordings) in only a single case report,[49] it has been indirectly observed in several well controlled CRPS studies, suggesting it may play a role in the syndrome at least with regard to determining its severity.[50-52] Mechanisms by which reductions in function of the sympathetic nervous system after injury might eventually transform in many patients into a clinical picture more consistent with exaggerated sympathetic responses (reduced skin temperature, dusky skin color, increased sweating) are incompletely understood.

### Inflammatory and immune related factors

Recent research has focused on the role of inflammatory and immune related mechanisms in CRPS, and animal models of CRPS type I also support a role for inflammatory mechanisms.[53 55] Evidence of the involvement of inflammatory mechanisms, especially in the acute phase, comes from studies documenting raised concentrations of proinflammatory neuropeptides and mediators (substance P, calcitonin gene related peptide, bradykinin) and cytokines (IL-1β, IL-2, and IL-6, and tumor necrosis factor α (TNF- α) in the systemic circulation, cerebrospinal fluid, and affected limbs of patients with CRPS.[56-65] These substances increase plasma extravasation (leading to edema), can produce vasodilation (leading to a warm red appearance in the affected area), and may increase hair growth and sweating.[66 67] Thus inflammatory mechanisms can induce several key clinical features of CRPS. There is evidence that the sympathetic nervous system is involved in facilitating inflammation after injury.[107 108] These findings show in principle that the various mechanisms that independently contribute to CRPS may interact.

Inflammation can be elicited not only enzymatically through the cyclo-oxygenase pathway, but also non-enzymatically through an oxidative stress pathway.[109 110] The ischemic reperfusion injury animal model described previously that reproduces many features of CRPS type I activates this oxidative stress pathway,[35 37] and pharmacological interventions that reduce oxidative stress in this model also reduce CRPS related symptoms.[35 38 39] Consistent with these animal data, at least one study indicates that indirect markers of oxidative stress are raised in patients with CRPS relative to healthy controls,[40] and this mechanism is the target of some CRPS interventions.

Although they did not specifically assess CRPS, several studies in patients undergoing limb surgery indicate that the use of a tourniquet (versus no tourniquet use) is associated with significantly greater pain and edema (up to six weeks after surgery); both of these features are characteristic of early CRPS.[111-113] Extended tourniquet use is known to be associated with ischemic reperfusion injury and raised oxidative stress.[35 114]

Immune related mechanisms are also probably involved in CRPS. For example, in a mouse model of CRPS type I, CRPS-like features including hyperalgesia and skin temperature changes emerge after limb fracture, but depletion of CD20+ B cells limits the development of these changes.[54] In humans, increased numbers of pro-inflammatory monocytes (CD14+ CD16+) and mast cells have been reported in patients with CRPS compared with healthy controls.[68-70] Altered innate immune responses (impaired neutrophil activity) have also been reported in patients with CRPS.[71]

Recent work suggests that antibodies from people with CRPS may be capable of transferring the condition to previously unaffected individuals, also supporting a role for immune mechanisms. IgG from patients with CRPS and a comparison group of healthy controls was given to mice that underwent a mild tissue injury.[72] Mice that received IgG from patients with CRPS, but not those that received IgG from controls, developed significant hyperalgesia and edema, both of which are characteristic of CRPS. Similar work found that IgG from patients with CRPS when injected into mice in the absence of any injury induced motor changes, another key characteristic of CRPS.[73] Data such as these have led to the suggestion that in some patients CRPS might be an expression of autoimmune processes.[74] This autoimmune model is further supported by the presence of autoantibodies directed against autonomic nervous system structures, including $\beta_2$ adrenergic and muscarinic type 2 receptors, in a subset of patients with CRPS.[75-77]

### Brain changes

Brain imaging studies over the past decade suggest that several brain changes are associated with CRPS. Two studies indicate that endogenous pain inhibitory pathways (opioid mediated) in the brain are impaired in patients with CRPS, with greater impairments associated with greater severity of pain.[78 79] For CRPS of the upper limb, reduced representation of the affected limb in both primary and secondary somatosensory cortices has also been consistently noted,[80-83] a finding supported by a recent meta-analysis.[84] However, new data suggest a surprising source for these effects—an increase in the somatosensory representation of the *unaffected* limb in patients with CRPS.[85]

Meta-analysis indicates that not only are there somatosensory changes in CRPS, but also motor changes, specifically disinhibition of the primary motor cortex.[86] Beyond changes in brain function, structural changes

have also been noted—patients with CRPS showed reduced gray matter volume compared with healthy controls in brain regions underlying the affective component of pain (insula and cingulate cortex).[87]

Evidence suggests that the altered somatosensory representation in patients with CRPS can normalize with successful treatment.[88 89] In light of the similar normalization of specific brain changes (such as reduced gray matter volume) seen with successful treatment of other forms of chronic pain,[115 116] at least some of the brain changes in CRPS are likely to be an effect rather than a cause. Nonetheless, these changes seem to be related to symptom expression in some cases, as indicated by findings that clinical pain intensity in patients with CRPS is associated with the extent of some of the observed brain changes.[81-83]

### Genetic factors

The role of genetic factors in CRPS is poorly understood. Studies that directly examined genetic associations with CRPS have identified several potential candidate polymorphisms, including those in genes encoding α1a adrenoceptors[90] and the HLA system (HLA-DQ8, HLA-B62).[91 92] The influences of the HLA system may be more prominent in patients with CRPS who have dystonia.[91 92] The identification of genetic influences in CRPS is made difficult by the heterogeneous phenotypic presentations related to different contributing mechanisms, as well as the need for large samples of a rare condition to produce conclusive findings.

### Psychological factors

Psychological factors were assumed for many years to be involved in the development of CRPS partly because of clinical impressions that these patients were psychologically different from other patients with chronic pain. However, many studies suggest that patients with CRPS are not psychologically different from other patients with chronic pain and that psychological factors alone do not cause CRPS.[117] Comorbid axis I psychiatric disorders, mainly major depression, are common in patients with CRPS (24-49% of patients in various studies),[118-120] although their prevalence does not seem to be higher than in other chronic pain conditions.[119] Recent work suggests that patients with CRPS—particularly those with greater depression levels, higher pain intensity, and more functional impairments—have an increased risk of suicide.[118]

Evidence exists that psychological factors such as anxiety, depression, and anger expression may have a greater impact on pain in patients with CRPS than in those without.[93-95] This might be due to the effects of psychological distress on sympathetic nervous system arousal and catecholamine release and the potential impact of sympatho-afferent coupling on CRPS pain.[30]

In addition, prospective studies suggest that increased psychological distress in conjunction with physical injury might affect the later development of CRPS, or at least the condition's severity. In older patients undergoing total knee arthroplasty (n=77), greater increases in the extent of depressive symptoms from before surgery to one month after surgery predicted greater severity of CRPS symptoms at six month and 12 month follow-up.[96] Similar effects were seen for early increases in anxiety after surgery as a predictor of the severity of CRPS at six months.[96] In addition, preoperative anxiety significantly predicted the presence of a CRPS-like syndrome at one month after surgery, but not at three or six month follow-up.[97]

Similarly, in patients with an upper extremity fracture (n=50), higher anxiety (but not depression) two days after fracture predicted significantly higher risk of a diagnosis of CRPS at two to four month follow-up.[98] However, a larger prospective study of early post-fracture patients (n=596) found that none of the psychological variables assessed, including depression, predicted CRPS status at three month follow-up.[99] Nonetheless, the possible influence of anxiety on CRPS outcomes was not examined in this last study, leaving it unclear whether anxiety may contribute to the risk and severity of CRPS after injury.

Learnt disuse of the affected limb can also be considered a psychological factor, because it is typically the behavioral result of a desire to avoid pain, often driven by fear of future pain exacerbations.[100 101] Although expert opinion has long held that avoiding disuse and reactivating the affected limb are cornerstones of treatment,[121] only limited research supports this opinion. Results of one controlled human experimental study, however, do highlight the potential importance of disuse for CRPS. Among healthy people without CRPS (n=30), 28 days of upper limb casting in the absence of any injury resulted in pain with joint movement and several clinical features associated with CRPS, including hyperalgesia, hair growth changes (in a subset only), and skin temperature changes.[102]

The importance of disuse in the development of CRPS is also supported by recent animal work.[103] In a rat limb fracture model of CRPS type I, immobilization alone (casting) elicited the same increases in expression of inflammatory mediators (IL-1β, IL-6, TNF-α) and similar clinical changes (allodynia, temperature changes, and edema) as those elicited by limb fracture with casting.[103] Results such as these highlight the importance of early mobilization of the affected limb after injury to help prevent the development of chronic CRPS.

## Natural course of CRPS

Clinical experience indicates that outcomes in patients with CRPS in tertiary pain care settings are often inadequate even with aggressive pain interventions. However, there are also reports suggesting high rates of resolution.[16] These discrepancies might be due to a substantial number of cases resolving with limited or no specific intervention early in the course of the condition, with a smaller subset of more persistent cases being seen in tertiary care pain clinics. A recent systematic review found some evidence to support this idea.[122]

### Acute CRPS

The most convincing evidence would come from studies of untreated patients with CRPS because confounding with treatment effects would not influence the results. One study looked at the natural course of untreated CRPS.[123] Thirty patients with post-traumatic CRPS were followed without treatment for an average of 13 months after diagnosis; three patients were withdrawn from the study to be given treatment, and CRPS resolved over the

course of the study in 26 of the 30 patients.[123] Some may be skeptical of this extraordinarily high rate of CRPS resolution, yet other studies support relatively high, if not quite so dramatic, resolution rates for acute CRPS (operationally defined in this review as CRPS <1 year in duration). For example, in a prospective series of 60 consecutive patients with tibial fracture who underwent standard care, 14 of the 18 patients diagnosed with CRPS at bone union were free of CRPS at one year follow-up.[124] Neither of the studies above used the 1994 or current IASP diagnostic criteria, which may have influenced the results. However, the US population study of CRPS described previously, which applied the 1994 IASP criteria, similarly found that 74% of diagnosed CRPS cases resolved with relatively conservative care.[16]

### Chronic CRPS

In contrast to these findings for acute CRPS, the limited data on the natural course of well established chronic CRPS (operationally defined as CRPS of >1 year in duration) suggest much lower resolution rates even with specialty pain care.[125] In one large (n=102) retrospective longitudinal study of patients over an average six year follow-up period, 30% of patients reported resolution of chronic CRPS (diagnosed using the 1994 IASP criteria), 16% reported progressive deterioration, and the remaining 54% reported stable symptoms.[126]

These findings underscore the importance of understanding how patterns of CRPS change over time. One question is how quickly CRPS emerges after injury. Although such data are sparse, the mechanisms involved in the emergence of CRPS (such as injury related sympathetic nervous system changes, peripheral and central sensitization, inflammatory and immune responses to injury) suggest that the initial onset of symptoms should occur within the first few weeks of the initiating event.

A prospective study in a large sample of post-fracture patients found that CRPS was more commonly diagnosed at three months after cast removal than at cast removal, and that diagnosis rates decreased after three months.[23] This suggests that CRPS develops during a three to four month window after the initiating injury. The onset of CRPS symptoms after this three to four month window seems to be increasingly unlikely and difficult to explain mechanistically.

### Delayed healing versus emerging CRPS

It is clinically accepted that early intervention in CRPS will lead to better outcomes, although there are few high quality data to support this view. The potential importance of early diagnosis and intervention raises the question of how to distinguish between normal but delayed healing versus emerging CRPS. In both cases, an inflammatory presentation (a warm, red, and hypersensitive limb) is common.[97] One potential discriminating factor is suggested by studies indicating that more severe pain early after fracture predicts those who will develop CRPS.[24 127] This idea is supported by the finding that greater intensity of knee pain before surgery is a predictor of the development of CRPS after total knee arthroplasty.[97] Thus, a clinical rule of thumb might be that the greater the intensity of early pain and the longer a CRPS-like presentation persists, the more likely it is to be CRPS rather than delayed normal healing.

### Warm and cold CRPS

Although not a formal diagnostic categorization, it is accepted that CRPS can be associated with two distinct presentations. "Warm CRPS" is associated with a warm, red, and edematous extremity, whereas "cold CRPS" presents with a cold, dusky, sweaty extremity. Acute CRPS is more often associated with a warm CRPS presentation, whereas chronic CRPS is more often characterized by a cold CRPS presentation,[128] although both subtypes can be seen in patients with CRPS of any duration.

Results of a retrospective longitudinal study reporting outcomes over an average eight year follow-up period suggest that CRPS is more likely to resolve in patients initially diagnosed with warm CRPS, the most common presentation in the acute CRPS phase, than in those initially diagnosed with cold CRPS.[129] Although there is no clear dividing line between acute and chronic CRPS, and these terms are inconsistently used in the literature, a recent prospective study of proinflammatory cytokines suggests that the inflammatory component that seems to underlie warm CRPS largely resolves within about 12 months of symptom onset, at least in patients on active treatment.[65]

This suggestion is supported by a recent report on patterns of cutaneous immune responses in patients with CRPS of different durations.[70] Local accumulation of mast cells was increased in CRPS of less than three months' duration but not in CRPS of longer than three months' duration.[70] Data regarding clinical features of CRPS also suggest that edema and warm or red skin, features caused by inflammatory processes, may become less prominent as the duration of CRPS increases.[2 128] These findings parallel observations of a transition from warm CRPS to cold CRPS as the condition becomes more chronic. One cross sectional study suggests that sympatho-afferent coupling, which may contribute to the sympathetically maintained component of CRPS pain, may also diminish over time.[130] The prospective cytokine data above suggest that the transition from inflammatory warm CRPS to cold CRPS may start during the first year after injury, providing a possible marker for the transition from acute to chronic CRPS.

### Traditional CPRS stages

CRPS often changes in character over time, but the changes are highly variable—no definitive sequence of stages occurs in all patients. For many years, clinical lore has held that there are three sequential stages of CRPS during which symptom patterns change in a consistent way.[131] Contrary to this idea, two studies using statistical pattern recognition techniques found that when patients are categorized by symptom patterns into three groups, there is no difference in pain duration between groups.[126 132] Such findings argue more for CRPS subtypes rather than a uniform three stage sequential model.

### CPRS spread

Data suggest that CRPS can spread outside of the originally affected limb,[133] although this is not a universal

phenomenon. A population based epidemiological approach is needed to define how common such spreading is. However, available studies in this area are based on samples from pain clinics that may be biased by referral patterns. For example, clinics that specialize in treating patients with CRPS probably receive more referrals of patients with extensive spreading, so data from such clinics would overestimate the frequency of spreading. Given this caveat, a retrospective study in 185 patients with CRPS (from a clinic specializing in treating CRPS associated with movement disorders) found that 48% reported spreading to another limb.[134]

Studies of patterns of CRPS spread suggest that proximal spread from the initial distal site of CRPS is common,[135] although in some cases this may reflect secondary myofascial pain related to altered use of the limb. The largest systematic study of CRPS spreading (n=185) suggests that contralateral spread is most common (mirror image spread), followed by ipsilateral spread (for example, hand to foot), or diagonal spread.[134] All four limbs were affected in more than 29% of cases in this study. The two most common spreading patterns (ipsilateral and contralateral) developed on average 19 months or more after the initial onset of symptoms,[134] although another study suggests that spreading may occur earlier.[135] Depending on the pattern of spread, Van Rijn and colleagues' results indicated that 37-91% of cases of spreading CRPS occurred in the context of a second trauma.[134] Mechanisms of spreading are not well understood. However, research in patients with unilateral CRPS found evidence of bilateral facilitated neurogenic inflammation,[136] bone demineralization,[137] impaired sympathetic nervous system function,[46] brain changes,[138 139] and systemically circulating autoantibodies against autonomic structures.[76 77] This suggests that bilateral systemic alterations in unilateral CRPS could contribute to later contralateral spread.

## Diagnosis

Because the pathophysiological mechanisms of CRPS are not fully understood, mechanism based diagnosis is not yet feasible. Therefore, the diagnosis of CRPS is based solely on clinical signs and symptoms. The fact that objective tests are not needed for diagnosis is directly related to the lack of definitive pathophysiological mechanisms in CRPS that could serve as a gold standard against which such tests could be referenced.

Additional objective testing (thermography, triple phase bone scan, quantitative sudomotor axon reflex test, or a trial sympathetic ganglion block) is not necessary to make the diagnosis, but in some cases may be used to support a clinical diagnosis. Because bone changes are not currently part of the diagnostic criteria used to define CRPS,[1] the value of a triple phase bone scan to support a diagnosis of CRPS is questionable. During the diagnostic process, objective medical tests may be needed to rule out other conditions that could account for the signs and symptoms that would otherwise be used to support a diagnosis of CRPS, given that CRPS is explicitly a diagnosis of exclusion (see criterion 4 in box 1). For example, duplex ultrasound testing might be used to rule out a deep vein thrombosis as the cause of pain, hypersensitivity, edema, and skin temperature changes in one limb.

In the past, the diagnosis of CRPS (known by various names) was inconsistent and based on multiple competing diagnostic criteria, none of which was widely accepted.[140-143] In 1994 the IASP published consensus based diagnostic criteria for CRPS that it was hoped would become the internationally accepted standard for both research and clinical care.[18] Subsequent validation research found problems with lack of specificity and potential overdiagnosis using these criteria,[2 25 144 145] prompting an international effort to develop and validate CRPS diagnostic criteria with high sensitivity but better specificity.[25] The resulting criteria (often referred to as the Budapest criteria) became the official IASP diagnostic criteria for CRPS in 2012.[1] Although the new criteria retained the sensitivity of the 1994 criteria (0.99 *v* 1.00), the new criteria are notably more specific (0.68) than the 1994 criteria (0.41), thereby reducing false positive diagnoses.[25]

Unlike the 1994 IASP criteria, a clinical diagnosis of CRPS using the 2012 IASP criteria (box 1) requires the presence of both subjective symptom reports and objective signs on clinical examination. Because objective signs are now needed to make a diagnosis and CRPS related autonomic features (color and temperature changes) may be labile, evaluation of diagnostic criteria over several clinic visits may in some cases help ensure accurate diagnosis. The 2012 IASP criteria include an alternative, more stringent, decision rule for the diagnosis of CRPS in research settings that requires symptoms in all four symptom categories and at least two of four sign categories. These research criteria result in even greater diagnostic specificity (0.79) to enhance homogeneity of research samples (fewer false positive diagnoses).[25]

## Treatment

Although data suggest that many acute cases of CRPS may resolve with conservative medical care, expert opinion is that chronic CRPS is a challenging and complex biopsychosocial condition. Chronic CRPS is most likely to respond to comprehensive, integrated multidisciplinary treatment that includes medical, psychological, and physical and occupational therapy components.[121] While this view is supported by clinical experience in patients with CRPS and numerous clinical trials of such programs in other types of chronic pain,[146] no randomized controlled trials (RCTs) of multidisciplinary care have been performed specifically in patients with CRPS.

Within an evidence based medicine approach, it would be preferable to use outcome data from RCTs to guide the management of CRPS as much as possible. It is beyond the scope of this article to provide a thorough review and evaluation of the CRPS treatment literature, and readers are referred to several systematic reviews and meta-analyses.[147-157] However, the results of two more recent reviews are described below.[150 153] Although the number of clinical trials in CRPS has been increasing in recent years,[154] each of the reviews published between 1997 and 2013 has drawn two general conclusions:

- There is little support from high quality RCTs for many of the most common treatment approaches to CRPS
- More and better quality clinical trials are needed in CRPS.

**Summary of treatments for complex regional pain syndrome (CRPS)**

| Treatment | Category | Supporting RCT status |
|---|---|---|
| Multidisciplinary treatment | Standard | None |
| Physical and occupational therapy | Standard | Positive[150 153] |
| Oral corticosteroids (for acute CRPS) | Standard | Positive[150 162] |
| Anticonvulsants | Standard | Equivocal[164] |
| Analgesic antidepressants | Standard | None |
| Transdermal lidocaine | Standard | None |
| Opioids | Standard | None |
| Sympathetic nervous system blocks | Standard | Negative[150 153] |
| Spinal cord stimulation | Standard | Positive (<5 year efficacy)[167 168] |
| Pain focused psychological therapy | Standard | None |
| Graded motor imagery or mirror therapy | Uncommon | Positive[153 158] |
| Calcitonin | Uncommon | Positive[153] |
| Vitamin C (prevention after injury) | Uncommon | Positive[150 171-174 176] |
| Topical dimethylsulfoxide (DMSO) | Uncommon | Positive (warm CRPS)[150] |
| Oral N-acetylcysteine | Uncommon | Positive (cold CRPS)[150] |
| Bisphosphonates | Emerging | Positive[150 153 181-184] |
| Subanesthetic intravenous ketamine | Emerging | Positive[150 153 186 187] |
| Intravenous immunoglobulin | Emerging | Positive[189] |
| Oral tadalafil | Emerging | Positive[190] |
| Intrathecal baclofen (CRPS + dystonia) | Emerging | Positive[191] |
| Low dose oral naltrexone | Emerging | None |

RCT=randomized controlled trial.

A 2013 Cochrane review of treatment for CRPS found at least low quality evidence for the efficacy of bisphosphonates, calcitonin, subanesthetic intravenous ketamine, graded motor imagery and mirror therapy (specific physical therapy interventions, with mirror therapy effective particularly in acute post-stroke CRPS), and CRPS focused physical and occupational therapy.[153] It also found low and medium quality evidence, respectively, that sympathetic ganglion blockade with local anesthetics and intravenous regional blocks with guanethidine are ineffective. Evidence was deemed insufficient to draw conclusions for other interventions.

There is moderate overlap between this Cochrane review and results of a systematic review published by a consortium of CRPS experts in the Netherlands.[150] This review found at least some evidence for the efficacy of subanesthetic intravenous ketamine, free radical scavengers (topical dimethylsulfoxide, oral N-acetylcysteine, or oral vitamin C for prevention), oral corticosteroids, bisphosphonates, calcium channel blockers, intravenous ketanserine, surgical sympathectomy, spinal cord stimulation, and physical and occupational therapy.

Both reviews found that physical and occupational therapy, bisphosphonates, and subanesthetic ketamine might be effective, and there was some agreement that sympathetic blocks are probably ineffective. Of those treatments likely to be effective, functional therapies are described by experts as the cornerstone of CRPS treatment,[121] for reasons that are not entirely clear bisphosphonates are not routinely used, and ketamine is generally considered to be an experimental therapy and can be associated with serious side effects.

There is clearly a disconnect between clinical practice and the evidence base. This is underscored by the second review, which concludes that many standard treatments in clinical practice have no supporting evidence (absence of RCTs or negative trials) for efficacy in CRPS, including opioid analgesics, antidepressants, anticonvulsants, sympathetic ganglion blockade, or epidural sympathetic blockade using local anesthetics.[150]

In the absence of sufficient high quality evidence from RCTs to support treatment decisions, the clinical care of patients with CRPS must be guided by the collective experience of other clinicians, as reflected in standard practice (acknowledging that there may be regional biases towards particular treatments). It should be emphasized that clinical acceptance as part of standard care does not necessarily imply efficacy, unless also supported by RCTs. The table summarizes the treatments used in CRPS.

CRPS experts, even those who use more invasive interventional techniques, broadly agree that effective treatment should be functionally focused, centering around physical and occupational therapy designed to normalize use of the affected limb and mitigate problems related to disuse.[121] Best evidence suggests that mirror therapy and graded motor imagery should be included in these functional therapy protocols,[153 158] although a more recent trial of graded motor imagery in routine clinical practice (n=35) did not replicate the pain reducing effects seen in more highly controlled trials.[159] Limited research suggests that inclusion of an exposure therapy component to target fear of pain and fear of using the affected limb may also help.[160 161] Despite some evidence for their utility, the specific approaches above are not yet routinely included in functional therapy for CRPS except at specialty treatment centers.

### Drug treatment

An initial trial of oral corticosteroids is often used in patients with acute phase CRPS to dampen the large inflammatory component believed to be common in the acute phase. Dosages of 30-40 mg per day of oral prednisolone for two weeks followed by a tapering period have been reported to be effective in acute CRPS.[162 163]

Other drugs commonly used in standard CRPS care include anticonvulsants (for example, gabapentin) and analgesic antidepressants (for example, duloxetine). One RCT suggests that gabapentin may have a small effect on pain in CRPS, with a somewhat larger effect on sensory deficits.[164]

The search strategy described above found no RCTs of the effects of antidepressants specifically in CRPS. Transdermal lidocaine patches applied to the affected area are a common component of early treatment, although no RCTs have evaluated their efficacy in CRPS. Each of these treatments is palliative rather than curative. Opioid analgesics are sometimes used if additional pain control is needed to facilitate engagement in functional therapies and resumption of more normal daily activities. Only one small RCT of opioid analgesics has included patients with CRPS (seven of 43 patients in the sample), with overall results indicating no significant analgesic effects of sustained release morphine (90 mg/day) over eight days.[165]

### Ganglion blocks

In addition to oral and transdermal agents, if sympathetic ganglion blocks (stellate ganglion, lumbar sympathetic) have not already been used, and an initial trial indicates

they provide sufficient relief to improve participation in functional therapies, a series of several blocks at weekly intervals is often used. Sympathetic blocks have not been shown to have significant efficacy in patients with CRPS overall.[153] However, clinical experience and one small randomized trial (n=7) suggest that in some patients they may provide additional pain relief beyond the duration of action of the local anesthetics used (≥3 days[166]). There is no evidence that sympathetic blocks are curative for any patients.

### Spinal cord stimulation

If after an extended trial (longer if CRPS is more acute) the above approach has not improved the patient's condition, it is common to move on to a trial of spinal cord stimulation. If this trial is successful, which it was in two thirds of patients (n=24/36) in the only RCT in these patients,[167] permanent implantation will follow, with continued emphasis on achieving improved function and normalizing daily activities. The one RCT of spinal cord stimulation in patients with CRPS (n=36 spinal cord stimulation; n=18 physical therapy) suggests it may be effective for pain reduction (but not necessarily functional improvement) for several years, but that efficacy is no greater than physical therapy alone five years after implantation.[167-169]

### Psychological interventions

Given the psychosocial complexity of CRPS, it is generally agreed that inclusion of pain focused cognitive behavioral therapy is beneficial as part of standard care for chronic CRPS.[121 170] However, no RCT evidence is available specifically in patients with CRPS to support this belief.

## Can CRPS be prevented?

### Vitamin C

In the absence of efficacious treatments for CRPS, it would be preferable to prevent CRPS from developing. Several RCTs have been published on the use of vitamin C for the prevention of CRPS after limb fracture or surgery.[171-175] This treatment is based on the known antioxidant effects of vitamin C that could theoretically reduce the inflammatory mechanisms (related to oxidative stress) that are thought to contribute to acute CRPS. A meta-analysis of the first four published studies on this topic suggested that vitamin C significantly reduced the likelihood of CRPS developing after limb fracture or surgery (risk ratio 0.22, 0.12 to 0.39; n=616 for the vitamin C; n=449 for control),[176] with 500 mg vitamin C recommended daily for at least 45 days after injury or surgery. However, a recent large RCT (n=336) that used this protocol for the prevention of post-fracture CRPS found that vitamin C was associated with an increased incidence of CRPS at six weeks after fracture relative to placebo, with no effect at subsequent time points.[175] The potential utility of vitamin C in the prevention of CRPS is therefore unclear.

### Ischemic reperfusion injury

Another potential means of prevention also relates to the possible role of oxidative stress (particularly in relation to ischemic reperfusion injury) in the development of CRPS. During limb surgery procedures, such as total knee arthroplasty, a tourniquet is routinely applied to the surgical limb to reduce blood loss, sometimes for as long as two hours. Given that ischemic reperfusion injury can occur on removal of the tourniquet, with its severity related to the duration of ischemia, minimizing the duration of tourniquet use during such procedures could potentially reduce the incidence of CRPS.

## CRPS in children

Although clinical lore suggests that CRPS presents differently in children than in adults, there is no empirical evidence on such differences and this assumption has been questioned.[177] CRPS is currently diagnosed in children using the same 2012 IASP criteria that are used in adults. Two detailed clinical evaluation studies (n=20; n=42) suggest that the same objective signs are seen in children and adolescents with CRPS as are seen in adults, including allodynia and hyperalgesia, edema, skin color and temperature changes, and motor changes.[178 179]

Data from more than 100 children and adolescents with CRPS meeting the 2012 IASP diagnostic criteria indicated that these children exhibited more functional impairments and disability than those with other forms of chronic pain, consistent with the high levels of impairment often noted in adult patients with CRPS.[180] A longitudinal study of patients (n=42) diagnosed as having CRPS in childhood found that on follow-up in adulthood an average of 12 years later, 52% still experienced pain, with 36% having documented recurrences of CRPS.[179] This suggests that in many cases of childhood CRPS there may be no sustained recovery. These longitudinal data contrast with the common clinical assumption, not yet supported by high quality trials, that children with CRPS respond more favorably to conservative functionally focused care than do adults, in many cases with complete resolution of the condition.[177]

## Emerging treatments

Several treatments for CRPS are emerging that go beyond the current standard of clinical care. The best supported of these is treatment with bisphosphonates, which several small RCTs suggest may be effective for CRPS.[181-184] The mechanistic relevance of treatment with bisphosphonates, which inhibit osteoclast activity, is suggested by recent work supporting a role for impaired bone metabolism in CRPS.[104] A definitive RCT of bisphosphonates is currently under way (ClinicalTrials.gov identifier: NCT02402530).

Other placebo controlled studies suggest that topical ketamine or a series of daily subanesthetic ketamine infusions may be useful in otherwise treatment resistant patients,[185-187] although liver injury has been noted with repeated ketamine infusions in some patients.[188] Additional experimental CRPS treatments supported by small RCTs include intravenous immunoglobulin (n=13),[189] oral tadalafil (n=24),[190] and intrathecal baclofen for CRPS related dystonia (n=36),[191] although high complication rates were noted with this last intervention.

An RCT of low dose naltrexone (an opioid antagonist) for CRPS is also currently ongoing. This intervention is based on the hypothetical ability of naltrexone to reduce

**RESEARCH QUESTIONS**

How do the individual mechanisms shown to be associated with complex regional pain syndrome (CRPS) interact to produce the full syndrome?

Do different subtypes of CRPS exist that reflect different underlying mechanisms?

Can clinical signs and symptoms be clearly tied to underlying mechanisms?

Do different CRPS subtypes, signs, and symptom patterns and different mechanisms predict differential responsiveness to specific treatments?

glial inflammation by blocking Toll-like receptor 4, case reports suggesting efficacy in CRPS,[192] and positive results of a small RCT (n=31) in patients with fibromyalgia.[193]

### Guidelines

Although several guidelines for the management of CRPS have been published over the past 20 years, evolving research and approaches to CRPS management make it particularly important to use the most recently developed guidelines. General treatment guidelines have been published by groups in the Netherlands,[150] UK,[194] Germany,[195] and the US.[148] Guidelines with a specific focus on interventional pain procedures, which cover interventional approaches in greater detail than in the general treatment guidelines, are also available.[157] Although the emphasis of the guidelines differs, a relatively high degree of overlap exists across the general treatment guidelines. Some regional differences are apparent, however, with US guidelines providing little information on the antioxidant agents (such as dimethylsulfoxide) that are recommended treatments in the Dutch and German guidelines.[148 150 195] In addition, specific criteria (if any) used for systematically evaluating efficacy data differ across guidelines, which can lead to different recommendations being made. For example, guidelines that focus on interventional procedures have more positive conclusions about the efficacy of sympathetic nervous system blocks and recommend these in routine treatment,[157] whereas other guidelines have more negative conclusions about these blocks.[150] Such differences highlight the need to consider clinical biases that may affect the interpretation of CRPS guidelines.

### Conclusion

Although CRPS is uncommon in the general population, it occurs in 4-7% of patients who have a limb fracture or limb surgery. In many cases, acute CRPS that is typically associated with a warm, red, and edematous presentation resolves with limited intervention. In a subset of patients, CRPS becomes chronic, often accompanied by a transition to a cold, dusky, and sweaty presentation. Initial symptoms typically emerge within weeks of injury, and the transition from acute to chronic CRPS usually occurs within the first year. Multiple mechanisms underlie CRPS, both peripheral and central, and these may differ across patients and even within patients over time. CRPS should be diagnosed on clinical grounds using the 2012 IASP diagnostic criteria.

Inadequate data are available to guide CRPS treatment solely on the basis of RCTs, although trials suggest that the most commonly used intervention (sympathetic blocks) is probably ineffective for the average patient. Support for the efficacy of spinal cord stimulation in CRPS derives from a single RCT. There is some evidence for the efficacy of physical and occupational therapy, bisphosphonates, subanesthetic ketamine, free radical scavengers, and corticosteroids (for acute CRPS). Analgesic antidepressants, anticonvulsants, and transdermal lidocaine are thought to be effective clinically, although their efficacy in CRPS has not been evaluated adequately in RCTs. It is clinically accepted that standard care should emphasize functional therapies that target disuse. Pharmacological, interventional, and psychological techniques are also used because they facilitate participation in functional therapies and ideally enhance quality of life. The number of clinical trials of CRPS specific interventions is growing, raising hope that more effective treatments may eventually emerge.

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# Physiotherapy management of complex regional pain syndrome

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## ABSTRACT

Complex Regional Pain Syndrome is a painful debilitating condition characterised by sensory, vasomotor, sudomotor, and trophic changes. Traditionally, physiotherapy treatments have been directed at peripheral symptoms, often with limited efficacy. In light of the growing scientific evidence promoting the major role of the central nervous system in the pathogenesis of Complex Regional Pain Syndrome, there has been a shift towards interventions considered to modulate central processing. A systematic review performed in 2009 aimed to assess the evidence regarding the physiotherapy management of Complex Regional Pain Syndrome. Techniques showing some promise include mirror therapy, Graded Motor Imagery, tactile discrimination training, and exposure therapy. This paper aims to elaborate on the scientific framework for these techniques and explore the current research regarding treatment efficacy. Hopefully, further wide dissemination of these ideas will spark more interest from clinical practitioners and clinicians alike in the quest to more completely understand and manage this complex condition.

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Key Words: Body perception disturbance, Graded Motor Imagery, mirror therapy, tactile discrimination training, exposure therapy.

## INTRODUCTION

Most physiotherapists either have encountered, or will encounter, a challenging case of Complex Regional Pain Syndrome (CRPS), often, but not necessarily following a patient's injury, myocardial infarction, or stroke (De Mos 2007, Veldman 1993). Traditionally, physiotherapy treatments have focussed mostly on attempted modification or management of peripheral symptoms, often with limited efficacy. More recently, spurred by scientific advances identifying the significant role of the central nervous system in the pathogenesis of CRPS, techniques which focus on central processes have been developed (Moseley 2010). Treatment strategies including mirror therapy, Graded Motor Imagery, tactile discrimination training and exposure therapy have been explored in one guise or another. However, there is little in the literature as to how these worlds of scientific evidence and best clinical practice come together. This paper addresses and attempts to bridge this divide, reviewing the scientific research that informs our adoption of these novel treatment techniques.

### Diagnostic Criteria and Pathophysiology

The clinical features of CRPS include burning pain, allodynia (pain from a non-painful stimulus) and hyperalgesia (increased response to a painful stimulus); motor disturbances ranging from decreased range, speed, co-ordination of movement, tremor and muscle spasms; changes in vascular tone, temperature, skin colour, sweating and oedema; trophic changes to skin, hair, nails and perceptual disturbances with distortions to the body-self (Harden and Bruehl 2006, Lewis and McCabe 2010).

There are two types of CRPS described: CRPS-1 can occur spontaneously or following trauma, with the symptoms unrelated to the region of a single nerve, and disproportionate to the inciting event. CRPS-2 occurs in association with nerve damage (Merskey and Bogduk 1994). The management of these are similar; however, it is important to identify the presence of nerve injury in case further intervention is warranted.

The exact cause of CRPS is still not fully understood, however there are a number of proposed pathophysiological mechanisms which contribute to the overall symptoms. Neurogenic inflammation, which involves the amplification of cytokines, bradykinins, endothelin, neuropeptide CGRP and Substance P, has been demonstrated in people who developed CRPS after injury (Birklein and Schmelz 2008, Guo et al 2004). It is postulated the elevation of these inflammatory mediators occurs as a result of inadequate inactivation after their release, so they continue to promote inflammation (Birklein and Kingery 2009). Another suggestion is that more receptors are available to receive these inflammatory mediators (Birklein and Kingery 2009). The overall effect is increased temperature, skin reddening, protein extravasation, oedema and augmented nociceptive stimulation.

The role of the sympathetic nervous system (SNS) in CRPS has remained controversial. It was originally proposed that the SNS was the main driver for CRPS symptoms, hence its previous name Reflex Sympathetic Dystrophy. Under normal circumstances sympathetic activity does not impact on the discharge of nociceptors; however in the case of CRPS, nociceptors appear to be under the influence of the SNS. This is referred to as sympathetically maintained pain (Raja et al 2010). In people with CRPS the epidermis of the skin within the region of hyperalgesia has been shown to contain a greater density of the receptors involved in sympathetically maintained pain compared to pain free skin and normal controls (Raja et al 2010). It was agreed however, that the SNS was not the sole cause of CRPS, as sympathetic nerve blocks did not provide significant relief for a number of patients (Galer et al 2001).

Based on physiological and functional imaging studies there is substantial evidence that in persistent pain states, reorganisation of the primary somatosensory cortex (the Penfield 'homunculus') (Flor 2003, Flor et al 2009), the secondary somatosensory cortex

(Pleger et al 2006), and the motor cortex can occur (Cohen et al 1991). It has been demonstrated that the degree of cortical reorganisation is directly related to the intensity of CRPS pain and the extent of hyperalgesia (Pleger et al 2005).

In the case of CRPS the cortical representation of the affected limb is smaller than that of the unaffected limb, with digit representations moving closer together (Juttonen et al 2002, Maihofner et al 2003, Pleger et al 2004). This can produce affects such as body perception disturbance, whereby people with CRPS describe their limb as feeling abnormal in terms of shape and size (Moseley 2005b), temperature (Lewis et al 2007), position (Lewis et al 2010) and orientation (Schwoebel et al 2001). It can produce feelings so intense that the limb no longer feels like the participant's own (Lewis et al 2007). It is postulated that this reorganisation can alter cortical processing, instating a conflict between sensory feedback and motor output. It has been shown that inducing a sensorimotor incongruence in normal participants can provoke sensations of spontaneous pain and feelings of peculiarity (McCabe et al 2005) and exacerbate pain in people with fibromyalgia (McCabe et al 2007). It is therefore credible that cortical reorganisation contributes to the pain experienced within CRPS. Cortical reorganisation can also produce motor dysfunction, leading to abnormal movement patterns during reaching and grasping tasks (Maihofner et al 2007).

In summary, these various mechanisms contribute to the multitude of symptoms that can develop in a person with CRPS.

## Physiotherapy Management

Over the years many different treatment modalities have been utilised for the management of CRPS, including medical management (analgesics, steroids, supplements) and interventional treatments (sympathetic nerve blocks, sympathectomy, amputation and spinal cord stimulator insertion). It is well recognised however, that physiotherapy plays an important role in the standard treatment of CRPS.

Physiotherapy encompasses a large array of different treatment techniques and modalities. In order to gain a clearer insight into the efficacy of the varied physiotherapy interventions for the treatment of adult CRPS-1 a systematic review of the literature was performed (Daly and Bialocerkowski 2009). An electronic search was conducted for the period 1987-2007 using various databases and searches of textbooks on pain. Each study was appraised by the Australian National Health and Medicine Research Council (NHMRC) hierarchy of evidence and the Critical Review form for Qualitative Studies: 180 articles were found, of which 166 were excluded as they did not meet the inclusion criteria. There were 11 articles included in the systematic review. After analysing and comparing the data regarding the effectiveness of the different treatments, the authors concluded that Graded Motor Imagery (GMI) produced the greatest benefit in terms of reducing pain when compared to conventional physiotherapy and medical management. There was reasonable evidence for modalities such as mirror therapy, desensitisation training, and graded exposure; however, there was no evidence to support the effectiveness of transcutaneous nerve stimulation or stress loading exercise. The study highlighted a distinct lack of high quality research on physiotherapy management of CRPS.

This review aims to expand this systematic review by exploring the latest scientific and clinical based research developments pertaining to these techniques and discuss how they may be applied in a therapeutic setting. In addition, it explores the current research utilising recent modalities such as prism glasses and virtual reality for managing CRPS.

## Mirror Therapy

Mirror therapy aims to create an illusion of normality in the affected limb. It was introduced by Ramachandran in 1992, for use with phantom limb pain and has since been adapted to aid in the management of numerous conditions, including stroke and pain after wrist fracture and hand surgery (Ramachandran and Alschuler 2009). When used for CRPS, mirror therapy involves concealing the affected limb behind the mirror, while the non-affected limb is positioned so that its reflection is superimposed to where the affected limb should be. The brain has been shown to prioritise visual input over proprioceptive input (Rock and Victor 1964), so when the unaffected limb moves it appears as though the affected limb is functioning normally.

The mechanisms of action for mirror therapy are still not fully understood. There are a number of theories described in the literature including increased attention to the limb, improved ownership of the limb (McCabe 2011), activation of the mirror neurone system (Matthys et al 2009, Rothgangel et al 2011), and a reduction of sensorimotor incongruence (Ramachandran et al 1995).

Mirror therapy has been shown to have positive and negative effects on the symptoms of CRPS (McCabe 2011). It is postulated that the discrepancies in results are due to differing methods of execution. According to McCabe (2011) mirror therapy should be performed with both limbs moving in a bilateral synchronous manner, so the person can feel the movement at the same time as observing the reflection of the normal limb moving. If movement of the affected limb is not performed in synchrony with the observed reflection, conflicting sensory feedback and motor output will be exaggerated and CRPS pain can be increased (McCabe 2011). Acerra and Moseley (2004) demonstrated that pain could be evoked in the affected limb of CRPS participants when the unaffected limb was stimulated in front of a mirror (via light touch, sharp touch and the application of cold). Interestingly, only participants with CRPS experienced pain, it did not occur in participants with similar pain symptoms (but no signs of CRPS-1) or control participants.

Mirror therapy also appears to have differing effects in the acute and chronic phases of CRPS. McCabe et al (2003) performed a pilot study which involved eight participants with CRPS-1 practicing mirror therapy for six weeks. It was demonstrated that visual feedback from the mirror significantly lowered pain intensity in acute CRPS-1 (less than eight weeks). These analgesic effects were prolonged with increasing duration of mirror therapy. In the intermediate stages of the disease (less than one year) mirror therapy reduced stiffness. Unfortunately, there was no beneficial outcome for the three chronic cases. These findings concur with other studies. In acute CRPS, Cacchio et al (2009) demonstrated an improvement to CRPS symptoms, whereas for chronic CRPS Tichelaar et al (2007) reported a poor response to mirror therapy.

When CRPS symptoms persist, patients can experience more physical impairments with changes in muscle strength, contractures, joint stiffness, or motor control. This can place more restrictions on the movement of the affected limb and further increase the incongruence between the affected limb and the mirror image. In these instances it is proposed that mirror therapy may overwhelm the sensitised system therefore exacerbating pain to a greater extent (Moseley 2005a). It has been suggested that a graded approach to cortical activation utilising techniques to activate cortical regions affiliated with movement preparation but not movement execution may be more suitable, as suggested to occur in Graded Motor Imagery (described in more detail in the following section) (Moseley 2005a). This theory was supported when it was demonstrated that during GMI, mirror therapy only imparted an effect when it followed imagery (Moseley 2005a).

In summary, the research indicates that mirror therapy can assist with pain reduction and improve function in the early stages of CRPS. Considering that it is an inexpensive and accessible form of treatment that can be performed within the clinic and continued at the patient's home, there is a basis for its use in early rehabilitation. In regards to chronic CRPS, there is limited efficacy when used as a first line treatment and in some instance it can exacerbate CRPS symptoms. Caution should be made to ensure patients are instructed on the appropriate technique, to minimise potential side-effects.

### Graded Motor Imagery

GMI follows a progressive three-stage motor imagery programme. In stage 1, participants see a series of photographic flash cards, and are asked to identify (as quickly as possible) whether the depiction is of a left or right limb. In stage 2, participants imagine moving the affected limb into the position demonstrated on the photograph, while the affected hand rests comfortably. Stage 3 involves mirror therapy, whereby both limbs are moved to adopt simple postures as demonstrated on the photograph (Mosley 2004).

GMI is considered to exert its effects through sequential activation of distinct (ordered) stages of brain function (Moseley 2005a). Parsons and Fox (1998) used positron-emitting tomography to image brain activation (through blood-flow measures) during right / left judgement tasks (stage 1). A large amount of activity was shown in the pre-motor and supplementary motor regions and the cerebellum, however there was no activity in the primary somatosensory and motor cortices. Imagery (stage 2) has been shown to activate the pre-motor, primary somatosensory and motor cortices (Lotze et al 1999). This indicates that stage 1 activates brain centres involved in higher order aspects of motor control and movement preparation without physical movement of the limb, prior to progressing to stage 2 where activation of the motor cortices occur (Moseley 2005a). This theory was supported during a clinical trial in which 20 participants with chronic CRPS-1 of one hand were randomly allocated to undertake the three components of the GMI programme in different orders (Moseley 2005a). It was demonstrated that participants who followed the sequenced GMI stages (stages 1, 2 then 3) had better outcomes with reduced pain rating and increased functional task ability (measured using the task-specific numeric rating scale) than participants who did not follow the sequence. It also showed that imagined movements were only successful in producing measurable improvement when they followed hand laterality recognition; and mirror movements were only useful when they followed imagined movements.

Early support for effective utilisation of GMI was demonstrated in a randomised controlled trial involving 13 participants with chronic CRPS-1 following non-complicated wrist fractures (Mosley 2004). Participants were randomly allocated into either a GMI group following the three stage programme or a control group who did not receive treatment. Each stage involved intensive repetition, with exercises practised three times an hour, every waking hour, for two weeks before being progressed to the next stage. On completion of the GMI programme there was a significant reduction in the neuropathic pain scale (by approximately 20 points, on a 100 point scale), an improvement in swelling and reduced limb laterality recognition time. These improvements were maintained for at least six weeks after completion of treatment. The outcome measures for the control group did not change. However, when two of the control participants crossed over to GMI, there was a significant reduction in all three variables.

This study was repeated with a larger sample size including people with phantom limb pain after amputation, brachial plexus avulsion injuries and a more heterogeneous group of CRPS-1 patients. The results showed that pain decreased and function increased for the GMI group relative to the control group; however pain reduction was about 50% less in this study than the previous one (Moseley 2006).

Based on the success of these studies, GMI has been adopted by clinics worldwide. Reports are now being published to discuss the clinical implications of this technique. Johnson et al (2012) performed an audit to assess the outcomes of GMI used within two CRPS speciality centres in the UK. For practical reasons the GMI protocol deviated from that used in the studies by Moseley, with reduced face to face contact, increased duration of the stages, and reduced frequency of practice. Although this makes comparison debateable, it provides a more realistic view of the efficacy of GMI when applied in real-life clinical situations. Unfortunately, the outcomes from this study would suggest that the clinical application of GMI may not be as promising as anticipated. When assessing pain intensity, the participants reported the 'worst' pain intensity reduced but the 'average' pain intensity remained the same following treatment. On the whole, only 3 out of the 32 patients who started GMI achieved a 50% pain reduction and in 12 out of the 32 patients, pain actually increased with treatment. Lagueux et al (2012) also utilised a modified version of GMI in a clinical trial based on 7 patients with CRPS present for less than 6 months. The results indicated a reduction in pain but no statistically or clinically significant difference to function.

It seems plausible that GMI may provide an avenue to start rehabilitation at a manageable level for a patient who complains that pain is too severe to perform any kind of limb movement. By regressing rehabilitation to a point whereby only the cortical regions involved in movement preparation are activated, pain may be provoked to a lesser extent. This could then be progressed in a steady manner to promote greater cortical activation, prior to commencing functional activation. However, as Johnson et al (2012) identified, there are some cases where pain can be intensified during its use. Further

research to identify potential subgroup populations where GMI may be unsuitable, as well as clearer recommendations for the application of GMI e.g. frequency of practice, duration of stages will assist to optimise the use of GMI in clinical practice.

### Tactile Discrimination

Tactile discrimination is slower in a CRPS-affected limb than in an unaffected limb (Moseley et al 2009) and in some cases, mislocalisation of sensory stimulation is present in the affected limb. Maihöfner et al (2006) demonstrated that when touching the digits of an affected CRPS hand, the sensation was felt to be in another place within the same hand in 8 out of 24 participants tested. It was also noted that the presence of mechanical hyperalgesia was a significant predictor for the incidence of sensory mislocalisation. These occurrences are considered to be related to cortical reorganisation. Flor et al (2001) demonstrated that the extent of reorganisation correlates with the magnitude of pain, and the degree of tactile acuity of the affected region. It has been suggested that tactile information processing is 'spatially' related (where the body is in space) rather than somatotopically defined (the body position in accordance to its location within the homunculus). Moseley et al (2009) studied ten participants with CRPS in a single arm. Participants received pairs of vibro-tactile stimuli, one delivered to each hand, at various asynchronies. They were asked to identify which hand had been stimulated first by releasing a foot switch to indicate left or right. This was performed with the arms held each side of the midline and then with the arms crossed over midline. The point at which participants were equally likely to select either hand was compared between conditions and between those with left and right-sided symptoms. The results showed that when arms were not crossed, the participants prioritised stimuli from the unaffected limb over those from the affected limb. In other words, it took participants longer to recognise and/or respond to the stimulus applied to the affected arm. When the arms were crossed the effect was reversed, requiring earlier delivery of the stimulus to the unaffected limb in order for it to be recognised as simultaneous to the affected limb. The study also discovered a strong correlation between the time to recognise stimulus to the affected arm and skin temperature. The earlier the affected limb needed to be stimulated in order for the two stimuli to be perceived as simultaneous, the cooler the affected limb was in relation to the unaffected limb. When the arms were crossed the temperature of the affected limb increased. It was postulated that this warming effect may indicate improved ownership of the limb. These results indicate that CRPS is associated with a deficit in tactile processing that is defined by the space in which the affected limb normally resides, not by the limb itself.

In order to normalise tactile acuity, techniques such as sensory discrimination training have been employed. Sensory discrimination training has been shown to be effective in improving pain and two-point discrimination for people with phantom limb pain. These changes were accompanied by normalisation of the somatosensory cortical organisation (Flor et al 2001). Similar results have been shown for people with CRPS (Pleger et al 2005) however it appears that the technique for delivering sensory training is paramount. Approaches which involve active participation from the participant, such as distinguishing the location and type of stimuli applied to the affected area, have been shown to be more effective at reducing pain and improving tactile acuity than passive stimulation (touching the affected region with no conscious thought to the stimuli) (Moseley et al 2008a).

In summary, tactile discrimination training techniques which encourage patients to concentrate on the delivered stimuli can improve tactile acuity and reduce pain. Following such training, functional imaging studies have demonstrated improvements in cortical re-organisation (Pleger et al 2005).

### Exposure Therapy

It is well documented that pain-related anxiety and fear are strong predictors of pain disability in people with various chronic musculoskeletal conditions (De Jong et al 2011). This can lead to a vicious cycle of pain, fear, and disability. In some cases people living with pain can develop activity avoidance or hypervigilance. In the acute phase of tissue injury these behaviours may be useful for healing but as pain persists they become detrimental. For people with CRPS these behaviours may lead to fear avoidance of using their limb, guarding and protecting it, and developing maladaptive coping strategies. This can lead to secondary changes associated with non-use, which can result in a further decline in function. De Jong et al (2011) explored the concept of fear avoidance of movement in terms of functional limitation in people with CRPS-1. In people with acute CRPS the severity of pain determined functional limitation, not fear. Conversely, in people with chronic CRPS perceived harmfulness of activity correlated stronger with functional limitation than the impact of pain intensity. Moseley et al (2008b) demonstrated that fear of movement and catastrophic thoughts can have a negative impact on swelling and pain in the affected limb when performing imagined movements. It is therefore important that fear-avoidance is addressed early.

One approach to tackle fear-avoidance is to perform graded exposure to the feared stimulus. Graded exposure therapy follows a structured process involving screening, education, and graded exposure (Vlaeyen and Linton 2000). Overall, the process aims to stimulate fear, then disconfirm the fear by providing new information on the feared activity, whereby inaccurate predictions about activities causing harm, are dispelled (Philips 1987).

Graded exposure has been explored in a number of pain conditions including chronic low back pain (Macedo et al 2010); post-traumatic neck pain (De Jong et al 2008, Wicksell et al 2008); and generic pain conditions (Bliokas et al 2007, George et al 2010) with mixed results. In regard to CRPS, a small study based on eight female participants with chronic CRPS, demonstrated that graded exposure was successful in decreasing levels of pain-related fear, pain disability, and pain intensity. Participants also reported reduced signs and symptoms of CRPS-1 (such as swelling or colour changes). At a six month follow-up, the eight participants had complete resolution of their symptoms (De Jong et al 2005).

Anecdotal evidence indicates that encouraging participants to face feared activities may however provoke pain and exacerbate CRPS symptoms. Ek et al (2009) therefore assessed the safety of exposure therapy by encouraging patients to focus on functional improvement while neglecting the pain. The outcomes were positive, from 102 people who completed the functional

exposure programme, 49 achieved full recovery in terms of function, 46 partial recovery, and five experienced no change. The authors also found that pain scores reduced in 76 patients, increased in 14, and did not change in 12. From those patients whose pain worsened or did not change, 10 had achieved full function. Interestingly, only four participants dropped out as they considered the interventions too strenuous and painful. The study concluded that treatment focussing on functional restoration can be applied safely and effectively for patients with chronic CRPS. This work was expanded to include assessment of specific CRPS symptoms, including oedema, skin temperature, skin colour, joint mobility, muscle strength, and pain during exposure therapy (Van de Meent et al 2011). These authors used a progressive-loading exercise programme, desensitising techniques, forced use of the affected limb in daily activities and management of pain-avoidance behaviour, without the use of specific CRPS-1 medication or analgesics. Participants were discouraged from complaining about the pain and treatment intensity was not reduced because of pain. On monitoring the symptoms of CRPS-1, two out of the 20 participants had a slight increase in oedema during treatment, whereas temperature differences and colour changes between limbs improved in some participants during treatment. Pain increased in five cases during treatment but on the whole declined following treatment. Joint mobility and arm strength increased; and following treatment, measures determining 'functional use', 'fear avoidance to activity', and 'quality of life' all showed improvement. There were no participants who withdrew from the study due to discomfort or adverse effects.

Due to the risk of initially increasing pain intensity, the studies exploring exposure therapy highlighted the importance of ensuring the patient was adequately educated and motivated to be compliant with treatment regimes, in order for it to be successfully tolerated. These studies provide reassuring evidence that treatments focussing on activity whilst ignoring pain can be safely applied with no deterioration of CRPS-1 symptoms.

### Virtual Reality

With the ever growing developments in technology, the theories regarding mirror therapy have been expanded into the virtual world, with studies looking into the efficacy of virtual reality systems for managing pain. There is currently evidence to demonstrate efficacy of virtual reality for acute pain (such as during routine medical procedures) (Gold et al 2005), burns (Hoffman et al 2000), cancer pain (Sander et al 2002, Schneider and Workman 2000), and more recently, CRPS. Sato et al (2010) developed a computer-based programme linked to a glove which was embedded with sensors to detect movement of the hand. The glove is worn on the unaffected hand but produces an image on the screen of the opposite (affected) hand. Participants are instructed to focus on the motion of the virtual hand while performing motor tasks such as reaching out, grasping, transferring, and placing. The programme was tested on five participants with chronic CRPS-1 who were seen weekly for this treatment for up to eight sessions. They found that four out of the five patients showed a 50% reduction in the pre-treatment pain score. In two patients, the analgesic effect continued after cessation of the therapy and no participants described any treatment related side-effects.

Virtual reality has been shown to produce analgesic effects through modulation of sensory and emotional aspects of pain processing with reduced activity demonstrated via fMRI in areas such as caudal anterior cingulate cortex which is involved in the emotional aspects of pain; the somatosensory areas, involved in registering location and intensity of pain; as well as the thalamus and insula (Hoffman et al 2004).

Unfortunately its widespread use is limited as the equipment is expensive and can only be used within the therapy clinic. With ongoing developments of next generation home gaming systems, it will be interesting to see if similar results may be achieved with accessible and cheaper alternatives. The added advantage of virtual reality and 'gaming' treatments are that they are based on activities which patients are more likely to find fun and/or interesting to do. This may improve compliance and activate the brains reward systems, leading to the release of dopamine which strengthens and consolidates learning and neurological plasticity (Harley 2004, Wise 2004).

### Minimising Body Perception Disturbance

People with CRPS-1 have been described in numerous texts to exhibit 'neglect-like' behaviours similar to that which may follow neurological insult such as stroke (Galer et al 1995, Galer and Jensen 1999). Following work by Förderreuther et al (2004) and Lewis et al (2007), the term 'neglect' for CRPS has been superseded by the term 'body perception disturbance'. In order to move the affected limb, people with CRPS-1 frequently comment on their need to consciously focus their mental and visual attention to the limb, often describing the limb as "not belonging to me" (Galer and Jensen 1999, Moseley 2005b, Lewis et al 2007).

Body perception disturbance not only involves changes in the perception of the body part itself but in how that body part relates to the body and the space in which it occupies. As discussed in the section regarding tactile discrimination, Moseley et al (2009) demonstrated that crossing the affected limb over to the other side of the body influenced sensory acuity and skin temperature. Sumitani et al (2007a) demonstrated that people with CRPS showed a shift in subjective body-midline with a bias towards the affected side which is contrary to previous thoughts of CRPS neglecting the space of the affected side.

In order to normalise body perception disturbance, treatments aimed at correcting cortical remapping are considered appropriate (Lewis et al 2007). It is postulated that delivering normal stimuli to the affected limb and encouraging the patient to engage with the limb may assist to normalise sensory and motor responses. This can include utilising the techniques described in the preceding sections, which are considered to influence cortical activation and organisation (Pleger et al 2005, Maihofner 2007). A number of other gadgets and appliances have also been trialled with the intention of tricking the brain to improve body perception, such as prism glasses and minifying lenses.

Prism glasses are based on the principles of mirror therapy, but were designed to allow portable treatments which can be performed more regularly. They utilise a wedge prism to add visual displacement towards the affected side while the vision in the other eye is blocked. When the patient moves the non-affected limb the prism inverts the image to appear as

though the affected limb is moving. Prism glasses have been used with success for managing hemianopia (blindness in half of the visual field in both eyes—either the left or the right field) (Bowers et al 2008, Giorgi et al 2009) and for patients with stroke and hemispatial neglect (Fujiwara et al 2011, Keane et al 2006). In terms of their use for CRPS, Sumitani et al (2007b) demonstrated that performing visual subjective body-midline judgment tasks while wearing the prism glasses with a 20° prismatic displacement of visual field toward the unaffected side for two weeks alleviated pain in five patients with CRPS. There was also an improvement in proprioception and limb position awareness. When the prism glasses were displaced 20° toward the affected side, pain increased.

Bultitude and Rafal (2010) provided a single case report of a patient with early CRPS managed with prism glasses and mirrors. Following activities involving the prism glasses, the patient noted a decrease in pain, swelling and temperature, and improvements to range of motion of the limb. After nine days of treatment, the patient was pain free.

Minifying lenses are inverted binoculars which make objects appear smaller. Their potential use was demonstrated in a study by Moseley et al (2008c) whereby 10 participants with unilateral arm pain performed various hand movements. Participants observed their arm moving under four conditions; with no visual appliance; through binoculars with no magnification; through magnified binoculars; and looking through inverted binoculars. Although movement aggravated pain in all conditions, it was intensified to a greater extent when the arm was magnified. Interestingly, the increase in pain intensity and swelling was least when the image of the arm was minified. This study adds further weight to the evidence for the link between vision and proprioception, and how central processes can be manipulated through visual input. It is possible minifying lenses create the illusion that fewer sensory neurones have been activated, distorting the afferent input and reducing cortical activation. Research to investigate this theory is still required.

## CONCLUSION

Although the pathophysiological mechanisms for CRPS are still not fully understood, there is increasing evidence for the role of the central nervous system in the development and/or maintenance of CRPS. Changes to cortical processing and organisation can lead to the development of symptoms such as body perception disturbance, sensory incongruities, and motor dysfunction. Over recent years there have been advances connecting neuroscience to clinical practice, with physiotherapeutic techniques focussing on central modulation growing in popularity. There is emerging evidence for techniques including mirror therapy, tactile discrimination training, GMI, graded exposure therapy, and virtual reality. Physiotherapists are at the forefront of initiating these techniques with CRPS patients. An understanding of the mechanisms of action and clinical effectiveness will help physiotherapists use these techniques in clinical practice.

## KEY POINTS

- Expanding research in the field of neuroscience is improving our understanding of CRPS.
- With advanced understanding of CRPS-related brain and spinal cord processes, treatment modalities are moving away from peripheral management to focus on central processing.
- Techniques such as mirror therapy, Graded Motor Imagery, tactile discrimination training, and graded exposure therapy show promise in the management of CRPS.
- Physiotherapists are at the forefront of initiating these techniques with CRPS patients.


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# Neurogenic neuroinflammation in fibromyalgia and complex regional pain syndrome

*Geoffrey Littlejohn*

**Abstract** | Although fibromyalgia and complex regional pain syndrome (CRPS) have distinct clinical phenotypes, they do share many other features. Pain, allodynia and dysaesthesia occur in each condition and seem to exist on a similar spectrum. Fibromyalgia and CRPS can both be triggered by specific traumatic events, although fibromyalgia is most commonly associated with psychological trauma and CRPS is most often associated with physical trauma, which is frequently deemed routine or minor by the patient. Fibromyalgia and CRPS also seem to share many pathophysiological mechanisms, among which the most important are those involving central effects. Nonetheless, peripheral effects, such as neurogenic neuroinflammation, are also important contributors to the clinical features of each of these disorders. This Review highlights the differing degrees to which neurogenic neuroinflammation might contribute to the multifactorial pathogenesis of both fibromyalgia and CRPS, and discusses the evidence suggesting that this mechanism is an important link between the two disorders, and could offer novel therapeutic targets.

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## Introduction

Fibromyalgia and complex regional pain syndrome (CRPS) share many features. Fibromyalgia was formerly known as fibrositis syndrome, a term that implied a notable contribution of peripheral inflammation to the condition.[1,2] CRPS was also initially considered to have an inflammatory origin.[3,4] However, understanding of fibromyalgia and CRPS has long since moved away from those early concepts, and these two pain syndromes are now considered to be primarily centrally driven.

Changes in several brain regions (including the middle cingulate, posterior insula, dorsolateral prefrontal cortex and parietal lobe) are independently linked to both CRPS and fibromyalgia, and are seen as possible drivers of both conditions.[5] Accordingly, current attention is focused on the role of abnormal neurophysiological processes within the brain and spinal cord in the pathogenesis of fibromyalgia and CRPS.[6] For example, substantial evidence suggests that central sensitization (the mechanism whereby normally non-noxious stimuli, such as gentle touch or movement, can stimulate low-threshold mechanoreceptors and so cause pain[7]) is a driving pathophysiological mechanism in both fibromyalgia and CRPS.[6–8] However, embedded within this abnormal central neurophysiology are a number of important peripheral inflammatory mechanisms, collectively termed neurogenic (as opposed to classic) neuroinflammation. Investigation of the role of neurogenic neuroinflammation in fibromyalgia and CRPS might contribute to improved understanding of the fundamental mechanisms leading to these enigmatic disorders, as well as to the identification of new therapeutic targets. These advances could help to improve the management of affected patients, through reduction of symptoms such as peripheral swelling, dysaesthesia and local pain. Ultimately, however, modulation of the central driving mechanisms will have the most profound effect on all symptoms of fibromyalgia and CRPS, both central and peripheral.

This Review summarizes observations regarding the neurogenic neuroinflammatory mechanisms that contribute to fibromyalgia and CRPS, and places them in the context of what is currently known about the overall pathophysiology of these two disorders. The central nervous system pathways implicated in fibromyalgia and CRPS are not described in detail, as several relevant reviews have already addressed this aspect of the pathophysiology of fibromyalgia and CRPS.[9,10]

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The author declares no competing interests.

## Pathophysiology

### Central mechanisms

In patients with fibromyalgia, descending pathways from the forebrain and midbrain modulate the sensitivity of deep second-order cells of the dorsal horn (which project to central pain-related regions) via both opioidergic and 5-hydroxytryptaminergic-noradrenergic pathways.[11] The opioidergic pathways seem to function normally,[12] whereas the function of 5-hydroxytryptaminergic-noradrenergic pathways is attenuated[13] in many patients with fibromyalgia. In turn, these midbrain regulatory pathways seem to be modulated by activity in the anterior cingulate cortex and the insula. Connectivity between the default-mode network and the insula is increased[14] and connectivity of the default-mode network with

**Key points**

- Fibromyalgia and complex regional pain syndrome (CRPS) have distinct clinical phenotypes but share features such as pain, allodynia and peripheral dysaesthesia
- Factors involving the brain and spinal cord lead to central sensitization, which has a dominant role in both disorders
- Neurogenic inflammation, resulting from the release of proinflammatory neuropeptides from C-fibres, is also prominent in both disorders and contributes to allodynia, tissue swelling and dysaesthesia
- Neurogenic inflammation involves interactions of the innate immune system with the peripheral and central nervous systems of patients with fibromyalgia or CRPS
- Although the pathogenesis of both fibromyalgia and CRPS is dominated by central mechanisms, components of neurogenic neuroinflammation might be useful therapeutic targets in patients with these disorders

other pain-inhibitory regions is decreased.[15] Moreover, glutamate levels are elevated in the cerebrospinal fluid (CSF)[16] and the posterior insula[17] of patients with fibromyalgia. Treatment with pregabalin[18] and memantine[19] causes lowering of glutamate levels in the insula, which correlates with a reduction in pain levels in patients with fibromyalgia. These observations imply that processes originating in the brain are critically important in influencing pain in fibromyalgia. However, along with the central factors involved in the pathophysiology of fibromyalgia, affected patients also show increased activity in the sympathetic nervous system[20] and altered function of the neuroendocrine axis,[6,21] which can independently lead to many further symptoms. Of note, many of the comorbid painful conditions associated with fibromyalgia are regional pain disorders in their own right, such as temporomandibular joint pain, pelvic or menstrual pain, and regional pain in the arm or low back.[22] These conditions can often have severe symptoms.

Although some evidence suggests that dysregulation of the autonomic nervous system is present in patients with CRPS, its contribution to key clinical features of CRPS is today considered far less important than it once was.[23] By contrast, central mechanisms seem to predominate, and not only affect the sensory pathways linked to pain but also result in neuroplastic effects that cause changes in sensory mapping and motor function.[24–26] However, the pathophysiology of CRPS is poorly defined. Although CRPS usually seems to be a highly localized condition, the cause of this localization of the manifestations of CRPS remains unclear. Clinical evidence of extensive regional or widespread allodynia is commonly found in patients with CRPS, and not just involving the symptomatic area (G.L., personal observations). Lowering of the pain threshold in a hemilateral distribution can also occur in patients with CRPS,[27] which might suggest either that the severe pain experienced in involved areas induces dysfunction of the descending noxious inhibitory pathways, resulting in widespread allodynia, or that this abnormality is part of the pathophysiology of CRPS in the first place. The dysfunction of descending inhibitory pathway that occurs in fibromyalgia is, therefore, probably also present in CRPS, although the evidence for its presence in CRPS is more limited than that for fibromyalgia.

**Box 1** | Neuroactive substances

- Neuropeptides are just one of several classes of neuroactive substances, which can include steroids, growth factors, eicosanoids and amino-acid transmitters
- Neuropeptides are secreted from neuronal cells; they generally facilitate communication between neighbouring neurons
- Neuropeptides are divided into families of molecules encoded by similar or identical genes; many neuropeptides are expressed as large precursor molecules that undergo post-translational processing to result in several different small proteins
- Over 100 different neuropeptides exist in the mammalian nervous system; their actions include analgesia, reward, food intake, metabolism, reproduction, learning, memory, and social behaviours[139]

### Peripheral mechanisms

In healthy individuals, a triple response (reddening of the stimulation site, surrounding erythema, and plasma extravasation resulting in a raised weal) occurs after either mechanical[28] or chemical (for instance application of capsaicin) stimulation of the skin.[29] This response is now termed neurogenic inflammation, and is caused by the release of proinflammatory peptides from the peripheral nerve endings of peptidergic C-fibres, a key neuronal type involved in nociception.[30,31] Exacerbation of these neuroinflammatory mechanisms is important in the early stages of both CRPS and fibromyalgia, and can persist over time to contribute to ongoing key symptoms in each disorder. These mechanisms are discussed in detail below.

After activation by a nociceptive stimulus, C-fibres not only transmit action potentials to the spinal cord from the periphery, but importantly can also transmit antidromically (that is, against the normal direction of propagation) from junction points back to the periphery.[32] A number of neuropeptides (Box 1), particularly substance P, calcitonin gene related peptide (CGRP) and neurokinin A, are released after stimulus–induced antidromic firing of C-fibres initiated either by axonal or dorsal root reflexes (Figure 1). Many other neuropeptides are also released, including adrenomedullin, neurokinin B, vasoactive intestinal peptide, neuropeptide Y and gastrin-releasing peptide. These neuropeptides increase skin blood flow, vascular permeability and egress of polymorphonuclear leukocytes, key features of neurogenic inflammation. CGRP (which acts via CGRP1 receptors) is the main transmitter that causes neurogenic vasodilatation of arterioles, owing to its actions on vascular smooth muscle and endothelial cells.[32] CGRP also increases sweat gland activation and promotes hair growth, features often seen in CRPS.[33] Substance P and neurokinin A act on neurokinin A1 receptors to increase vascular permeability.[32] Substance P and CGRP directly attract and activate cell types involved in both innate (mast cells, keratinocytes, dendritic cells) and adaptive (T lymphocytes) immunity.[32] Mast cells are located adjacent to both sensory neurons and blood vessels, and their activation leads to

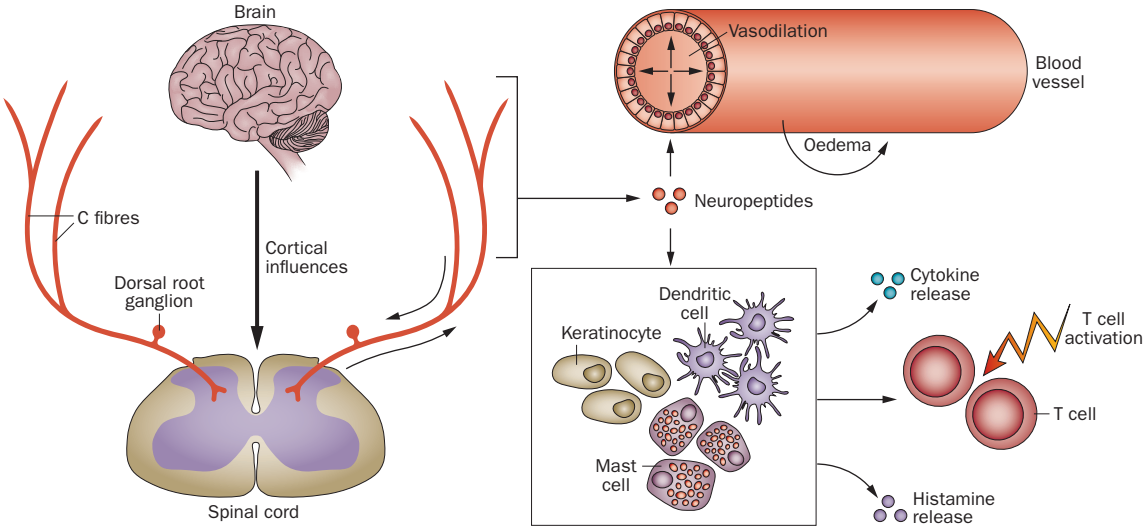


**Figure 1** | Central and peripheral effects associated with release of neuropeptides by terminal C-fibres. Left panel: C-fibres transmit nociceptive input to the outer laminae of the spinal cord, where they interact with second-order neurons. These interactions are modulated by influences emanating from the brain and brain stem. Right panel: The C-fibres release neuropeptides, such as substance P, as part of an axonal reflex in peripheral tissues. These neuropeptides act on adjacent blood vessels and cells (including immune-related cells) to cause vasodilatation, oedema resulting from fluid extravasation, and activation of innate and humoral responses.

degranulation and release of several additional neuroactive and vasoactive substances, including bradykinin, histamine, prostaglandins, TNF, vascular endothelial growth factor and 5-hydroxytryptamine. Many of these substances, such as histamine and TNF, in turn sensitize other nearby nociceptive terminals, such as Aδ myelinated fibres, resulting in further amplification of inflammatory changes (comprising vasodilatation, tissue swelling and pain) in the affected site.[33] Other neuropeptides, such as the potent vasoconstrictor endothelin-1 (ET-1)—which is mainly secreted from inflammatory cells and keratinocytes, the predominant cell type in the epidermis—can also contribute to sensitization of primary afferent neurons, although in many cases the precise role of these neuropeptides in neurogenic inflammation remains unclear.

Neurogenic inflammation, therefore, results from the effects of certain neuropeptides on peripheral blood vessels, other sensory neural structures, and regional innate immune cells. Responses of these cells include secretion of cytokines such as TNF that in turn have immune and inflammatory effects both locally and systemically. Cytokines, in contrast to neuropeptides, are released by a variety of cells, including immune cells, and have actions on a variety of other cells. The sympathetic nervous system interacts with this process through upregulation of α-adrenergic receptors in local inflammation, and also through as yet poorly characterized changes in central mechanisms.[34]

## Potential triggering events

Peripheral nociceptive input from ischaemia–reperfusion injury is noted to be a trigger of CRPS.[35–37] Although conjectural, perhaps in patients with CRPS an initial trauma to a body part causes an abnormal response in a neural pathway involving this brain–spinal cord–peripheral region, and the subsequent excessive activation of neurogenic neuroinflammation might be attributable to an intrinsic vulnerability of the pain-modulatory pathways. Trauma is also a common trigger of fibromyalgia, but the regional effects are less intense than in CRPS, and the pain and tenderness are more widespread. However, considerable evidence shows that these widespread changes occur on a background of dysfunctional descending nociceptive pathways.[38,39]

The evidence for psychological predisposition to fibromyalgia or CRPS is limited. However, a number of psychological factors modulate fibromyalgia symptoms.[40] Among these, catastrophizing has been linked to increased symptoms and neuroimaging changes.[41] Again, in a similar fashion to fibromyalgia, although no specific personality type or single psychological factor has been clearly identified as a predictor of CRPS,[42] both conditions are associated with high levels of stress, poor coping skills and thinking styles such as catastrophizing. Of note, patients with fibromyalgia or CRPS often report increased exposure to stressful life events.[43–46] Factors that exacerbate stress, such as anxiety, also seem to have a role in the clinical features of CRPS.[47] Abnormal reactivity to stress would act through central mechanisms. In both syndromes, genetic factors are also probably important.[48,49]

## Clinical features of fibromyalgia

Clinical features that probably relate to neurogenic inflammation in patients with fibromyalgia include swelling in peripheral tissues, reticular skin discolouration (livedo reticularis), dermatographia, cutaneous dysaesthesia and notable allodynia (Figure 2), which are discussed in detail below.

Cutaneous vascular-related phenomena that might be relevant to neurogenic inflammation include cold-induced vasospasm and Raynaud phenomenon, which

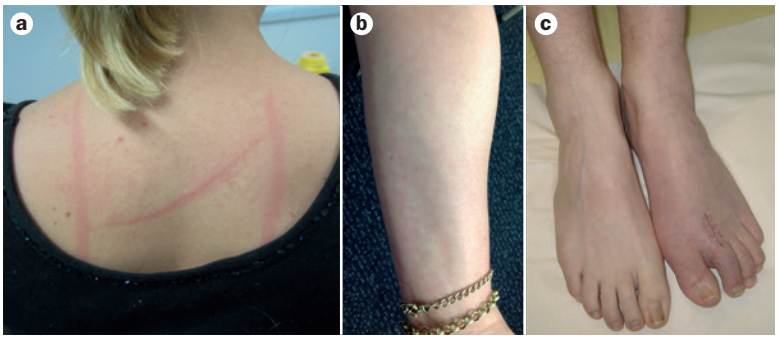


**Figure 2** | Clinical features of neurogenic inflammation in fibromyalgia and complex regional pain syndrome. **a** | Dermatographia elicited after gentle stroking of skin in a patient with fibromyalgia. **b** | Reticular skin discolouration in forearm of patient with fibromyalgia. **c** | Redness, swelling and allodynia of the left foot and ankle in a patient who developed complex regional pain syndrome after undergoing surgery for a metatarsal bone fracture.

are seen in ≤40% of patients with fibromyalgia (compared to <5% of healthy controls).[50–53] Reticular skin discolouration and livedo reticularis of varying severity occur in up to 64% of patients with fibromyalgia.[53,54] Many have dermatographia (also termed reactive hyperaemia), characterized by an exaggerated flare in the skin surrounding a mechanical stimulation site.[55] Additionally, patients often report local tissue swelling or fluid retention, which is a consequence of plasma extravasation;[56,57] in one study, 73% of patients with fibromyalgia had self-reported swelling versus 2% of healthy controls ($n = 60$ per group; $P < 0.001$).[58] Although swelling is commonly reported by patients with fibromyalgia, no studies have objectively assessed the prevalence of this clinical feature.

One study compared 50 patients with fibromyalgia (25 with Raynaud phenomenon, livedo reticularis, or both, and 25 without these manifestations) and 25 healthy control individuals. Levels of fibronectin, a marker of endothelial activation, were significantly higher in the patients who had fibromyalgia and Raynaud phenomenon, livedo reticularis, or both, than in the other two groups ($P < 0.0001$ for both comparisons).[53] Endothelial dysfunction in patients with fibromyalgia can also be influenced by sympathetic nervous system dysfunction (discussed below).

Neurogenic flare (that is, mechanically induced or capsaicin-induced reflex vasodilatation) is increased in patients with fibromyalgia compared to unaffected controls, and the extent of allodynia correlates positively with the severity of the skin flare.[59] Skin flare responses in patients with fibromyalgia are also closely correlated with slow-wave sleep deprivation, increased fatigue and a decreased pain threshold, which are all key features of fibromyalgia.[60]

The observed increase in deposition of albumin and IgG at the dermoepidermal junction in patients with fibromyalgia is also probably due to plasma extravasation from blood vessels as part of neurogenic inflammation.[61,62] This notion is supported by studies showing a correlation between the percentage of damaged or degranulated mast cells and the extent of IgG deposition in the dermis and vessel walls.[63,64] Mast cell numbers are increased by severalfold in the skin of patients with fibromyalgia, which is consistent with induction and activation of mast cells by neurogenic processes.[65]

In summary, a number of observations in the literature (albeit derived from small, selective, cross-sectional and comparative studies) present a consistent picture suggesting that neuroinflammatory mechanisms do contribute to specific clinical features of fibromyalgia. Larger, longitudinal studies using improved methods of assessing neurogenic inflammation (such as skin blister fluid analysis) are now required to characterize the components and relative importance of this process in fibromyalgia.

## Clinical features of CRPS

Neurogenic inflammation—comprising tissue swelling, vasomotor changes and marked allodynia—also contributes substantially to the clinical features of CRPS.[33] Indeed, these features make CRPS the most readily clinically detected of all chronic pain syndromes. Inflammatory features of CRPS are especially prominent early in the disease course, particularly the first 6 months. By contrast, in fibromyalgia, inflammation-related symptoms tend to fluctuate over long periods of time. Levels of osteoprotegerin (OPG) are also elevated in the early phase of CRPS, indicative of acute effects on bone remodelling.[66] The common and prominent CRPS features of bone marrow oedema and osteopenia are also probably related to neurogenic inflammation, through secretion of neuropeptides such as OPG. Additionally, late clinical features, such as visceral pain, rashes, skin ulceration and fibrosis of palmar aponeuroses and joint capsules might also relate to persistent neurogenic inflammation in CRPS.[44,67,68]

About 80% of patients with CRPS exhibit an increased skin temperature during the first 6 months of the disorder.[69] The accompanying reddish discolouration of the involved region is likely to relate to the vasodilatatory effects of neuropeptides such as CRGP. In the other 20% of patients, the involved regions are cold and have bluish discolouration at disease onset; these effects might be mediated by vasoconstrictive neuropeptides, such as ET-l.[33] Increased sweating occurs in up to 50% of patients with CRPS and increased local hair growth in about 15%, both of which can be caused by neuropeptides such as CRGP.[33]

Reflex vasodilation is greatly increased in both involved and non-involved limbs of CRPS patients; however, protein extravasation is limited to the affected side.[70] Clinical features that probably relate to neurogenic inflammation in patients with CRPS include variable and often considerable tissue swelling, vasomotor changes, trophic changes (that is, of the bone, hair, nails and skin), and notable allodynia of the involved tissues (Figure 1, Table 1).

## Factors involved in neuroinflammation

### Glial cells

Astrocytes and microglia, collectively termed glia, are implicated in chronic pain.[71] At the level of the spinal

**Table 1** | Clinical features of fibromyalgia and CRPS associated with neurogenic neuroinflammation

| Study | Feature | Neuropeptide-related mechanism |
|---|---|---|
| Chiu *et al.* (2012)[32] | Swelling | Increased vascular permeability |
| Chiu *et al.* (2012)[32]<br>Birklein & Schmelz (2008)[33] | Vasomotor changes, dermatographia, reticular skin discolouration, skin colour and temperature changes | Vasodilatation* and vasoconstriction‡ |
| Birklein & Schmelz (2008)[38]<br>Herbert & Holzer (2002)[62] | Allodynia | Sensitization of nociceptors |
| Uceyler *et al.* (2007)[97] | Cutaneous dysaesthesia, numbness, pins and needles sensation | Structural effects on C-fibres |
| Kramer *et al.* (2014)[66] | Osteopenia (in CRPS) | Abnormal bone remodelling |
| Birklein & Schmelz (2008)[33] | Increased hair or nail growth (in CRPS) | High local neuropeptide levels |

*From Chiu *et al.*[32] ‡From Birklein & Schmelz.[33] Abbreviation: CRPS, complex regional pain syndrome.

cord, activation of peptidergic primary afferent C-fibres leads to the release of various neurotransmitters and neuropeptides, including glutamate, substance P, CGRP, brain-derived neurotrophic factor (BDNF), $CX_3CL1$ ($CX_3$ chemokine ligand 1, also known as fractalkine) and ATP.[72] Their receptors are present on nearby resident innate immune cells within the central nervous system, microglia and astrocytes.[72] For instance, expression of Toll-like receptor 4 (TLR4) is upregulated in microglia after activation.[71] Upregulation of TLR4 in turn increases production of nitric oxide, prostaglandins, leukotriene, nerve growth factor (NGF), excitatory amino acids and neurotoxic superoxides.[73,74] In addition, activated microglia and astrocytes release proinflammatory cytokines, such as IL-1, IL-6 and TNF.[71,75] This process is termed neuroinflammation.[72]

The most common triggers of neuroinflammation include infectious micro-organisms, autoimmunity and toxins; the resultant activation of immune cells, vascular cells and neurons is linked in a tightly knit manner.[72] However, augmented neuronal activity itself can trigger neuroinflammation in peripheral tissues.[32] Other triggers include psychological stress, and in this setting the term 'neurogenic' (as opposed to 'classic') neuroinflammation has been proposed.[72] Thus, the nervous system can drive neurogenic neuroinflammation independently of the presence of external noxious triggers. This neurogenically driven cascade of events seems to be associated with many of the clinical features seen in patients with both fibromyalgia and CRPS.

### Neuropeptides in fibromyalgia

Substance P levels are markedly elevated in the CSF of patients with fibromyalgia.[76,77] CSF levels of BDNF and NGF are also elevated,[78,79] but studies of other neuropeptides are limited.[80] Substance P and other neuropeptides are widely distributed in the brain, and high levels of these neuropeptides are found in regions that are specific to regulating emotion (hypothalamus, amygdala, and the periaqueductal grey).[81] The cell bodies of C-fibres in dorsal root ganglia also produce neuropeptides.

Psychological factors, such as stress, probably initiate the cascade of events leading to the elevated levels of substance P in C-fibre bodies within dorsal root ganglia. Substance P is fundamental to an evolutionarily conserved, whole-organism stress response.[82] A study of combat veterans with post-traumatic stress disorder showed that their basal levels of substance P in the CSF were elevated, and that subsequent release of substance P was increased by psychological stress.[83] Psychological factors such as stress are the probable initiators of increased production of a variety of neuropeptides in the dorsal horn of the spinal cord, the CSF and in the nerves and tissues. Elevated tissue levels of neuropeptides subsequently contribute to many of the characteristic clinical features of fibromyalgia, as indicated above, and elevated central levels contribute to central sensitization.[7]

The evidence suggests that small-fibre function and structure are impaired in patients with long-standing fibromyalgia compared to healthy controls, and that numbers of nonmyelinated fibres are reduced in the skin of affected patients.[84–87] Electron microscopy shows abnormalities of nonmyelinated fibres and associated Schwann cells,[88] and these changes are also observed in paediatric patients with fibromyalgia.[89] Microneurography shows that the majority of patients with fibromyalgia have structurally abnormal C-fibre nociceptors.[90] The relationship between small-fibre function and C-fibre neurogenic inflammation needs to be clarified, but together these changes might explain the high rates of dysaesthesia and other sensory symptoms in patients with fibromyalgia.[91]

### Neuropeptides in CRPS

Increased serum levels of substance P and CGRP occur in CRPS.[92] Plasma extravasation is seen in involved tissues from patients with CRPS on scintigraphy studies using $^{111}$In-labelled IgG as a marker of increased vascular permeability.[93] Electrical stimulation of peptidergic C-fibres in clinically involved, but not control (uninvolved) skin, causes substance-P-related plasma protein extravasation.[70]

Epidemiological evidence indicates that disorders involving abnormalities of neuropeptides in their pathophysiology (such as asthma and migraine[94]) are linked to CRPS.[95] Additionally, CRPS is associated with the use of angiotensin-converting enzyme inhibitors, which are involved in the metabolism of neuropeptides.[96] As observed in fibromyalgia, small-fibre changes affecting

both C-fibres and Aδ fibres are present in CRPS[67,97,98] and are associated with a proinflammatory cytokine profile.[97]

### Cytokines in fibromyalgia

In addition to secretion of neuropeptides, activated polymodal C-fibres also secrete cytokines.[32] Proinflammatory cytokines can cause sensitization of peripheral neurons through upregulation of responsiveness to nitric oxide and prostaglandin $E_2$ and might, therefore, contribute to fibromyalgia symptoms. Substance P, glutamate and BDNF can also activate glial cells to release proinflammatory cytokines and a variety of neuropeptides (see above), all of which can exacerbate pain amplification.[71] Nociceptive neurons have close links to the immune system, and many molecules involved in tissue damage recognition pathways are expressed on both immune cells and neurons.[32]

The actions of various cytokines have been postulated to link to particular clinical features of fibromyalgia.[99] Cytokines have effects on the hypothalamic–pituitary–adrenal axis, the sympathetic nervous system and T lymphocytes, which in turn might be associated with fibromyalgia.[100] Studies of cytokine levels in patients with fibromyalgia suggest that levels of the proinflammatory cytokines IL-1, IL-6 and IL-8 are elevated, whereas TNF levels are normal, and levels of the anti-inflammatory cytokines IL-4 and IL-10 are unchanged or reduced.[101–103] However, many of these studies have methodological problems, such as small sample sizes, heterogeneous selection criteria, differing assay techniques, lack of appropriate control groups, and the failure to account for the effects of comorbid conditions (such as obesity) that affect cytokine levels.[101–103] A study that did account for many of these potential confounders, conducted in 707 patients with chronic multisite musculoskeletal pain, provided evidence of an increased innate immune response. Specifically, chronic pain was more strongly associated with lipopolysaccharide–stimulated proinflammatory cytokines (particularly IFN-γ and TNF) than with anti-inflammatory cytokines.[102] This proinflammatory cytokine profile might promote central sensitization.[102]

The source of the increased plasma or serum levels of cytokines in fibromyalgia is unclear. Their presence could reflect peripheral production by activated polymodal C-fibres or neuropeptide stimulation of immune cells in peripheral tissues. Alternatively (or additionally), these cytokines might be derived from activated glial cells in the central nervous system. The finding of elevated levels of IL-8 in the CSF of patients with fibromyalgia supports this idea.[104]

### Cytokines in CRPS

Peripheral trauma itself, in the absence of clinical CRPS, causes release of NGF and cytokines that can activate and sensitize nociceptors.[33] Levels of proinflammatory cytokines, such as TNF and IL-6, are increased in suction-induced blister fluids[105–107] and blood[108] from patients with CRPS. Moreover, the expression and levels of anti-inflammatory cytokines such as IL-4 and IL-10 are reduced.[33,109] Patients with CRPS also show elevated CSF levels of certain proinflammatory cytokines (such as IL-1β and IL-6) but not TNF. The quality of the evidence varies in studies of inflammatory markers detected in blood and blister fluid in acute and chronic CRPS.[110] However, in general, CRPS is associated with the presence of a proinflammatory cytokine profile in the blood, blister fluid and CSF. Levels of proinflammatory cytokines are also elevated in the affected limbs of patients with CRPS,[111] and these changes are amplified after transcutaneous electrical stimulation, a feature that is considered to indicate the presence of neurogenic inflammation.[33]

In animal models of CRPS, skin temperature differences, oedema and pain behaviours can be reversed by administration of neurokinin A1 antagonists, neuropeptide-blocking agents,[112] and glucocorticoids.[113] These interventions modulate a number of released cytokines. Further, in humans with early CRPS the cutaneous innate immune system is activated, as shown by exaggerated sensory and sympathetic signalling, activation and proliferation of keratinocytes and mast cells, inflammatory mediator release, and pain.[114] By contrast, in patients with chronic CRPS, keratinocyte proliferation is reduced, resulting in epidermal thinning, and mast cell numbers are normal.[114] Antibodies to $\beta_2$ adrenergic and M2 muscarinic receptors on neurons are found in about 35% of patients with CRPS, but the clinical relevance of these findings remains unclear.[115] A working model of neurogenic inflammation in CRPS traditionally starts with injury to peripheral nerves, followed by activation of peripheral neuroimmune mechanisms. However, as is seen in fibromyalgia, it is likely that central mechanisms subsequently come to dominate the pathophysiology of CRPS.[34]

## The sympathetic nervous system

The sympathetic nervous system contributes to the clinical features of both fibromyalgia and CRPS.[20,44] Indeed, many previous treatments were based on this association.[116,117] Patients with fibromyalgia show high levels of emotional distress and reduced heart rate variability, indicating ongoing sympathetic hyperactivity. Other studies show that noradrenaline injections exacerbate fibromyalgia-related pain.[118,119] Similar observations have been reported in patients with CRPS; for instance, increased heart rate, reduced heart rate variability, and inability to protect cardiac output during orthostatic stress.[120] Patients with CRPS also show hyperresponsiveness to a vasoconstrictive stimulus (infusion of increasing concentrations of noradrenaline into the dorsal hand vein).[121]

Important interactions between the sympathetic nervous system and the innate immune system occur via dendritic cells, which are modulated by adrenoreceptors.[122] Patients with CRPS show increased levels of α-adrenoreceptors in skin biopsies.[123] Elevated levels of proinflammatory IL-8 but not IL-1β have been found in the CSF of patients with fibromyalgia.[104] These observations are consistent with glial cell activation and might also be related to increased sympathetic activity. However, the exact influence of the sympathetic nervous

**Table 2** | Potential strategies for targeting neurogenic neuroinflammation in fibromyalgia and CRPS

| Neurophysiological target | Intervention | Comments |
|---|---|---|
| Stress system activation | Education, exercise, psychological strategies | Core management approach (modulate central drivers) |
| Sympathetic nervous system activation | α-Adrenergic blockers* | Decrease sympathetic input |
| Central (brain) nociceptive pathway modulation | Gabapentinoids, memantine* | Decrease neuropeptide release or glutamate levels, or both |
| Descending pain-modulation pathways in spinal cord | 5-hydroxytryptamine–noradrenaline reuptake inhibitors* | Decrease dorsal horn sensitization |
| Spinal cord sensitization | *N*-methyl-D-aspartate receptor inhibitors (for example, ketamine)* | Decrease dorsal horn sensitization |
| Central inflammatory mechanisms | Low-dose naltrexone* | Downregulate activated glial cells |
| Peripheral (± central) inflammatory mechanisms | Glucocorticoids, intravenous immunoglobulin, cytokine inhibitors* | Modulate neuroinflammatory processes |

*Only weak evidence of benefit. Abbreviation: CRPS, complex regional pain syndrome.

system on neuroinflammation in fibromyalgia and CRPS remains unclear.[44]

## Therapeutic implications

Neurogenic neuroinflammation clearly comprises a complex set of interacting components with many potentially targetable feedback loops. However, similar to the inflammation occurring in rheumatoid arthritis, the overall process of neurogenic neuroinflammation can probably be downregulated by targeting elements at several levels (Table 2), the most relevant of which are discussed below.

Some evidence suggests that emotional distress and activation of the stress system are present in both fibromyalgia and CRPS.[47,124] The stress response probably drives the peripheral neurogenic process, and can be targeted through education, exercise and psychological strategies.[6] Decreasing sympathetic nervous system inputs through pharmacological interventions, such as propranolol or phenoxybenzamine, might also benefit some patients;[125,126] further strategies to modulate interactions between stress and events upstream of the spinal cord include targeting central (brain and spinal cord) neurotransmitters using drugs such as the gabapentinoids, and modulating descending pain control pathways using drugs such as 5-hydroxytryptamine–noradrenaline reuptake inhibitors.[6] Suppression of neurogenic inflammation does not seem likely to be achieved with NSAIDs. Glucocorticoids have been reported to be beneficial in early CRPS, but the available evidence is of poor quality.[127] Neither glucocorticoids nor NSAIDs are proven to be effective in fibromyalgia.[128]

No clinically available drugs that target neuropeptides are effective in the treatment of either fibromyalgia or CRPS.[129] Biologic drugs that target inflammatory cytokines, such as TNF, have not been proven to be beneficial.[99,127] Intravenous or subcutaneous polyvalent IgG therapy has been proposed for both fibromyalgia and CRPS,[130,131] but convincing evidence of its efficacy from randomized trials is lacking.

A number of drugs target central mechanisms in fibromyalgia and CRPS. Naltrexone is a μ-opioid receptor antagonist that can cross the blood–brain barrier and suppress glial cell activation. At low doses, this agent increases TLR4 levels but does not inhibit other opioid receptors in the central nervous system and, consequently, endogenous antinociceptive pathways involving μ-receptors continue to function. In animal models, low-dose naltrexone can reverse neural pain from chronic constrictive nerve injury.[132] Low-dose naltrexone might reduce symptom severity in patients with fibromyalgia and CRPS,[133] but these results remain to be confirmed. Other attenuators of glial cell activation include ibudilast, which has shown some benefit in treating pain in CRPS,[134] and minocycline, which has shown benefits in animal models that might translate to patients with fibromyalgia.[135] Drugs such as ketamine that target *N*-methyl-D-aspartate receptors (which are present in activated microglia, as well as in dorsal horn transmission neurons) might also downregulate symptoms due to neuroinflammation in patients with fibromyalgia or CRPS, but no adequate trial evidence exists to support this approach.[136,137] Other drugs that target glutamate within the brain and spinal cord, such as memantine, might also downregulate neurogenic inflammation in fibromyalgia and CRPS.[19,138]

## Conclusions

Neurogenic neuroinflammation is a key pathophysiological mechanism in both fibromyalgia and CRPS. However, improved knowledge of this process is required to further understand its contribution to the clinical features of these two disorders, and specifically to determine whether neurogenic neuroinflammation is an epiphenomenon or a stress-driven pathophysiological mechanism in its own right. The effect of highly specific targeting of various components of neurogenic neuroinflammation is a current focus of clinical research. This work is expected to lead to improved explanations of the links between central factors—including stress—and peripheral end-organ effects that might be associated with activation of nociceptive pathways, and further contribute to the central sensitization that characterizes both fibromyalgia and CRPS.

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