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

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[Overview of Reviews]

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

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ABSTRACT

Background

Complex regional pain syndrome (CRPS) is a chronic pain condition that usually occurs in a limb following trauma or surgery. It is characterised by persisting pain that is disproportionate in magnitude or duration to the typical course of pain after similar injury. There is currently no consensus regarding the optimal management of CRPS, although a broad range of interventions have been described and are commonly used. This is the first update of the original Cochrane review published in Issue 4, 2013.

Objectives

To summarise the evidence from Cochrane and non-Cochrane systematic reviews of the efficacy, effectiveness, and safety of any intervention used to reduce pain, disability, or both, in adults with CRPS.

Methods

We identified Cochrane reviews and non-Cochrane reviews through a systematic search of Ovid MEDLINE, Ovid Embase, Cochrane Database of Systematic Reviews, CINAHL, PEDro, LILACS and Epistemonikos from inception to October 2022, with no language restrictions. We included systematic reviews of randomised controlled trials that included adults (≥18 years) diagnosed with CRPS, using any diagnostic criteria.

Two overview authors independently assessed eligibility, extracted data, and assessed the quality of the reviews and certainty of the evidence using the AMSTAR 2 and GRADE tools respectively. We extracted data for the primary outcomes pain, disability and adverse events, and the secondary outcomes quality of life, emotional well-being, and participants' ratings of satisfaction or improvement with treatment.

Main results

We included six Cochrane and 13 non-Cochrane systematic reviews in the previous version of this overview and five Cochrane and 12 non-Cochrane reviews in the current version. Using the AMSTAR 2 tool, we judged Cochrane reviews to have higher methodological quality than

non-Cochrane reviews. The studies in the included reviews were typically small and mostly at high risk of bias or of low methodological quality. We found no high-certainty evidence for any comparison.

There was low-certainty evidence that bisphosphonates may reduce pain intensity post-intervention (standardised mean difference (SMD) -2.6, 95% confidence interval (CI) −1.8 to −3.4, P = 0.001; I^2 = 81%; 4 trials, n = 181) and moderate-certainty evidence that they are probably associated with increased adverse events of any nature (risk ratio (RR) 2.10, 95% CI 1.27 to 3.47; number needed to treat for an additional harmful outcome (NNTH) 4.6, 95% CI 2.4 to 168.0; 4 trials, n = 181).

There was moderate-certainty evidence that lidocaine local anaesthetic sympathetic blockade probably does not reduce pain intensity compared with placebo, and low-certainty evidence that it may not reduce pain intensity compared with ultrasound of the stellate ganglion. No effect size was reported for either comparison.

There was low-certainty evidence that topical dimethyl sulfoxide may not reduce pain intensity compared with oral N-acetylcysteine, but no effect size was reported.

There was low-certainty evidence that continuous bupivacaine brachial plexus block may reduce pain intensity compared with continuous bupivacaine stellate ganglion block, but no effect size was reported.

For a wide range of other commonly used interventions, the certainty in the evidence was very low and provides insufficient evidence to either support or refute their use. Comparisons with low- and very low-certainty evidence should be treated with substantial caution. We did not identify any RCT evidence for routinely used pharmacological interventions for CRPS such as tricyclic antidepressants or opioids.

Authors' conclusions

Despite a considerable increase in included evidence compared with the previous version of this overview, we identified no high-certainty evidence for the effectiveness of any therapy for CRPS. Until larger, high-quality trials are undertaken, formulating an evidence-based approach to managing CRPS will remain difficult. Current non-Cochrane systematic reviews of interventions for CRPS are of low methodological quality and should not be relied upon to provide an accurate and comprehensive summary of the evidence.

PLAIN LANGUAGE SUMMARY

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

Key messages

There is a critical lack of high-quality evidence for the benefits and risks of most treatments for adults with complex regional pain syndrome (CRPS). Larger, well-designed studies and higher-quality reviews are needed to provide accurate evidence for benefits and risks of treatments for adults with CRPS.

What is complex regional pain syndrome?

CRPS is a disabling chronic pain condition. People with CRPS experience persistent pain, usually in the hands or feet, that is not proportionate in severity to any underlying injury. It often involves a variety of other symptoms in the affected body part such as swelling, discolouration, stiffness, weakness, and changes to skin quality.

What did we want to find out?

A broad range of therapies are used to treat CRPS. The effects of these therapies are summarised across a number of Cochrane and non-Cochrane reviews. Our aim was to combine the information from these reviews into one accessible document. We specifically wanted to find out which treatments are effective in reducing pain and disability in adults with CRPS. We also wanted to find out whether these treatments cause any unwanted effects.

What did we do?

We searched for Cochrane and non-Cochrane reviews in the medical literature using online databases, from their beginning to October 2011, in the previous version of this overview, and between October 2011 and October 2022 in the current version. We included reviews that evaluated any treatment aiming to reduce pain intensity and disability in adults with CRPS. We judged the quality of the included reviews and summarised their results. We also rated our confidence in the evidence included in the reviews, based on factors such as study methods and size.

What did we find?

We included six Cochrane and 13 non-Cochrane systematic reviews in the previous version of this overview and five Cochrane and 12 non-Cochrane reviews in the current version. These reviews included evidence relating to a large range of treatments, including drugs, surgical procedures, rehabilitation, and complementary and alternative therapies. For most treatments, there were only a small number of published studies and the quality of these studies was low. The review evidence suggests the following:

- Compared with placebo (or 'dummy') treatment, bisphosphonates (a class of medicines that slow down bone loss) may reduce pain intensity shortly after treatment, but they are probably associated with some side effects.
- Compared with a placebo (or sham) treatment, blocking the branches of the sympathetic nervous system with an anaesthetic probably does not reduce pain intensity.
- There may not be any differences in the pain-reducing effects of a topical cream called dimethyl sulfoxide (DMSO) and an amino acid supplement called N-acetyl cysteine, but it is unclear whether either treatment works at all.
- One type of nerve block, called a brachial plexus block, may reduce pain intensity more than another type of block, called a bupivacaine stellate ganglion block.

For the majority of the commonly used drug, surgical, rehabilitation, and complementary and alternative therapies for CRPS, we found only very low-quality evidence or no evidence at all. As a result, we cannot be certain about their effects on pain and disability in CRPS.

What are the limitations of the evidence?

All of the included non-Cochrane reviews were conducted in a way that affects the reliability of their findings. The studies included within both the Cochrane and non-Cochrane reviews had several limitations, particularly due to the small number of included participants. The results presented within this overview demonstrate unclear benefits and risks for most treatments for adults with CRPS.

How up-to-date is this evidence?

This overview updates our previous overview. The evidence is up-to-date to October 2022.

BACKGROUND

This is the first update of the original Cochrane review published in Issue 4, 2013.

Description of the condition

Complex regional pain syndrome (CRPS) is a chronic pain condition that usually occurs distally in a limb, in response to trauma or surgery (Birklein 2015; Bruehl 2015). It is characterised by persisting pain that is disproportionate in magnitude or duration to the typical course of pain after similar injury (Bruehl 2010; Marinus 2011). The diagnostic label of CRPS was introduced in the 1990s by the International Association for the Study of Pain (IASP) (Merskey 1994). Iterative revisions to improve specificity have resulted in the current 'Budapest criteria' (Harden 2010), presented in Table 1. CRPS encompasses a variety of previous diagnostic labels including reflex sympathetic dystrophy (RSD), reflex neurovascular dystrophy, Sudeck's atrophy, causalgia and algodystrophy or algoneurodystrophy. CRPS is classified as a chronic primary pain condition in the International Classification of Diseases-11 (ICD-11) (Treede 2019).

The predominant feature of CRPS is severe and persistent pain in the affected limb which is accompanied, at least initially, by clear autonomic and inflammatory changes (Birklein 2017; Bruehl 2015). People with CRPS may present with some or all of the following symptoms and signs: sensory disturbances; temperature change; abnormal patterns of sweating; swelling and oedema; reduced joint range of motion; movement abnormalities such as weakness, tremor or dystonia; trophic changes such as skin atrophy or altered hair and nail growth; localised osteoporotic changes (Bruehl 2010; de Mos 2009; Krämer 2014; Shipton 2009); and alterations in body perception or schema (Lewis 2007; Lotze 2007; Moseley 2006).

CRPS can be classified into two main diagnostic subtypes: type I, in which no peripheral nerve injury can be identified, and type II, in which symptoms are associated with discrete peripheral nerve damage (Bruehl 2015), although this distinction is not always easily made (Ott 2018). In 2021, the IASP CRPS Special Interest Group published a consensus proposal of diagnostic updates to be included in the ICD-11 (Goebel 2021). These updates aim to resolve ambiguities in the IASP CRPS diagnostic criteria and include two important changes to CRPS subtypes: (i) that diagnostic signs of CRPS II must extend beyond any identified damaged nerve territory and, as such, should no longer be classed as a neuropathic pain condition in accordance with current criteria; and (ii) the addition of a third formal CRPS subtype “CRPS with Remission of Some Features” for patients who were previously documented as having fulfilled an IASP diagnosis but who no longer display the signs and symptoms required to meet these criteria.

The underlying pathophysiological mechanisms of CRPS are incompletely understood. Contemporary theories propose complex contributions from multiple systems including aberrant inflammatory and immune responses (Birklein 2014; Goebel 2013; Parkitny 2013), altered sympathetic nervous system function (Knudsen 2019), central sensitisation of nociceptive pathways (Eisenberg 2005), brain changes (Azqueta-Gavaldon 2020; Lee 2022), and genetic factors (Herlyn 2010; Van Rooijen 2012).

The incidence of CRPS has been estimated at between 5.5 and 26.2 cases per 100,000 people annually. It is three to four times more common in women than in men and its incidence peaks at 50 to 70 years of age (de Mos 2007; Sandroni 2003). CRPS occurs most commonly following wrist fracture and, although rare, appears to occur spontaneously (de Mos 2007; de Mos 2008; Sandroni 2003). Data from higher methodological quality studies demonstrate a 3.7% to 14.0% incidence risk of CRPS within four months of wrist fracture (Rolls 2020). CRPS onset is most accurately predicted by early high pain intensity, irrespective of whether it develops after fracture (Moseley 2014) or after surgery (Bruehl 2022; Savaş 2018). Findings from studies investigating the clinical course of chronic CRPS are inconsistent but indicate that, in people with CRPS lasting 12 months or more, long-term outcomes are poor, with pain and motor dysfunction persisting beyond 12 months for 51% to 89% of patients (Johnson 2022).

CRPS has considerable societal and economic impacts. People with CRPS report that constant pain and functional decline lead to losses of identity, independence and integrity, and negatively affect personal relationships (Raja 2021). Between 30% to 40% of people working before the onset of CRPS do not return to work and, of those who do, between 27% to 35% return under reduced capacities (Johnson 2022). Limited data suggest that CRPS carries a substantial economic burden, with total individual annual healthcare costs increasing 2.17-fold after diagnosis (Elsamadicy 2018).

Description of the interventions

This overview includes systematic reviews of any intervention aimed at treating pain, disability or both in CRPS. In 2019, the European Pain Federation CRPS task force published standards to guide care (Goebel 2019), proposing three key elements for the treatment of CRPS: (i) pain management; (ii) physical and vocational rehabilitation; (iii) identifying and treating stress. A broad and varied range of interventions are used to manage one or all of these key elements in CRPS. These can be broadly grouped under pharmacotherapy (oral, intravenous or topical), interventional procedures, neuromodulation, rehabilitation, complementary and alternative therapies, and psychological therapies.

Oral, intravenous and topical pharmacotherapy

A variety of pharmacological interventions have been described for the treatment of CRPS and, in practice, combinations of these drugs are commonly used. Oral and intravenous pharmacological options can be divided into the following broad categories (Harden 2022; Mangnus 2022a):

- Anti-inflammatory therapies (e.g. non-steroidal anti-inflammatory drugs (NSAIDs) corticosteroids, cyclooxygenase-2 (Cox-2) inhibitors)
- Free radical scavengers (e.g. mannitol, vitamin C)
- Immunomodulators (e.g. tumour necrosis factor-α inhibitors, immunoglobulin)
- Anticonvulsants (e.g. pregabalin, gabapentin)
- Antidepressants and anxiolytics (e.g. amitriptyline, doxepin)
- Opioids (e.g. morphine, tramadol)
- N-methyl D-aspartate (NMDA) receptor antagonists (e.g. ketamine, memantine)
- Antihypertensives and α-adrenergic antagonists (e.g. clonidine, phentolamine)

- Bisphosphonates (e.g. pamidronate, alendronate)
- Calcitonin

Topical analgesics are medications applied to body surfaces such as skin or mucous membranes (Derry 2017a). These treatments are applied to the skin as creams, or made into patches or plasters and stuck to the skin at the site of the affected tissues. Topical analgesics may include lidocaine patches, and creams containing local anaesthetic, capsaicin or dimethyl sulphoxide (DMSO).

Interventional procedures

Interventional proceudres such as intravenous sympathetic nerve blocks involve the infusion of pharmacological agents while the affected limb is tourniqueted and may use a variety of agents, such as guanethidine, lidocaine or clonidine (Harden 2022). Blocking of sympathetic nervous activity may be achieved by injection of anaesthetic directly into sympathetic neural structures such as the stellate ganglion or the lumbar sympathetic chain, or alternatively, into the epidural space (Nelson 2006; Wie 2021). Sympathectomy involves the destruction of sympathetic neural pathways chemically, through the injection of agents such as alcohol or phenol, or surgically, through excision or electrocoagulation (Nelson 2006; Straube 2013).

Neuromodulation

Neuromodulation includes an array of invasive and non-invasive treatment approaches that aim to provide pain relief through targeted electrical stimulation of the nervous system (Knotkova 2021). Implanted spinal neuromodulation interventions involve the surgical implantation of electrodes into epidural space of the spinal cord or dorsal root ganglion (O'Connell 2021). Non-invasive forms of brain stimulation, such as transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) use electromagnetic coils and electrodes, respectively, to deliver electrical currents that modulate the neuronal excitability of underlying brain structures and associated neural networks (Knotkova 2021).

Rehabilitation

Both occupational and physiotherapy rehabilitation are frequently used to treat CRPS and these incorporate a variety of approaches, sometimes used in isolation, but more commonly delivered in a multimodal format that may include manual therapy, tactile desensitisation, electrotherapy (including transcutaneous electrical nerve stimulation (TENS)), sensory-motor training (including graded motor imagery and mirror therapy), therapeutic exercise and pain education (Miller 2019).

Complementary and alternative therapies

Complementary and alternative therapies are a broad set of healthcare practices that are not part of conventional medical care, and may have origins outside of Western practice (WHO 2023). Such approaches include acupuncture, Tai Chi and qigong (Urits 2021).

Psychological therapies

Psychological therapies include cognitive behavioural therapy (CBT), acceptance and commitment therapy (ACT), counselling and relaxation techniques (Harden 2022; Williams 2020), or exposure-based treatments (Vlaeyen 2012).

How the intervention might work

There are many possible therapeutic mechanisms for the broad range of potential interventions used to treat pain and disability in CRPS.

Oral, intravenous and topical pharmacotherapies aim to alter physiological pathways involved in the generation of pain, inflammation, peripheral and central sensitisation, abnormal sympathetic activity, motor disturbances or bone loss (Harden 2022; Mangnus 2022a).

Interventional procedures such as nerve blocks or sympathectomy are thought to reduce sympathetic symptoms by temporarily or permanently disrupting sympathetic nervous system output to the affected body area (Birklein 2017; Harden 2022).

Neuromodulation approaches, such as implanted spinal neuromodulation or non-invasive brain stimulation, seek to reduce pain by altering activity in areas of the central nervous system that are involved in the experience of pain (O'Connell 2018; O'Connell 2021).

Rehabilitation approaches typically include exercise regimes as well as passive techniques such as manual therapy, massage and various forms of electrotherapy to improve range of movement (ROM), strength, and functional use of the affected body part. CRPS-specific rehabilitation techniques aim to improve pain and function by altering cortical (brain) processing specific to the affected body part using strategies such as sensory-motor training, and tactile sensory discrimination training (Moseley 2012).

Complementary and alternative therapies are thought to reduce pain via a range of mechanisms. For acupuncture specifically, contemporary theories propose activation of endogenous opioid systems (Harris 2009) and alteration of brain activation patterns associated with pain processing (Scheffold 2015). Practices such as Tai Chi or qigoing may exert analgesic effects by improving musculoskeletal health and body awareness, and relaxation (Kong 2016).

Psychological therapies primarily aim to manage pain, distress and disability by addressing the cognitive, behavioural and/or emotional aspects of living with the condition. They may target unhelpful pain-related behaviours and beliefs by improving self-efficacy, self-management skills and psychological flexibility (Williams 2020). Exposure-based treatments, such as 'exposure in vivo', combine psychological theory and rehabilitation to reduce disability specifically by targeting pain-related fear (den Hollander 2022).

Why it is important to do this overview

There is no consensus regarding the optimal management of CRPS and a broad range of therapeutic interventions including pharmacological, interventional, psychological and rehabilitation treatments may be used clinically (Grieve 2019; Miller 2019). Several systematic reviews of interventions for CRPS have been published since the previous version of this overview (O'Connell 2013). The varied scope and methodology of these reviews may inhibit decision-makers' access to the evidence. Furthermore, information provided in current clinical guidelines from the Netherlands (Perez 2014), the UK (Goebel 2018), and US (Harden 2022) reflects both the evidence as well as pragmatic considerations such as country-

specific policies, access and healthcare pathways, and possibly the interests of key stakeholders. An updated single, accessible and rigorous summary of the evidence is required to support decision-making for patients, clinicians, and policymakers. This Cochrane overview aims to provide an updated critical summary of the systematic review evidence of all treatments for CRPS.

OBJECTIVES

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

METHODS

Criteria for considering reviews for inclusion

Types of reviews

We included all Cochrane reviews of randomised controlled trials (RCTs) that assessed the effects of any intervention used to reduce pain or disability in adults with CRPS. We also chose to consider non-Cochrane reviews as, given the broad range of available treatments, to exclude them might have provided an incomplete summary of the available evidence. We therefore included non-Cochrane systematic reviews where they covered interventions that were not covered by identified Cochrane reviews or where they were more up-to-date. To be included, any non-Cochrane review was required to achieve a judgement of 'Yes' on the third criterion on the AMSTAR tool for assessing the quality of systematic reviews (Shea 2007), that is, "Was a comprehensive literature search performed?". We considered this a minimum requirement for a review to be systematic.

Types of participants

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

Types of interventions

We included reviews of any intervention aimed at reducing pain, disability, or both, for CRPS.

Types of outcome measures

Primary outcomes

1. Pain intensity or severity, as measured using a visual analogue scale (VAS), numerical rating scale (NRS) or Likert scale.
2. Disability, measured through self-report scales or functional testing protocols.
3. Adverse events, including the number and nature of adverse event withdrawals and serious adverse events, where possible.

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

Secondary outcomes

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

We grouped outcomes into post-intervention (up to 1 month post-treatment), short-term (> 1 month to 3 months post-treatment), medium-term (> 3 months to 6 months post-treatment) and long-term periods (> 6 months post-treatment). Where reviews reported outcome data for multiple time points within a period, we included a single effect per time period, taking the effect measured closest to the beginning of the period for post-intervention, and closest to the end of the period for all other time periods.

Search methods for identification of reviews

Electronic searches

We searched electronic databases using a combination of controlled vocabulary (MeSH) and free-text terms. We incorporated search terms to target CRPS and systematic reviews but, because we wished to identify reviews that included any intervention, we did not include intervention-specific terms. We incorporated the BMJ Clinical Evidence search filter for systematic reviews. In the updated version of this overview, we searched Epistemonikos instead of the defunct DARE. For the previous and current versions, we searched the following databases:

- Ovid MEDLINE (1948 to 7 October 2022) (Appendix 1);
- Ovid Embase (1980 to 7 October 2022) (Appendix 2);
- Cochrane Database of Systematic Reviews Issue 10 of 12, October 2022 (Appendix 3);
- Database of Abstracts of Reviews of Effects (DARE) (Issue 4 2011) (Appendix 3);
- CINAHL (1982 October 2022) (Appendix 4);
- PEDro (1929 to October 2022) (Appendix 5);
- LILACS (All years to October 2022) (Appendix 6);
- Epistemonikos (October 2011 to 10 October 2022) (Appendix 7).

The search results by source are presented for the previous and current versions of this overview in Appendix 8.

Searching other sources

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

Language

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

Data collection and analysis

Selection of reviews

Two overview authors (NOC and BW in the original overview; and MCF and AGC, KMS, CB or NOC in this updated overview) independently screened the titles and abstracts of identified studies and excluded studies that were clearly not relevant. Where it was not clear from the abstract whether a study was relevant, we checked the full review to confirm its eligibility. Two overview authors (NOC and BW in the original overview; and MCF and AGC, KMS, CB or NOC in this updated overview) independently applied the selection criteria to the full papers of identified reviews. Disagreement between overview authors was resolved through discussion. Where resolution was not achieved, a third overview author (JHM) considered the study(ies) in question.

Data extraction and management

A pilot data extraction form was designed and piloted by three authors (MCF, AGC and NOC). Two overview authors (MCF and AGC, KMS, CB or NOC) independently extracted data using the finalised data extraction form. We resolved discrepancies by consensus. Where agreement could not be reached, a third overview author (JHM) considered the paper and we made a majority decision. The data extraction form included the following information:

- objectives of the review
- date of publication
- date of most recent search
- resources searched
- characteristics of the included participants (e.g. CRPS diagnostic criteria & subtypes)
- included interventions and comparators
- outcomes and time points assessed (primary and secondary)
- comparisons performed and meta-analysis details
- assessment of the risk of bias or methodological quality of the included evidence
- assessment of the certainty of included evidence

When data were presented in tabular or figure format, we extracted data from the included reviews. We planned to contact the authors of the reviews or the original study reports via email if the required information could not be extracted from the reports.

Assessment of methodological quality of included reviews

Two authors (MCF and AGC, KMS, CB or NOC) used the Assessing the Methodological Quality of Systematic Reviews (AMSTAR 2; second version of the original AMSTAR) tool (to judge the methodological quality of the included reviews (Shea 2017) (see Appendix 9). We applied this to both Cochrane and non-Cochrane reviews. For this review, we assessed all 16 AMSTAR 2 domains, but considered the following seven domains 'critical':

- protocol registered before the commencement of the review (item 2)
- adequacy of the literature search (item 4)
- justification for excluding individual studies (item 7)
- risk of bias from individual studies being included in the review (item 9)
- appropriateness of meta-analytical methods (item 11)
- consideration of risk of bias when interpreting the results of the review (item 13)
- assessment of the presence and likely impact of publication bias (item 15)

To rate the overall confidence in the results of a review, we considered the potential impact of an inadequate rating detected in critical and non-critical items using the following criteria (Shea 2017):

- High (no or one non-critical weakness): high confidence means that the systematic review provides an adequate and comprehensive summary of the results of the available studies that address the question of interest.
- Moderate (more than one non-critical weakness): moderate confidence means that the review has more than one weakness but no critical flaws, and may provide an accurate summary of the results of the available studies that were included in the review.
- Low (one critical flaw with or without non-critical weaknesses): low confidence means that the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.
- Critically low (more than one critical flaw with or without non-critical weaknesses): critically low confidence means that the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

We planned to downgrade the overall rating from moderate to low confidence where multiple non-critical weaknesses diminished confidence in the review.

Assessment of the risk of bias and certainty of the evidence in included reviews

Included reviews assessed the methodological quality and risk of bias of included studies in several ways. We used the judgements made by the authors of the original reviews regarding the risk of bias and methodological quality of evidence and have reported it critically within the context of our assessment of the quality of the review itself. When reviews did not use GRADE (Schünemann 2020) to assess the certainty in the evidence, two reviewers (MCF and NOC) conducted these assessments for each type of intervention, each diagnostic group (CRPS I and II), and each outcome domain. For narratively reported comparisons, we only conducted GRADE assessments for those that reported no between-group differences, or between-group differences with an effect size and measure of precision, or a statement regarding statistical significance.

We used the following to assign GRADE judgements:

- Serious study limitations: we downgraded once if less than 75% of studies were at low risk of bias across all risk of bias criteria.
- Inconsistency: we downgraded once if point estimates varied widely across studies, confidence intervals showed minimal or no overlap, statistical tests for heterogeneity were statistically significant, or the I^2 statistic was greater than 50%.
- Indirectness: we downgraded once if greater than 50% of participants were outside the target group.

- Imprecision: we downgraded once if there were fewer than 400 participants for continuous outcomes and fewer than 300 events for dichotomous data.
- 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 suspicion of publication bias.

When the Cochrane Risk of Bias (ROB) tool was used to assess serious study limitations, we considered trials with a single domain at high risk of bias as being at high overall risk of bias. When other methodological quality tools were used, we followed their scoring system to evaluate overall quality. When no tool was used to evaluate risk of bias or methodological quality, we downgraded the certainty of evidence since, in our judgement, an absence of information regarding bias or quality represents a clear source of uncertainty.

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. For imprecision, we retained one of the additional criteria used in the previous version of the overview (O'Connell 2013), by downgrading twice if the pooled sample size was < 50 participants per arm. Where conclusions were not made from a pooled analysis, the same rule was applied to the sample of the individual studies. We applied this criterion whether or not a positive result was reported for that intervention because, although small studies tend to produce positive results through publication biases, they may also return spurious negative results as a result of the play of chance (Moore 2010; Nüesch 2010).

We applied the following definitions regarding the certainty of the evidence (Balshem 2011):

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

We decreased the certainty of evidence rating by one (-1), two (-2), or three (-3) levels, up to a maximum of -3, (or very low) for any criteria, based on the level of concern it raised. Where we found 'very serious' limitations for a given domain, we downgraded the certainty of evidence by two levels.

Data synthesis

The precise comparisons presented were primarily determined by the content of the included reviews. For reviews that included a broad range of heterogeneous interventions, we grouped these pragmatically under pharmacotherapy, interventional prodedures, neuromodulation, rehabilitation, and complementary and alternative therapy sections. Where data were provided by reviews in sufficient detail, we reported comparisons according to the Population, Intervention, Comparator, Outcome and Time (PICOT), clearly stating where results applied to CRPS I, II or a mixed group. We reported a single measure of pain intensity where multiple measures were provided, prioritising pain at rest over pain with movement. Where measures of pain intensity were provided for multiple areas of the affected limb, we prioritised those closest to the extremity.

Where we deemed statistical pooling of interventions to be inappropriate in included reviews (e.g. by combining placebo controls with active controls), we reported the included interventions narratively. We did not calculate effect sizes where the necessary data were not reported in the review as this would have required the strong assumptions of equal numbers allocated to each group, zero attrition in each study and no protocol violations.

We planned to consider "responder" analyses based upon a 30% or greater reduction in pain to represent a moderately important benefit, and a 50% or greater reduction in pain intensity to represent a substantially important benefit, as suggested by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines (Dworkin 2008), for dichotomised outcomes (responder analyses). The IMMPACT thresholds are based on estimates of the degree of within-person change from baseline that participants might consider clinically important. There is little consensus or evidence regarding what the threshold should be for a clinically important difference in pain intensity based on the between-group difference post-intervention. The OMERACT 12 group have reported recommendations for a minimally important difference for pain outcomes (Busse 2015). They recommend a threshold of 10 mm on a 0 mm to 100 mm 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 patients. We planned to use this threshold but interpret it appropriately and cautiously.

Overlap between reviews

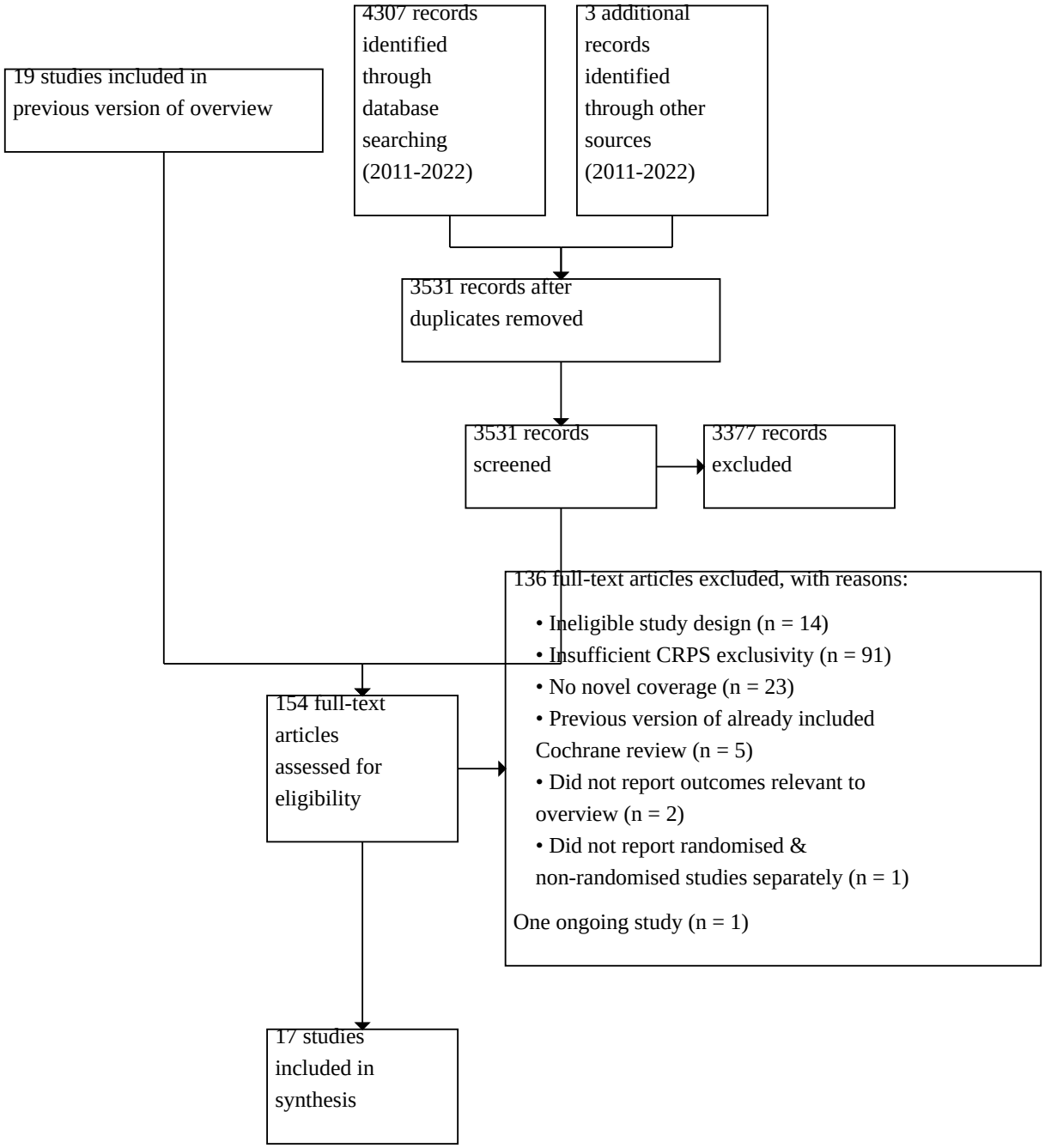
To visually assess the overlap of primary studies across included reviews, we created a citation matrix using guidance from Pieper 2014. We followed recommendations in the Cochrane Handbook (Pollock 2022) to prioritise information from the "most comprehensive" reviews. First, we prioritised information from Cochrane reviews over non-Cochrane reviews. For non-Cochrane reviews, where reviews considered all interventions for CRPS, each review was compared to the most recent in order to establish whether the older review identified any RCTs that had not already been identified, or data which were not adequately reported in the most recent review. Where this was not the case, the older review was excluded. Similarly, where more than one review investigated the same intervention, or class of interventions, the equivalent process was followed. We only considered data from original studies presented in more than one included review once in any analysis.

RESULTS

See Figure 1 for a flow diagram of the search process. Our updated database search extended from October 2011 to October 2022. We identified 4307 records from the database searches and three additional records through citation alerts. After de-duplication (n

= 779) we screened the titles and abstracts of 3531 records, from which we screened full-text articles of 154 reviews for eligibility, together with 19 included reviews from the previous version of this overview. Of these, 136 were excluded (see Table 2 for the reasons for exclusion) and one review was ongoing, leaving 17 included reviews.

Figure 1. Study flow diagram



Description of included reviews

A list of the reviews and original studies which have contributed to this overview is presented in Table 3 and a detailed description of the characteristics of the included reviews is presented in Table 4.

We included 17 systematic reviews, including five Cochrane (Challapalli 2005; Moore 2014; O'Connell 2016; Straube 2013; Smart 2022) and 12 non-Cochrane systematic reviews (Chauvineau 2005; Chevreau 2017; Cossins 2013; Duong 2018; Fassio 2022; Fischer 2010; Forouzanfar 2002; Orhurhu 2019; Peng 2018; Smith 2005; Tran 2010; Xu 2016). The median (range) year of review publication was 2014 (2002 to 2022). All included Cochrane reviews and only two of the non-Cochrane reviews (Fassio 2022; Orhurhu 2019) established the review methods prior to conducting the review.

The five Cochrane reviews and seven of the 12 non-Cochrane reviews (Chevreau 2017; Cossins 2013; Fassio 2022; Fischer 2010; Forouzanfar 2002; Orhurhu 2019; Peng 2018) specified review outcomes of interest. All 12 reviews specified pain intensity as an outcome measure, two reviews (Smart 2022; Peng 2018) specified disability or function as an outcome, eight reviews (Challapalli 2005; Chevreau 2017; Fassio 2022; Moore 2014; O'Connell 2016; Orhurhu 2019; Smart 2022; Straube 2013) specified adverse events as an outcome, two reviews (Smart 2022; Chevreau 2017) specified quality of life as an outcome and four reviews (Fischer 2010; Moore 2014; Smart 2022; Straube 2013) specified a patient-reported rating of improvement or satisfaction with treatment as an outcome. Four reviews (O'Connell 2016; Smart 2022; Chevreau 2017; Orhurhu 2019) specified their follow-up time points of interest.

CRPS specificity of included reviews

Two Cochrane reviews (O'Connell 2016; Smart 2022) included participants with CRPS only. The remaining three Cochrane reviews included a mix of neuropathic pain populations but included studies that were specific to CRPS I and CRPS II populations (or their alternative diagnostic labels). Of the non-Cochrane reviews, six were specific to CRPS I/RSD populations (Chauvineau 2005; Chevreau 2017; Fassio 2022; Fischer 2010; Forouzanfar 2002; Smith 2005), four included both CRPS I/RSD and CRPS II/causalgia (Cossins 2013; Duong 2018; Tran 2010; Xu 2016), one was specific to post-stroke shoulder-hand syndrome (Peng 2018), and one included mixed chronic pain conditions with CRPS reported separately (Orhurhu 2019). No included reviews were specific to CRPS II. Only trials specific to CRPS or its alternative diagnostic labels were included in this overview. Two of the seventeen included reviews restricted the minimum duration of CRPS to three months (Moore 2014; Orhurhu 2019).

Interventions evaluated in included reviews

Of the five Cochrane reviews, one review (Moore 2014) evaluated a specific pharmacological intervention (gabapentin); one review (Smart 2022) evaluated a broad range of rehabilitation interventions; and three reviews evaluated specific interventional techniques using a range of agents: systemic administration of local anaesthetic agents (Challapalli 2005), local anaesthetic sympathetic blockade (O'Connell 2016), and cervico-thoracic or lumbar sympathectomy (Straube 2013). Of the non-Cochrane reviews, four reviews evaluated distinct pharmacological classes or medicines: anti-inflammatory treatments (Fischer 2010); bisphosphonates (Chauvineau 2005; Chevreau 2017) and ketamine (Orhurhu 2019). One review (Fassio 2022) evaluated all pharmacological treatments, and one review (Xu 2016) evaluated all intravenous therapies. One review (Peng 2018) evaluated traditional manual acupuncture and one review (Smith 2005) evaluated a range of rehabilitation interventions including acupuncture. Four reviews (Cossins 2013; Duong 2018; Forouzanfar 2002; Tran 2010) evaluated a broad range of pharmacological, interventional, neuromodulation, rehabilitation and complementary and alternative treatments.

Comparisons

The five Cochrane reviews specified placebo (or sham) or other active treatments as comparators of interest, with three reviews (Moore 2014; O'Connell 2016; Smart 2022) also specifying no treatment as a comparator of interest. Eight of 12 non-Cochrane reviews (Chauvineau 2005; Cossins 2013; Duong 2018; Fischer 2010; Forouzanfar 2002; Smith 2005; Tran 2010; Xu 2016) failed to specify a comparator of interest. Only two reviews (O'Connell 2016; Smart 2022) specified a threshold for the between-group minimal clinically important difference.

Risk of bias and methodological quality of included evidence

Fourteen reviews (Challapalli 2005; Chauvineau 2005; Chevreau 2017; Cossins 2013; Duong 2018; Fassio 2022; Fischer 2010; Forouzanfar 2002; Moore 2014; O'Connell 2016; Orhurhu 2019; Peng 2018; Smart 2022; Straube 2013) used a formal tool to assess the risk of bias or methodological quality of the included evidence. Seven reviews (Duong 2018; Fassio 2022; Moore 2014; O'Connell 2016; Orhurhu 2019; Peng 2018; Smart 2022) used the Cochrane Risk of Bias tool (Higgins 2011) in its standard form or with modifications, three reviews (Challapalli 2005; Chevreau 2017; Straube 2013) used the Oxford Quality Score/Jadad scale (Jadad 1996), two reviews (Cossins 2013; Forouzanfar 2002) used a 15-item methodological quality checklist (de Vet 1997), one review (Fischer 2010) used the 'Delphi list' (Verhagen 1998) and one review (Chauvineau 2005) used 'Aguilar's method' (Cucherat 1997). Three reviews (Smith 2005; Tran 2010; Xu 2016) failed to use any tool to assess the risk of bias or methodological quality of the included evidence.

Certainty of included evidence

Five reviews (Moore 2014; O'Connell 2016; Orhurhu 2019; Smart 2022; Straube 2013) used GRADE to judge the overall certainty of evidence. One review (Xu 2016) determined levels of evidence for clinical guidelines using recommendations from Guyatt 2006 and Van Kleef 2009, and one review (Cossins 2013) determined the level of evidence using methods from Van Tulder 1997.

Methodological quality of included reviews

AMSTAR 2 ratings for the included reviews are summarised in Table 5. Four Cochrane reviews (Moore 2014; O'Connell 2016; Smart 2022; Straube 2013) were judged as high quality. One Cochrane review (Challapalli 2005) was judged as low quality because it did not account for risk of bias in primary studies when interpreting the results of the review, and because of several other non-critical weaknesses. Two non-Cochrane reviews were judged as low quality, either because it was not stated that review methods were established prior to conducting the review (Cossins 2013) or because review authors did not provide a list of excluded studies and justify the exclusions (Orhurhu 2019), in addition to other non-critical weaknesses. The remaining non-Cochrane reviews (Chauvineau 2005; Chevreau 2017; Duong 2018; Fassio

2022; Fischer 2010; Forouzanfar 2002; Peng 2018; Smith 2005; Tran 2010; Xu 2016) were all judged as having critically low quality, due to multiple critical and non-critical weaknesses.

Effect of interventions

A summary of effects for pain, disability and adverse event outcomes for all interventions is provided in Table 6, Table 7, Table 8, Table 9 and Table 10.

The outcomes reported below are only those for which data were available in included reviews. Where comparisons did not provide a time point for outcome measurement, we reported them as post-intervention. All included trials had a two-arm parallel-group design unless specified otherwise.

Oral, intravenous and topical pharmacotherapy

Anticonvulsants

Gabapentin

One Cochrane review, judged as high quality (Moore 2014) specifically investigated the effects of gabapentin in CRPS.

Oral gabapentin versus placebo

Moore 2014 included a single cross-over trial for this comparison (Van de Vusse 2004, n = 58, CRPS I ['IASP criteria']), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Moore 2014 reported no observed differences in the proportion of participants experiencing 'very much improved' Global Perceived Effect pain scores post-intervention (risk ratio (RR) 4.00, 95% CI 0.90 to 17.83, P = 0.07). We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and once for imprecision.

Adverse events: Moore 2014 reported increased incidence of participants experiencing at least one adverse event (RR 1.64, 95% CI 1.15 to 2.32), somnolence (RR 4.72, 95% CI 1.45 to 15.35) and dizziness (RR 9.44, 95% CI 2.32 to 38.39) in the gabapentin group, but there were no observed differences for peripheral oedema (RR 0.31, 95% CI 0.03 to 2.93) or ataxia (RR 9.0, 95% CI 0.5 to 162.53). We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Anti-inflammatory therapies

Corticosteroids

Two non-Cochrane reviews, judged as critically low quality (Duong 2018; Fischer 2010), included evidence on the effects of corticosteroids in CRPS.

Oral prednisolone versus oral piroxicam

Fischer 2010 included a single trial for this comparison (Kalita 2006, n = 60, post-stroke CRPS [diagnostic criteria not reported (NR)]), which they rated as high quality using the Delphi list.

Disability: Fischer 2010 reported no significant between-group differences post-intervention (Barthel Index, mean (standard deviation (SD)) prednisolone 1.97 (4.43), piroxicam 2.57; (5.56)). We judged the certainty in evidence as very low, downgraded once for inconsistency and twice for imprecision.

Continued oral prednisolone versus withdrawal of oral prednisolone

Duong 2018 included a single trial (enriched enrolment randomised withdrawal trial) for this comparison (Kalita 2016, n = 58, post-stroke CRPS [criteria NR]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Duong 2018 reported a between-group difference (visual analogue scale (VAS) mean (SD) 2.4 (1.0) vs 4.9 (2.1); P < 0.01) post-intervention in favour of continued oral prednisolone. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and twice for imprecision.

Disability: Duong 2018 reported no significant between-group differences in Barthel Index or Modified Rankin Scale scores post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and twice for imprecision.

Oral prednisone versus placebo

Fischer 2010 included a single trial for this comparison (Lukovic 2006, n = 60, CRPS I [criteria NR]), which they rated as poor quality using the Delphi list.

Pain intensity: Fischer 2010 reported no significant between-group differences post-intervention (VAS, mean (SD), prednisone 6.0 (0.4), placebo 5.9 (0.7)). We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and twice for imprecision.

Non-steroidal anti-inflammatory drugs (NSAIDs)

One non-Cochrane review, judged as critically low quality (Duong 2018) included evidence on the effects of NSAIDs in CRPS.

Intravenous parecoxib versus placebo

Duong 2018 included a single trial for this comparison (Breuer 2014, n = 20 upper limb CRPS [Harden 2007]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Duong 2018 reported no between-group differences post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Free radical scavengers

Dimethyl sulfoxide (DMSO)

One non-Cochrane review, judged as critically low quality (Fischer 2010), included evidence on the effects of DMSO in CRPS.

Topical DMSO versus placebo

Fischer 2010 included two trials for this comparison (Goris 1987, n = 20, RSD [criteria NR], cross-over); Zuurmond 1996, n = 30, RSD [criteria NR]), which they rated as poor and high quality respectively, using the Delphi list.

Pain intensity: Fischer 2010 reported a significant between-group difference (VAS, median (range) DMSO 2.9 (-2.8 to 7.0), placebo 1.0 (-3.9 to 9.0)) post-intervention in favour of the DMSO group

for Zuurmond 1996. We judged the certainty in evidence as very low, downgraded once for inconsistency and twice for imprecision.

Participant ratings of improvement: Fischer 2010 reported improved patient-reported subjective clinical well-being in favour of the DMSO group post-intervention for Goris 1987, but did not report between-group differences (GRADE assessment not possible).

Topical DMSO versus oral N-acetylcysteine

Fischer 2010 included a single trial for this comparison (Perez 2003, n = 146, CRPS I [criteria NR]), which they rated as high quality using the Delphi list.

Pain intensity: Fischer 2010 reported no significant between-group differences post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as low, downgraded once for inconsistency and once for imprecision.

Mannitol

One non-Cochrane review, judged as critically low quality (Fischer 2010), included evidence on the effects of mannitol in CRPS.

Intravenous mannitol versus placebo

Fischer 2010 included a single trial for this comparison (Perez 2008, n = 41, CRPS I [criteria NR]), which they rated as high quality using the Delphi list.

Pain intensity: Fischer 2010 reported no significant difference between groups (0 to 100 VAS, mean (SD), mannitol 53.1 (25.3), placebo 48 (31.8)) post-intervention. We judged the certainty in evidence as very low, downgraded once for inconsistency and twice for imprecision.

Quality of life: Fischer 2010 reported no significant between-group differences in physical functioning (median (IQR) mannitol: 10.0 (-5.0 to 20), placebo: -5.0 (-10.0 to 15.0)) or social functioning (mannitol: 0.0 (-12.5 to 12.5), placebo: 0.0 (-25.0 to 12.5)) quality of life scores post-intervention. We judged the certainty in evidence as very low, downgraded once for inconsistency and twice for imprecision

Bisphosphonates

Two non-Cochrane reviews, judged as critically low quality (Chauvineau 2005; Chevreau 2017) specifically investigated the effects of bisphosphonates in CRPS, and another two non-Cochrane reviews, also judged as critically low quality (Duong 2018; Fassio 2022) included evidence on the effects of bisphosphonates in CRPS. The following evidence was preferentially reported from Chevreau 2017 after we identified what we judged to be inappropriate pooling of placebo- and active-controlled trials in the meta-analysis performed by Fassio 2022.

Bisphosphonates versus placebo

Chevreau 2017 included four trials for this comparison, testing oral alendronate (Manicourt 2004, n = 40, lower limb CRPS I), intravenous pamidronate (Robinson 2004, n = 27, upper and lower limb CRPS I), intravenous clodronate (Varenna 2000, n = 32, upper and lower limb CRPS I), and intravenous neridronate (Varenna 2013, n = 82, upper and lower limb CRPS I). The CRPS diagnostic criteria were not reported for any of these trials. Using the Jadad scale, Manicourt 2004, Varenna 2000 and Varenna 2013 were scored 5/5 and Robinson 2004 was scored 3/5. Fassio 2022 included an additional trial testing intramuscular neridronate (Varenna 2021, n = 78, CRPS I [criteria NR]), which they rated at low overall risk of bias using the Cochrane ROB tool.

Pain intensity: Chevreau 2017 reported a between-group difference (standardised mean difference (SMD), -2.6, 95% confidence interval (CI) −1.8 to −3.4; P = 0.001; I^2 = 81%, 4 trials, n = 181) post-intervention in favour of bisphosphonates. Fassio 2022 reported a clinically important between-group difference (0 to 100 VAS, mean difference (MD) -21.80; 95% CI -30.28 to -13.32) in favour of neridonate post-intervention. We judged the certainty in evidence as low, downgraded once for inconsistency and once for imprecision.

Quality of life: Chevreau 2017 reported a between-group difference in SF-36 physical functioning scores in favour of bisphosphonates post-intervention for Robinson 2004 but did not provide point estimates or measures of precision (GRADE assessment not possible).

Adverse events: Chevreau 2017 reported a higher proportion of participants experiencing at least one adverse event in the bisphosphonate group (RR 2.10, 95% CI 1.27 to 3.47; number needed to treat for an additional harmful outcome (NNTH) 4.6, 95% CI 2.4 to 168.0; 4 trials, n = 181). Fassio 2022 reported 26 adverse events in the neridronate group compared with 17 in the placebo group for Varenna 2021 but did not provide point estimates or measures of precision (not included in GRADE assessment). We judged the certainty in evidence as moderate, downgraded once for imprecision.

Intranasal pamidronate versus intranasal calcitonin

Chauvineau 2005 included a single trial for this comparison (Cohen 1998, n = 14, upper limb algodystrophy [criteria NR]), which they rated moderate quality using 'Aguilar's method'.

Pain intensity: Chauvineau 2005 reported no significant between-group differences in VAS scores at post-intervention, short-term and medium-term follow-up, but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Intravenous pamidronate versus oral prednisolone

Duong 2018 included a single trial for this comparison (Eun Young 2016, n = 21, upper limb post-stroke CRPS [criteria NR]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Duong 2018 reported a between-group difference in VAS pain scores post-intervention in favour of pamidronate but did not provide point estimates or measures of precision (GRADE assessment not possible).

Calcitonin

One non-Cochrane review, judged as critically low quality (Tran 2010) included evidence on the effects of calcitonin in CRPS.

Intranasal calcitonin versus placebo

Tran 2010 included a single trial for this comparison (Bickerstaff 1991, n = 38 upper limb CRPS [criteria NR]). No assessment of risk of bias or methodological quality was conducted.

Pain intensity: Tran 2010 reported no between-group differences post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Calcitonin plus physiotherapy versus physiotherapy alone

Tran 2010 included two trials for this comparison, testing subcutaneous calcitonin (Gobelet 1986, n = 24 upper and lower limb CRPS [criteria NR]) and intranasal calcitonin (Gobelet 1992, n = 66, upper and lower limbs CRPS [criteria NR]). No assessments of risk of bias or methodological quality were conducted.

Pain intensity: Tran 2010 reported no between-group differences post-intervention for Gobelet 1986 but did not provide point estimates or measures of precision. There was a significant between-group difference post-intervention (four-point pain scale, mean (SD) 0.45 (0.68) vs 0.69 (0.93)) in favour of calcitonin plus physiotherapy reported for Gobelet 1992. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Intranasal calcitonin versus oral paracetamol

Tran 2010 included a single trial for this comparison (Sahin 2006, n = 35, upper limb CRPS [criteria NR]). No assessment of risk of bias or methodological quality was conducted.

Pain intensity: Tran 2010 reported no between-group differences post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Immunomodulators

Immunoglobulin

One non-Cochrane review, judged as critically low quality (Duong 2018) included evidence on the effects of immunoglobulin in CRPS.

Intravenous immunoglobulin versus placebo

Duong 2018 included a single cross-over trial for this comparison (Goebel 2010, n = 12, CRPS [Harden 2007]), which they rated at low overall risk of bias using the Cochrane ROB tool.

Pain intensity: Duong 2018 reported lower pain scores during treatment with intravenous immunoglobulin but did not provide between-group differences (GRADE assessment not possible).

Participant ratings of improvement: Duong 2018 reported increased patient-reported improvement during treatment with intravenous immunoglobulin but did not provide between-group differences (GRADE assessment not possible).

Infliximab

One non-Cochrane review, judged as critically low quality (Xu 2016) included evidence on the effects of the monoclonal antibody infliximab in CRPS.

Intravenous infliximab versus placebo

Xu 2016 included a single trial for this comparison (Dirckx 2013, n = 13, CRPS I [criteria NR]). No assessment of risk of bias or methodological quality was conducted.

Pain intensity: Xu 2016 reported no between-group differences post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Quality of life: Xu 2016 reported a significant between-group difference in EuroQol scores post-intervention in favour of intravenous infliximab, but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Lenalidomide

One non-Cochrane review, judged as critically low quality (Duong 2018) included evidence on effects of the thalidomide derivative and TNF-α antagonist lenalidomide in CRPS.

Oral lenalidomide versus placebo

Duong 2018 included a single trial for this comparison (Manning 2014, n = 147, CRPS [Harden 2007]), which they rated at unclear overall risk of bias using the Cochrane ROB.

Pain intensity: Duong 2018 reported no between-group differences in pain scores (proportion of participants with ≥ 30% improvement in pain from baseline) post-intervention, but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and once for imprecision.

Disability: Duong 2018 reported no between-group differences in 'activity rating' post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and once for imprecision.

NMDA receptor antagonists

Ketamine

One non-Cochrane review, judged as low quality (Orhurhu 2019) specifically investigated the effects of ketamine infusions for CRPS .

Intravenous ketamine versus placebo

Orhurhu 2019 included two trials for this comparison (Schwartzman 2009, n = 60, CRPS I & II [Bruehl 1999]; Sigtermans 2009, n = 19, CRPS I [Bruehl 1999/Merskey 1994]), which they rated at unclear and high overall risk of bias respectively using the Cochrane ROB tool.

Pain intensity: Orhurhu 2019 reported a clinically important between-group difference post-intervention in favour of ketamine (weighted mean difference (WMD), 0-10 NRS, -2.38, 95% CI -3.53 to -1.23; I^2 = 34.9%; Tau^2 = 0.34; 2 trials, n = 79) but no between-group difference at medium-term (WMD -0.55, 95% CI -1.50 to 0.39; I^2 = 0%; 2 trials, n = 79). We judged the certainty in evidence as very low, downgraded once for serious study limitations and twice for imprecision.

Magnesium

One non-Cochrane review, judged as very low quality (Duong 2018) included evidence on the effects of magnesium for CRPS.

Intravenous and intramuscular magnesium versus placebo

Duong 2018 included two trials for this comparison (Fischer 2013, n = 56, CRPS [criteria NR], intravenous magnesium, cross-over); Van der Plas 2013, n = 22, CRPS [criteria NR], intramuscular magnesium), which they rated at unclear overall risk of bias using the Cochrane ROB tool.

Pain intensity: Duong 2018 reported no between-group differences on numeric rating scale scores (11-point NRS) scores at post-intervention, short-term and medium-term follow-up for Fischer 2013, but did not provide numerical data. An improvement in NRS scores was reported in the intramuscular magnesium group for Van der Plas 2013, but no between-group differences were provided (GRADE assessment not possible). We judged the certainty in evidence for Fischer 2013 as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Memantine

One non-Cochrane review, judged as low quality (Cossins 2013) included evidence of the effects of memantine for CRPS.

Oral memantine plus oral morphine versus placebo plus oral morphine

Cossins 2013 included a single trial for this comparison (Gustin 2010, n = NR ('small'), upper limb CRPS [Merskey 1994]), which they rated as high quality using a 15-item quality checklist (de Vet 1997).

Pain intensity: Cossins 2013 reported a significant between-group difference in VAS scores post-intervention in favour of the memantine and morphine group but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for inconsistency and twice for imprecision.

Other pharmacological therapies

Botulinum toxin A

One non-Cochrane review, judged as critically low quality (Duong 2018) included evidence on the effects of botulinum toxin A in CRPS.

Intradermal/subcutaneous botulinum toxin A versus placebo

Duong 2018 included a single trial for this comparison (Safarpour, n = 8, CRPS [Harden 2007]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Duong 2018 reported no between-group differences in Brief Pain Inventory scores post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Participant satisfaction with treatment: Duong 2018 reported no between-group differences in Patient Satisfaction Scale scores post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Adverse events: Duong 2018 reported increased pain on injection in the botulinum toxin A group but did not provide between-group differences (GRADE assessment not possible).

Isosorbide dinitrate

One non-Cochrane review, judged as critically low quality (Duong 2018) included evidence on the effects of the nitrate isosorbide dinitrate in CRPS.

Topical isosorbide dinitrate versus placebo

Duong 2018 included a single trial for this comparison (Groeneweg 2009, n = 24, upper limb CRPS [criteria NR]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Duong 2018 reported no between-group differences post-intervention, but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Disability: Duong 2018 reported no between-group differences in Disabilities of the Arm, Shoulder and Hand (DASH) scores post-intervention, but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Sarpogrelate hydrochloride

One non-Cochrane review, judged as critically low quality (Tran 2010) included evidence on the effects of the serotonin receptor antagonist sarpogrelate hydrochloride in CRPS.

Oral sarpogrelate hydrochloride plus conventional care versus conventional care alone

Tran 2010 included a single trial for this comparison (Ogawa 1998, n = 30, CRPS [criteria NR]). No assessment of risk of bias or methodological quality was conducted.

Pain intensity: Tran 2010 reported no between-group differences in VAS scores post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Tadalafil

One non-Cochrane review, judged as critically low quality (Tran 2010) included evidence on the effects of the phosphodiesterase-5 inhibitor tadalafil in CRPS.

Oral tadalafil versus placebo

Tran 2010 included a single trial for this comparison (Groeneweg 2008, n = 24 lower limb CRPS [Bruehl 1999]). No assessment of risk of bias or methodological quality was conducted.

Pain intensity: Tran 2010 reported a between-group difference post-intervention in favour of the tadalafil group (VAS, tadafil 15% reduction vs placebo 0%, P = 0.004, measures of variance NR). We judged the certainty in evidence as very low, downgraded once serious study limitations, once for inconsistency and twice for imprecision.

Interventional procedures

Neuraxial therapy

Epidural clonidine

One non-Cochrane review, judged as critically low quality (Tran 2010) included evidence on the effects of epidural pharmacological administration in CRPS.

Epidural clonidine (300 µg and 700 µg) versus placebo

Tran 2010 included a single three-arm cross-over trial for this comparison (Rauck 1993, n = 26, upper and lower limb CRPS [criteria NR]). No assessment of risk of bias or methodological quality was conducted.

Pain intensity: Tran 2010 reported a significant between-group difference in VAS scores in favour of both clonidine groups post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Epidural clonidine 300 µg versus epidural clonidine 700 µg

Two arms of the same three-arm cross-over trial (Rauck 1993) provided data for this comparison.

Pain intensity: Tran 2010 reported no significant between-group differences in VAS scores post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Adverse events: Tran 2010 reported a significant between-group increase in the number of participants experiencing sedation in the 700 µg clonidine group but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Intrathecal pharmacological administration

One non-Cochrane review, judged as critically low quality (Duong 2018) included evidence on the effects of intrathecal administration of a range of pharmacological agents in CRPS.

Intrathecal baclofen 'fast' (0.75 mg/mL^{-1}) versus 'slow' (3 mg/mL^{-1}) infusions

Duong 2018 included a single cross-over trial for this comparison (Van der Plas 2011, n = 14, CRPS [criteria NR]), which they rated at low overall risk of bias using the Cochrane ROB tool.

Pain intensity: Duong 2018 reported no between-group differences in NRS scores post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for inconsistency and twice for imprecision.

Participant rating of improvement: Duong 2018 reported no between-group differences in Global Impression Scale scores post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for inconsistency and twice for imprecision.

Adverse events: Duong 2018 reported an increase in adverse events in the 'fast' baclofen infusion group but did not provide between-group differences (GRADE assessment not possible).

Intrathecal clonidine versus intrathecal adenosine

Duong 2018 included a single cross-over trial for this comparison (Rauck 2015, n = 20, upper and lower limb CRPS [Harden 2007]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Duong 2018 reported no between-group differences in 'pain success' (proportion of participants reporting > 30% decrease in pain from baseline) post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Participant rating of improvement: Duong 2018 reported no between-group differences in patient-reported global assessment of effect scores post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Intrathecal glycine versus placebo

Duong 2018 included a single cross-over trial for this comparison (Munts 2009, n = 18, CRPS [criteria NR]), which they rated at unclear overall risk of bias using the Cochrane ROB tool.

Pain intensity: Duong 2018 reported no between-group differences in NRS scores post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Disability: Duong 2018 reported no between-group differences in Radboud Skills Questionnaire or Walking Skills Questionnaire scores post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Participant rating of improvement: Duong 2018 reported no between-group differences in participant-reported Global Impression Scale scores post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Adverse events: Duong 2018 reported no between-group differences in adverse events but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Intrathecal methylprednisolone versus placebo

Duong 2018 included a single cross-over trial for this comparison (Munts 2010, n = 10, CRPS [criteria NR]), which they rated at unclear overall risk of bias using the Cochrane ROB tool.

Pain intensity: Duong 2018 reported no between-group differences in NRS scores post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as

very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Participant rating of improvement: Duong 2018 reported no between-group differences in Global Impression Scale scores post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Adverse events: Duong 2018 reported an increase in myoclonus in the intrathecal methylprednisolone group but did not provide between-group differences (GRADE assessment not possible).

Intravenous Regional Blockade (IVRB)

One Cochrane review, judged as low quality (Challapalli 2005) specifically investigated the effects of IVRB in CRPS, and five non-Cochrane reviews, judged as critically low quality (Fassio 2022; Fischer 2010; Forouzanfar 2002; Tran 2010; Xu 2016) included evidence on the effects of IVRB using a range of pharmacological agents in CRPS.

Atropine IVRB versus placebo

Tran 2010 included a single cross-over trial for this comparison (Glynn 1993, n = 30, CRPS [criteria NR]). No assessment of risk of bias or methodological quality was conducted.

Pain intensity: Tran 2010 reported no between-group difference in VAS scores post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and twice for imprecision.

Droperidol IVRB versus placebo

Xu 2016 included a single cross-over trial for this comparison (Kettler 1988, n = 6, RSD [criteria NR]). No assessment of risk of bias or methodological quality was conducted.

Pain intensity: Xu 2016 reported no between-group difference post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and twice for imprecision.

Guanethidine IVRB versus placebo

Xu 2016 included three trials for this comparison (Blanchard 1990, n = 21, RSD; Livingstone 2002, n = 57, upper limb CRPS I; Ramamurthy 1995, n = 60, RSD) (criteria NR). No assessments of risk of bias or methodological quality were conducted.

Pain intensity: Xu 2016 reported no significant between-group differences post-intervention for Blanchard 1990 and Ramamurthy 1995, but there was a significant increase in pain intensity in the IVRB group at medium-term follow-up for Livingstone 2002. Point estimates or measures of precision were not reported for any of the comparisons. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Adverse events: Xu 2016 reported minimal changes in blood pressure in the IVRB group for Blanchard 1990 (no between-group differences provided), and no between-group differences in adverse events for Ramamurthy 1995 (point estimates or measures of precision not provided). At medium-term follow-up, a significant between-group difference in the incidence of vasomotor instability was reported in the IVRB group for Livingstone 2002 but point estimates or measures of precision were not provided. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Ketanserin IVRB versus placebo

Forouzanfar 2002 identified two cross-over trials for this comparison (Bounameaux 1984, n = 9, RSD; Hanna 1989, n = 9, RSD) (criteria NR), which they rated as low quality using de Vet 1997 criteria.

Pain intensity: Forouzanfar 2002 reported no significant between-group differences in pain scores post-intervention for Bounameaux 1984, but there was a significant between-group difference in VAS scores for Hanna 1989. Point estimates or measures of precision were not provided for either comparison. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Lidocaine IVRB versus placebo

Challapalli 2005 identified a single cross-over trial for this comparison (Wallace 2000, n = 16, CRPS I & II [criteria NR]), which they rated 3/5 using the Jadad scale.

Pain intensity: Challapalli 2005 reported no statistically significant within group reduction in spontaneous pain post-intervention, but no between-group differences were provided (GRADE assessment not possible).

Adverse events: Challapalli 2005 reported a significant between-group difference in light-headedness, with an increased incidence in the IVRB group, but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and twice for imprecision.

Methylprednisolone and lidocaine bier block versus placebo

Fischer 2010 identified a single study for this comparison (Taskaynatan 2004, n = 22, CRPS I [criteria NR]), which they rated as high quality using the Delphi list.

Pain intensity: Fischer 2010 reported no significant between-group differences post-intervention (VAS, mean (SD) 5.7 (1.3), placebo 4.8 (0.9)) . We judged the certainty in evidence as very low, downgraded once for inconsistency, and twice for imprecision.

Guanethidine plus lidocaine IVRB versus reserpine plus lidocaine IVRB versus lidocaine IVRB alone

Xu 2016 identified a three-arm cross-over trial for this comparison (Rocco 1989, n = 12 [criteria NR]). No assessment of risk of bias or methodological quality was conducted.

Pain intensity: Xu 2016 reported no between-group differences post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and twice for imprecision.

Adverse events: Xu 2016 reported mild depression and diarrhoea in the reserpine group but did not provide between-group differences (GRADE assessment not possible).

Lidocaine IVRB versus lidocaine IVRB with 30 mg, 60 mg or 120 mg ketorolac

Xu 2016 identified a four-arm cross-over trial for this comparison (Eckmann 2011, n = 12, lower limb CPRS [criteria NR]). No assessment of risk of bias or methodological quality was conducted.

Pain intensity: Xu 2016 reported pain reductions in all three ketolorac groups but did not provide between-group differences with placebo (GRADE assessment not possible).

Adverse events: Xu 2016 reported a higher incidence of mild drowsiness, faintness, and shakiness with ketorolac administration, but did not provide between-group differences (GRADE assessment not possible).

Parecoxib, lidocaine and clonidine IVRB versus lidocaine and clonidine IVRB versus intravenous parecoxib, lidocaine and clonidine

Fassio 2022 identified a single three-arm study for this comparison (Frade 2005, n = 30, CRPS I [criteria NR]), which they rated at unclear overall risk of bias using the Cochrane ROB tool.

Pain intensity: Fassio 2022 reported a significant between-group difference post-intervention in favour of the parecoxib, lidocaine and clonidine IVRB group compared with both comparator groups but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and twice for imprecision.

Local anaesthetic sympathetic blockade (LASB)

One Cochrane review, judged as high quality (O'Connell 2016) specifically investigated the effects of LASB using a range of pharmacological agents on CRPS.

Lidocaine stellate ganglion block versus placebo

O'Connell 2016 included two trials for this comparison (Aydemir 2006, n = 25, upper limb CRPS I [Bruehl 1999], 3-arm trial; Price 1998, n = 7, upper and lower limb CRPS I & II [Merskey 1994], cross-over), both rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: O'Connell 2016 reported no between-group differences in VAS scores post-intervention for both studies (Aydemir 2006 and Price 1998), but individual between-group estimates were not provided by the trial authors. The review authors judged the certainty in evidence as moderate, downgraded once for imprecision.

Lidocaine stellate ganglion block versus stellate ganglion ultrasound

Two arms of the same three-arm cross-over trial (Aydemir 2006) provided data for this comparison.

Pain intensity: O'Connell 2016 reported no significant between-group differences in VAS scores post-intervention, but between-group estimates were not provided by the trial authors. The review authors judged the certainty in evidence as low, downgraded once for inconsistency and once for imprecision.

Bupivacaine stellate ganglion block versus guanethidine IVRB

O'Connell 2016 included a single trial for this comparison (Bonelli 1983, n = 19, RSD [criteria NR], which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: O'Connell 2016 reported no significant between-group differences in 100-mm linear scale scores post-intervention but did not provide point estimates or measures of precision. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and once for imprecision.

Botulinum toxin A plus bupivacaine sympathetic block versus bupivacaine sympathetic block alone

O'Connell 2016 included a single cross-over trial for this comparison (Carroll 2009, n = 9, lower limb CRPS I [Merskey 1994]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: O'Connell 2016 reported a significant reduction in 10-cm VAS scores in the botulinum toxin A group post-intervention, but the trial authors did not report between-group differences (GRADE assessment not possible).

Adverse events: O'Connell 2016 reported that a single participant experienced nausea and emesis in the botulinum toxin A group but no between-group difference was provided (GRADE assessment not possible).

Lidocaine and clonidine sympathetic block of the lumbar plexus versus pulsed radiofrequency of the lumbar plexus

O'Connell 2016 included a single trial for this comparison (Freitas 2013, n = 40, lower limb CRPS I [Bruehl 1999]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: O'Connell 2016 reported no significant between-group differences post-intervention but did not provide point estimates or measures of precision. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and once for imprecision.

Lidocaine stellate ganglion block versus oral prednisone

O'Connell 2016 included a single trial for this comparison (Lim 2007, n = 38, upper limb post-stroke CRPS [criteria NR]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: O'Connell 2016 reported no between-group differences in hand pain post-intervention (0 to 3 scale, MD 0.00, 95% CI −0.35 to 0.35). The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and once for imprecision.

Lidocaine sympathetic block versus lidocaine and clonidine IVRB

O'Connell 2016 included a single trial for this comparison (Nascimento 2010, n = 43, upper limb CRPS I [Merskey 1994]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: O'Connell 2016 reported no significant between-group differences in 0-10 cm VAS scores post-intervention but did not provide point estimates or measures of precision. The review authors judged the certainty in evidence as very low, downgraded

once for serious study limitations, once for inconsistency and once for imprecision.

Adverse events: O'Connell 2016 reported an increase in the incidence of dizziness in the lidocaine sympathetic block group but did not provide point estimates or measures of precision (GRADE assessment not possible).

Ropivacaine/triamcinolone thoracic sympathetic block versus subcutaneous ropivacaine/triamcinolone

O'Connell 2016 included a single trial for this comparison (Rocha 2014, n = 36, upper limb CRPS [Merskey 1994/Harden 2010]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: O'Connell 2016 reported no observed between-group differences post-intervention (Brief Pain Inventory, 0 to 10 scale, MD −1.25, 95% CI −3.20 to 0.70), but there was a clinically important between-group difference in favour of the sympathetic block group at long-term follow-up (MD −2.39, 95% CI −4.72 to −0.06). The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and once for imprecision.

Adverse events: O'Connell 2016 reported an increase in the incidence of dyspnoea in the sympathetic block group compared with the subcutaneous ropivacaine/triamcinolone group (24% vs 6%) but did not provide point estimates or measures of precision (GRADE assessment not possible).

Continuous bupivacaine stellate ganglion block versus continuous bupivacaine brachial plexus block

O'Connell 2016 included a single trial for this comparison (Toshniwal 2012, n = 33, upper limb CRPS I [Bruehl 1999]), which they rated at high overall risk of bias using the Cochrane ROB tool.
Pain intensity: O'Connell 2016 reported a significant between-group difference in pain scores (0 to 10 scale, 0.7 vs 3.3) in favour of continuous brachial plexus block post-intervention, but no measures of precision were provided. The review authors judged the certainty in evidence as low, downgraded once for inconsistency and once for imprecision.

Adverse events: O'Connell 2016 reported an increase in the incidence of positive catheter tip culture (61.1% vs 8.3%) and decreased catheter migration (5.2% vs 7.1%) in the sympathetic block group, but no effect size measures of precision were provided (GRADE assessment not possible).

Lidocaine image-guided versus lidocaine nonimage-guided stellate ganglion block

O'Connell 2016 included a single trial for this comparison (Yoo 2012, n = 42, upper limb post-stroke CRPS [Harden 2010]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: O'Connell 2016 reported no observed between-group differences (VAS, 0 to 10 scale, MD −0.58, 95% CI −1.51 to 0.35) post-intervention. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, once for imprecision, and once for indirectness.

Adverse events: O'Connell 2016 reported an increase in the incidence of haematoma at injection site (24% vs 6%) in the non-image guided block compared with the image-guided block, but did not provide point estimates or measures of precision (GRADE assessment not possible).

Stellate ganglion block plus rehabilitation versus rehabilitation alone.

O'Connell 2016 included a single trial for this comparison (Zeng 2003, n = 60, post-stroke shoulder-hand syndrome [criteria NR]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: O'Connell 2016 reported no observed between-group differences post-intervention (Verbal Rating Scale 0 to 10 scale, MD 0.2, 95% CI −1.3 to 1.7). The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and once for imprecision.

Lidocaine and bupivacaine stellate ganglion block plus conventional care versus conventional care alone

O'Connell 2016 included a single trial for this comparison (Rodriguez 2005, n = 82, upper limb CRPS I & II [Merskey 1994; Reinders 2002]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: O'Connell 2016 reported a between-group difference (at least 50% pain reduction, absolute risk reduction 17%; number needed to treat for an additional beneficial outcome (NNTB) = 6) at short-term follow-up in favour of the stellate ganglion block group but did not provide point estimates or measures of precision. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and once for imprecision.

Sympathectomy

One Cochrane review, judged as high quality (Straube 2013) specifically investigated the effects of cervico-thoracic or lumbar sympathectomy for CRPS.

Percutaneous radiofrequency thermal lumbar sympathectomy versus phenol lumbar sympathetic neurolysis

Straube 2013 identified a single study for this comparison (Manjunath 2008, n = 20, CRPS [Bruehl 1999]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Straube 2013 reported no significant between-group differences post-intervention or at medium-term follow-up but did not provide point estimates or measures of precision. The review authors judged the certainty in evidence as very low (reasons for downgrading evidence NR).

Adverse events: Straube 2013 reported that all participants experienced post-injection soreness, one participant in the phenol group experienced post-sympathectomy neuralgia, and one participant in the phenol group experienced paraesthesia during needle positioning but did not provide between-group differences (GRADE assessment not possible).

Neuromodulation

Implanted spinal neuromodulation interventions

Two non-Cochrane reviews, judged as critically low quality (Duong 2018; Tran 2010) included evidence on the effects of implanted spinal neuromodulation interventions in CRPS.

Standard, burst, 500 Hz and 1000 Hz spinal cord stimulation versus placebo

Duong 2018 identified a single five-arm cross-over trial for this comparison (Kriek 2017, n = 40, CRPS [Harden 2007]), which was rated at low overall risk of bias using the Cochrane ROB tool.

Pain intensity: Duong 2018 reported significant between-group differences post-intervention in favour of all SCS (spinal cord stimulation) groups compared with placebo but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for inconsistency and twice for imprecision.

Participant ratings of improvement: Duong 2018 reported significant between-group differences in Global Perceived Effect post-intervention in favour of all SCS groups compared with placebo but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for inconsistency and twice for imprecision.

SCS versus dorsal root ganglion stimulation (DRGS)

Duong 2018 identified a single study for this comparison (Deer 2017, n = 146, lower limb CRPS [Harden 2007]), which was rated at high overall risk of bias using the Cochrane ROB tool.

Quality of life: Duong 2018 reported significant between-group differences in the physical component, general health and social functioning scales of the SF-36 at long-term follow-up in favour of DRGS, but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Participant satisfaction with treatment: Duong 2018 reported no between-group differences in patient satisfaction at long-term follow-up, but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Adverse events: Duong 2018 reported no between-group differences in adverse events at long-term follow-up but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Spinal cord stimulation plus physiotherapy versus physiotherapy alone

Tran 2010 identified three separate reports of a single trial for this comparison (Kemler 2000, n = 54; Kemler 2004, n = NR; Kemler 2008, n = NR [all Bruehl 1999]). No assessments of risk of bias or methodological quality were conducted.

Pain intensity: Tran 2010 reported a between-group difference (VAS, mean (SD) 2.4 (2.5) vs 0.2 (1.4); P < 0.001) in favour of SCS at medium-term follow-up (Kemler 2000), and a significant between-group difference was maintained at long-term follow-up (Kemler 2004), but point estimates or measures of precision were not provided for this time point. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Disability: Tran 2010 reported no between-group differences in functional status at medium-term follow-up but did not provide point estimates or measures of precision (Kemler 2000). We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Quality of life: Tran 2010 reported no between-group differences in quality of life at medium-term follow-up but did not provide point estimates or measures of precision (Kemler 2000). We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Participant ratings of improvement: Tran 2010 reported a significant between-group difference in GPE scores (proportion achieving 6/7 GPE, 36% vs 6%, measures of variance NR) in favour of SCS at medium-term follow-up (Kemler 2000), and a significant between-group difference was maintained at long-term follow-up (Kemler 2004), but point estimates and measures of precision were not provided for this time point. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency and twice for imprecision.

Adverse events: Tran 2010 reported that 42% of participants in the SCS group experienced a device-related complication over the five-year study period (Kemler 2000; Kemler 2004; Kemler 2008), but did not provide between-group differences or measures of precision (GRADE assessment not possible).

Non-invasive brain stimulation

One non-Cochrane review, judged as low quality (Cossins 2013) included evidence on the effects of non-invasive brain stimulation in CRPS.

Repetitive transcranial magnetic stimulation (rTMS) versus placebo

Cossins 2013 identified two trials for this comparison (Picarelli 2010, n = NR [Merskey 1994]; Pleger 2004, n = NR [Merskey 1994], cross-over), which they rated as high quality using a 15-item quality checklist (de Vet 1997).

Pain intensity: Cossins 2013 reported significant between-group differences in VAS scores in favour of rTMS post-intervention for both Picarelli 2010 and Pleger 2004 but the positive effect was not sustained at medium-term follow-up for Picarelli 2010. Point estimates or measures of precision were not provided for these comparisons. We judged the certainty in evidence as very low, downgraded once for inconsistency and twice for imprecision.

Rehabilitation

One Cochrane review, judged as high quality (Smart 2022) specifically investigated the effects of a broad range of rehabilitation/physiotherapy interventions for CRPS.

Sensory-motor training strategies

Graded Motor Imagery

Graded motor imagery (GMI) versus standard care

Smart 2022 identified three trials for this comparison (Moseley 2004, n = 13, upper limb CRPS I [Bruehl 1999]; Moseley 2006, upper and lower limb CRPS I [Bruehl 1999] n = 37, Schreuders 2014, n = 18, upper limb CRPS I [Bruehl 1999]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported a clinically important between-group difference (VAS 0-100, MD -14.45, 95% CI -23.02 to -5.87, P = 0.001; I^2 = 29%; 2 trials, n = 49) in favour of GMI post-intervention (Moseley 2004, Moseley 2006). At short-term follow-up, no between-group differences were reported for Schreuders 2014 but numerical data were not reported by the trial authors. At medium-term follow-up there was a clinically important between-group difference in favour of GMI (MD −21.00, 95% CI −31.17 to −10.83) reported for Moseley 2006. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Disability: Smart 2022 reported a between-group improvement in patient-specific functional scale scores (0 to 10 scale, MD 1.87, 95% CI 1.03 to 2.71, P < 0.001; I^2 = 41%; 2 trials, n = 49) in favour of GMI post-intervention (Moseley 2004, Moseley 2006). There was also a between-group difference at medium-term follow-up in favour of GMI (MD 2.30, 95% CI 1.12 to 3.48, P < 0.001) reported for Moseley 2006. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

GMI versus waiting-list control

Smart 2022 identified a single cross-over trial for this comparison (Strauss 2021, n = 22; upper limb CRPS II [criteria NR by trial authors]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported no evidence of between-group differences post-intervention (0 to 10 VAS, MD –0.58, 95% CI –1.94 to 0.78). The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Adverse events: Smart 2022 reported increased swelling of the affected limb in two participants and increased pain in 12 participants during training, and increased pain after completing training in two participants, but no other numerical data were reported by the trial authors. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Mirror therapy

Mirror therapy versus placebo

Smart 2022 identified a single three-arm trial for this comparison (Cacchio 2009a, n = 24, upper limb post-stroke CRPS I [Bruehl 1999]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported that seven out of eight participants in the mirror therapy group experienced reduced pain (0-100 VAS, median change -51 mm, range -70 to -18) compared with one out of eight in the placebo group post-intervention, but the review authors stated they could not calculate an effect size due to missing between-group data. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Mirror therapy plus stroke rehabilitation versus placebo mirror therapy plus stroke rehabilitation

Smart 2022 identified a single study for this comparison (Cacchio 2009b, n = 48, upper limb post-stroke CRPS I [Bruehl 1999]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported a clinically important between-group differences in favour of the mirror therapy group post-intervention (0-10 VAS, MD -2.9, 95% CI -4.23 to -1.57; P < 0.001) and at medium-term follow-up (MD -3.4, 95% CI -4.71 to -2.09; P < 0.001). The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Disability: Smart 2022 reported significant between-group differences in Wolf Motor Function test scores in favour of the mirror therapy group post-intervention (0 to 5 scale, MD -1.9, 95% CI -2.36 to -1.44; P < 0.001) and at medium-term follow-up (MD -2.3, 95% CI -2.88 to -1.72; P < 0.001). The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Mirror therapy versus mental imagery

Smart 2022 included the 3-arm trial by Cacchio 2009a for this comparison.

Pain intensity: Smart 2022 reported that seven out of eight participants in the mirror therapy group experienced reduced pain on movement (0-100 VAS, median change -51 mm, range -70 to -18) compared with two out of eight in the mental imagery group post-intervention, but the review authors reported they could not calculate an effect size due to missing between-group data. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Mirror therapy plus stroke rehabilitation versus stroke rehabilitation alone

Smart 2022 identified two studies for this comparison (Saha 2021, n = 38, post-stroke upper limb CRPS [criteria NR by trial authors]; Vural 2016, n = 30, post-stroke upper limb CRPS I [Veldman 1993]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported a clinically important between-group difference (0-10 NRS, MD -1.40, 95% CI -2.26 to -0.54; P < 0.001) in favour of mirror therapy post-intervention for Saha 2021 and a between-group difference (median within group change, 0 to 10 VAS, 3 vs 1) in favour of mirror therapy post-intervention for Vural 2016, but the review authors stated they could not determine an effect size for the latter trial because of missing point estimates and measures of precision. The review authors judged the certainty in evidence as very low, downgraded twice for serious study limitations, and once for imprecision.

Disability: Smart 2022 reported an improvement in Functional Independence Measure (FIM) scores (18 to 126 scale, MD 21.95, 95% CI 9.71 to 34.19; P < 0.001) in favour of the mirror therapy group post-intervention for Saha 2021 and an improvement in Fugl-Meyer Assessment hand scores (0-14 scale, median within-group change 3 vs 0) in favour of mirror therapy post-intervention for Vural 2016, but the effect size and measures of precision were

not reported by authors of the latter trial. The review authors judged the certainty in evidence as very low, downgraded twice for serious study limitations, and once for imprecision.

Mirror visual feedback plus medical management versus contrast baths plus medical management

Smart 2022 identified a single 3-arm trial for this comparison (Sarkar 2017, n = 30, upper and lower limb CRPS [Harden 2007]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported a clinically important between-group difference (11-point NRS, MD −2.65, 95% CI −3.14 to −2.16; P < 0.001) in favour of the mirror visual feedback group post-intervention. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Mirror visual feedback plus medical management versus contrast baths and exercise plus medical management

Smart 2022 included the same three-arm trial by Sarkar 2017 for this comparison.

Pain intensity: Smart 2022 reported a clinically important between-group difference (11-point NRS, MD -2.60, 95% CI -3.08 to -2.12; P < 0.001) in favour of the mirror visual feedback group post-intervention. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Virtual reality

Virtual body swapping with mental rehearsal versus 'watching movement only'

Smart 2022 identified a single three-arm trial for this comparison (Hwang 2014, n = 39, upper and lower limb CRPS I & II [Bruehl 1999]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported no between-group differences in the 11-point pain scale post-intervention, but numerical data were not reported by the trial authors. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Virtual body swapping with mental rehearsal versus mental rehearsal only

Smart 2022 included the same three-arm trial by Hwang 2014 for this comparison.

Pain intensity: Smart 2022 reported no between-group differences in 11-point pain scale scores post-intervention, but numerical data were not reported by the trial authors. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Virtual body swapping with mental rehearsal versus virtual body swapping alone

Smart 2022 identified a single trial for this comparison (Jeon 2014, n = 10, upper and lower limb CRPS I [Harden 2007]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported no between-group differences post-intervention, but numerical data were not reported by the trial authors. Smart 2022 judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Virtual reality versus sham virtual reality

Smart 2022 identified a single trial for this comparison (Lewis 2021, n = 45, upper limb CRPS [Harden 2010]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported a between-group difference post-intervention (11-point NRS, MD 1.2; SMD 0.7) but stated the effect size could not be confirmed due to missing measures of variance. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Tactile discrimination

Four tactile discrimination training protocols compared with each other

Smart 2022 identified a single four-arm cross-over trial for this comparison (Moseley 2009, n = 10; upper limb CRPS I [Bruehl 1999]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported no between-group differences in 100-mm VAS scores post-intervention, but numerical data were not reported by the trial authors. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Adverse events: Smart 2022 reported increased pain during tactile discrimination training, but no between-group differences were provided. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Prism adaptation

Prism adaptation treatment versus placebo

Smart 2022 identified a single trial for this comparison (Halicka 2021, n = 49; upper limb CRPS I [Harden 2010]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported no evidence of benefit over placebo in 11-point NRS scores post-intervention or at medium-term follow-up, but the trial authors did not report mean differences and 95% CIs. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Participant ratings of improvement: Smart 2022 reported no evidence of benefit over placebo in Patient's Global Impression of Change scores post-intervention or at medium-term follow-up, but the trial authors did not report median differences with measures of variation. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Electrophysical agents

Stellate ganglion ultrasound versus placebo

Smart 2022 identified a single three-arm trial for this comparison (Askin 2014, n = 45; upper limb CRPS I [Bruehl 1999]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported no evidence of between-group differences in 10-cm VAS scores post-intervention, but the trial authors did not report point estimates or measures of precision. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Disability: Smart 2022 reported no evidence of between-group differences in DASH scores post-intervention, but the trial authors did not report point estimates or measures of precision. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Stellate ganglion ultrasound versus TENS

Smart 2022 identified a single trial for this comparison (Hazneci 2005, n = 30; upper limb RSD [Kozin 1992]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported a clinically important between-group difference (0-10 VAS, MD 2.13, 95% CI 1.47 to 2.79; P < 0.001) in favour of TENS post-intervention. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Electromagnetic field therapy (EMF) versus placebo

Smart 2022 identified three trials for this comparison (Benedetti 2018, n = 30, upper and lower limb CRPS I [Harden 2007], Büyükturan 2018, n = 42, upper limb CRPS I [Harden 2007]; Durmus 2004, n = 40, upper limb CRPS I [Merskey 1994]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported no between-group differences in 10-cm VAS scores post-intervention for Durmus 2004 (effect size could not be calculated by review authors due to missing data), but there were clinically important between-group differences for Benedetti 2018 (10-cm VAS, MD -2.2, 95% CI -1.99 to -2.41; P < 0.001) and Büyükturan 2018 (10-cm VAS 1.6, 95% CI 0.83 to 2.37, P < 0.001) post-intervention, both in favour of the EMF groups. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Disability: Smart 2022 reported that for Benedetti 2018 there was a between-group difference in lower limb disability post-intervention (Maryland Foot Score, 0 to 100, MD 14.4, 95% CI 11.36 to 17.44; P < 0.001; n = 18) in favour of EMF, and a between-group difference in upper limb disability post-intervention (DASH, 0-100, MD -14.0 95% CI -4.41 to -23.59; P < 0.004; n = 12) in favour of placebo. There was no between-group difference on Quick-DASH scores post-intervention reported for Büyükturan 2018 (0 to 100, MD 2, 95% CI -3.91 to 7.91). The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Adverse events: Smart 2022 reported there were no adverse events for Benedetti 2018. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

TENS versus placebo

Smart 2022 identified a single trial for this comparison (Bilgili 2016, n = 30, upper limb CRPS I [Merskey 1994]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported no observed between-group differences in 10-cm VAS scores post-intervention (MD -9, 95% CI -18.5 to 0.5; P = 0.074) in favour of TENS post-intervention. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Disability: Smart 2022 reported no observed between-group differences in Duruöz Hand Index scores (scoring NR) (MD -3.6, 95% CI -13.38 to 6.18; P = 0.48) post-intervention. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Laser therapy versus interferential therapy

Smart 2022 identified a single trial for this comparison (Dimitrijevic 2014, n = 50, upper and lower limb CRPS I [Harden 2005]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported a between-group difference (0 to 100 VAS, MD -8.6, 95% CI -16.27 to -0.93; P = 0.03) in favour of laser therapy post-intervention. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Adverse events: Smart 2022 reported there were no adverse events. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

CO_2 bath therapy and exercise versus exercise alone

Smart 2022 identified a single trial for this comparison (Mucha 1992, n = 40, upper limb algodystrophy [criteria NR]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported a between-group difference in pain post-intervention in favour of the CO_2 bath group, but numerical data were not reported by the trial authors. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Whirlpool baths versus neuromuscular electrical stimulation

Smart 2022 identified a single trial for this comparison (Devrimsel 2015, n = 60, upper limb CRPS I [Harden 2010]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported a between-group difference (10-cm VAS, MD -0.65, 95% CI -1.03 to -0.27; P < 0.001) in favour of the whirlpool bath group post-intervention. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Adverse events: Smart 2022 reported there were no adverse events. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Fluidotherapy plus stroke rehabilitation versus stroke rehabilitation alone

Smart 2022 identified a single trial for this comparison (Ozcan 2019, n = 32, upper limb post-stroke CRPS I [Harden 2010]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported no between-group differences in 10-cm VAS scores post-intervention, but the trial authors did not report point estimates or measures of precision. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Disability: Smart 2022 reported no between-group differences in FIM scores post-intervention, but the trial authors did not report point estimates or measures of precision. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Exposure-based interventions

Pain exposure physical therapy versus usual physiotherapy

Smart 2022 identified a single trial for this comparison (Barnhoorn 2015, n = 56, upper and lower limb CRPS I [Harden 2007]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported no significant between-group differences (1 to 10 VAS, MD 0.61, 95% CI -0.70 to 1.92) at long-term follow-up. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Disability: Smart 2022 reported no observed between-group differences in upper limb (DASH, 0 to 100 scale, MD 6.47, 95% CI -5.97 to 18.90) and lower limb (Lower Limb Tasks Questionnaire, 0 to 40 scale, MD 5.11, 95% CI -0.45 to 10.68) disability scores at long-term follow-up. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Quality of life: Smart 2022 reported no observed between-group differences in EuroQol-5D index scores (maximum score 1, MD -0.01, 95% CI -0.10 to 0.08) at long-term follow-up. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Exposure in vivo versus usual physiotherapy

Smart 2022 identified a single trial for this comparison (den Hollander 2016, n = 46, upper and lower limb CRPS I [Merskey 1994]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported clinically important between-group differences in Neuropathic Pain Scale scores in favour of the exposure intervention post-intervention (0 to 10, MD -2.04 95% CI -3.01 to -1.07; P = 0.001) and at medium-term follow-up (MD -2.82, 95% CI -4.18 to -1.46; P = 0.001). The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Disability: Smart 2022 reported between-group differences in upper limb disability post-intervention (Radboud Skills Questionnaire, 0-5, MD -1.08, 95% CI -1.60 to -0.56; P = 0.001) and at medium-term follow-up (MD -1.30, 95% CI -0.92 to -1.69; P = 0.001); and a significant between-group difference in lower limb disability at medium-term follow-up (Walking Ability Questionnaire, 0 to 10, MD -3.62, 95% CI -6.78 to -0.47; P = 0.02) but no between-group differences post-intervention. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Quality of life: Smart 2022 reported between-group differences in SF-36 physical component summary scores (SF-36 PCS, 0 to 100, MD 25.93, 95% CI 15.92 to 35.91, P = 0.001) and mental component summary (SF-36 MCS, 0 to 100, MD 16.23, 95% CI 6.85 to 25.63; P = 0.001) post-intervention and at medium-term follow-up (SF-36 PCS: MD 22.64, 95% CI 10.15 to 35.13; P = 0.001; SF-36 MCS: MD 19.63, 95% CI 10.78 to 28.47; P = 0.001), all in favour of the exposure intervention. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Multimodal physiotherapy

Physiotherapy versus minimal care

Smart 2022 identified a single three-arm trial for this comparison (Oerlemans 1999, n = 135, upper limb CRPS I [Veldman 1993]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported a between-group difference in pain intensity in favour of physiotherapy post-intervention and no between-group differences at long-term follow-up, but the trial authors did not report point estimates or measures of precision. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Disability: Smart 2022 reported a between-group difference in disability in favour of physiotherapy at long-term follow-up (Impairment Level Sum Score, 5-50, MD -3.7, 95% CI -7.13 to -0.27, P = 0.03). There were no between-group differences for several measures of upper limb disability (Radboud Skills Questionnaire, modified Greentest, Radboud Dexterity Test) at long-term follow-up. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Quality of life: Smart 2022 reported no between-group differences in health-related quality of life (Sickness Impact Profile) at long-term follow-up but the trial authors did not report numerical data. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Physiotherapy versus occupational therapy

Smart 2022 included the same three-arm trial by Oerlemans 1999 for this comparison.

Pain intensity: Smart 2022 reported no between-group differences at long-term follow-up, but the trial authors did not report point estimates or measures of precision. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Disability: Smart 2022 reported no between-group differences for several measures of upper limb disability (Impairment Level Sum Score, Radboud Skills Questionnaire, modified Greentest, Radboud Dexterity Test) at long-term follow-up, but the trial authors did not report point estimates or measures of precision. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Quality of life: Smart 2022 reported no between-group differences in health-related quality of life (Sickness Impact Profile) at long-term follow-up, but the trial authors did not report point estimates or measures of precision. We judged the certainty in evidence for this comparison as very low, downgraded once for serious study limitations, once for inconsistency and once for imprecision.

Upper limb aerobic exercise and physiotherapy versus physiotherapy alone

Smart 2022 identified a single trial for this comparison (Topcuoglu 2015, n = 40, upper limb post-stroke CRPS I [Bruehl 1999]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported a clinically important between-group difference in daytime pain post-intervention (10-cm VAS, MD -1.9, 95% CI -3.23 to -0.57; P < 0.005). The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Other physiotherapy-based interventions

Manual lymphatic drainage therapy versus conventional care

Smart 2022 identified two trials for this comparison (Duman 2009, n = 34, upper limb RSD [Bruehl 1999]; Uher 2000, n = 40, lower limb CRPS I [criteria NR]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported no between-group differences post-intervention for either study but were unable to extract accurate numerical data to calculate an effect size. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Electro-acupuncture and massage versus rehabilitation

Smart 2022 identified a single trial for this comparison (Li 2012a, n = 120, post-stroke shoulder-hand syndrome [Steinbrocker 1948]), which they rated at high overall risk of bias using the Cochrane ROB tool.

Pain intensity: Smart 2022 reported a clinically important between-group difference in pain on movement post-intervention (NRS, MD -1.70, 95% CI -2.09 to -1.31; P = 0.01) and at short-term follow-up (MD -1.40, 95% CI -1.78 to -1.02; P < 0.001) in favour of the electro-acupuncture and massage group. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Disability: Smart 2022 reported no between-group differences in Fugl-Meyer hand scores post-intervention, or in Fugl-Meyer upper limb scores at short-term follow-up, but no point estimates or measures of precision were provided. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Adverse events: Smart 2022 reported there were no adverse events. The review authors judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision.

Complementary and alternative therapies

Acupuncture

One non-Cochrane review, judged as critically low quality (Peng 2018) specifically investigated the effects of acupuncture in shoulder-hand syndrome. Another two non-Cochrane reviews, also judged as critically low quality (Forouzanfar 2002; Smith 2005) included evidence on the effects of acupuncture in CRPS.

Acupuncture versus sham acupuncture

Forouzanfar 2002 identified three trials for this comparison (Fialka 1993, n = 14, RSD; Kho 1995, n = 28, RSD; Korpan 1999, n = 14, CRPS I) (criteria NR for all trials), which they rated as low quality using de Vet 1997 criteria. Smith 2005 identified an additional trial for this comparison (Ernst 1995, n = 14, CRPS I [criteria NR]) but no assessment of risk of bias or methodological quality was conducted.

Pain intensity: Forouzanfar 2002 reported no significant between-group differences in VAS scores for two studies post-intervention (Fialka 1993; Kho 1995) and a significant between-group difference in VAS scores for one study (Korpan 1999) in favour of the acupuncture group post-intervention but did not provide point estimates or measures of precision. Smith 2005 reported a reduction in VAS scores in favour of the acupuncture group post-intervention for Ernst 1995 but provided no measure of statistical significance (GRADE assessment not possible). We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and once for imprecision (three studies).

Participant ratings of improvement: Smith 2005 reported an improvement in patient subjective success scores in favour of the acupuncture group post-intervention but did not provide point estimates or measures of precision (GRADE assessment not possible).

Traditional manual acupuncture plus rehabilitation versus rehabilitation alone

Peng 2018 identified 20 trials of participants with shoulder-hand syndrome for this comparison (diagnostic criteria provided where reported): Chai 2016, n = 118; Chang 2005, n = 80 (Kozin 1992); Chen 2015, n = 94 (Miao 1996); Gao 2016, n = 100; Li 2012b, n = 60 (Miao 1996); Li 2015a, n = 92; Liang 2016, n = 30; Liao 2006 n = 90; Niu 2015, n = 108 (Miao 1996); Shang 2008, n = 80 (Miao 1996); Shen 2014, n = 60 (Miao 1996); Sun 2012, n = 60 (Miao 1996); Tie 2016, n = 100 (Miao 1996); Wan 2013, n = 120 (Miao 1996); Wang 2017a, n = 142; Wu 2014, n = 200 (Miao 1996); Xu 2015, n = 80 (Miao 1996); Zhao 2004, n = 54; Zhang 2015, n = 92; Zhong 2011 ('Zhu' criteria). The review authors judged all trials at unclear overall risk of bias.

Pain intensity: Peng 2018 reported a clinically important between-group difference (VAS, MD 1.49, 95% CI 1.15 to 1.82; I^2 = 71%; Tau^2 = 0.17; nine trials, n = 834) in favour of manual acupuncture post-intervention. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, once for imprecision and once for indirectness.

Disability: Peng 2018 reported a between-group difference in upper limb disability (Fugl-Meyer Assessment, MD 8.42, 95% CI 6.74 to 10.10; I^2 = 94%; Tau^2 = 13.07, 20 trials, n = 1918) in favour of manual acupuncture post-intervention. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, once for imprecision and once for indirectness.

Qigong

One non-Cochrane review, judged at critically low quality (Smith 2005) included evidence on the effects of qigong in CRPS.

Qigong versus placebo

Smith 2005 identified a single trial for this comparison (Wu 1999, n = 26, upper and lower limb CRPS I [criteria NR]). No assessment of risk of bias or methodological quality was conducted.

Pain intensity: Smith 2005 reported a significant between-group difference in the number of participants who reported a decrease in pain (VAS, 91% vs 36%, magnitude of decrease not specified) but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, downgraded once for serious study limitations, once for inconsistency, and twice for imprecision.

Relaxation therapy

One non-Cochrane review, judged at critically low quality (Smith 2005) included evidence on the effects of relaxation therapy in CRPS.

Autogenic relaxation training plus home treatment versus home treatment alone

Smith 2005 identified a single trial for this comparison (Fialka 1996, n = 18, upper CRPS I [criteria NR]). No assessment of risk of bias or methodological quality was conducted.

Pain intensity: Smith 2005 reported no significant between-group differences in VAS scores post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, once for serious study limitations, once for inconsistency, and twice for imprecision.

Other interventions

Occlusal splints

One non-Cochrane review, judged as low quality (Cossins 2013) included evidence on the effects of occlusal splints in CRPS.

Occlusal splint versus control (not specified)

Cossins 2013 identified a single trial for this comparison (Fischer 2008, n = NR, upper limb CRPS I [Bruehl 1999]). which they rated as high quality using de Vet 1997 criteria.

Pain intensity: Cossins 2013 reported no significant between-group differences in NRS scores post-intervention but did not provide point estimates or measures of precision. We judged the certainty in evidence as very low, once for inconsistency and twice for imprecision.

DISCUSSION

Summary of main results

Our objective was to provide an overview of Cochrane and non-Cochrane systematic review evidence of all interventions for treating pain and disability in adults with CRPS. We included data from 17 systematic reviews and synthesised the results reported for 127 RCTs. Despite a considerable increase in included evidence, the findings of this overview do not differ largely from those of the previous version. There are very few well-designed, well-reported, and large RCTs of the many interventions proposed for the treatment of CRPS. We found moderate-certainty evidence that, compared with placebo, local anaesthetic sympathetic blockade probably does not reduce pain intensity, and that bisphosphonates probably increase the risk of experiencing an adverse event of any nature. A summary of results from comparisons for which there is only low- or very low-certainty evidence is presented in Appendix 10. The critical lack of high-quality evidence prevents us from drawing any firm conclusions regarding the efficacy or effectiveness of any intervention for treating pain and disability in adults with CRPS.

Overall completeness and applicability of evidence

We included both Cochrane and non-Cochrane reviews to ensure that this overview represents a comprehensive summary of all eligible systematic reviews published prior to the search dates. However, because we used published systematic reviews instead of original trials as the sole evidence source, and only five included reviews were published within the last five years, important trial evidence may have been excluded. The inclusion of two broad systematic reviews of pharmacotherapy (Fassio 2022) and physiotherapy (Smart 2022) published close to our search dates may mitigate this issue to some degree. Despite the inclusion of a large body of data from 17 reviews including the results from a total of 127 RCTs, we identified several factors that limit the overall completeness and applicability of the evidence at both review and trial levels.

The included evidence investigated a broad range of pharmacological, interventional, and rehabilitation treatments. Many of the included trials were small, involved short follow-up periods and were exploratory. Long-term (> 6 months) results were reported for only five included trials, offering limited information about the ongoing utility of most interventions. We found few instances where a specific intervention was tested in more than a single trial. Many included trials tested interventions against active comparators without prior evidence of efficacy using placebo control. We did not identify any RCT evidence for routinely used pharmacological interventions for CRPS such as tricyclic antidepressants or opioids. The description of included interventions in non-Cochrane reviews was poor although, in some instances, this may have been due to the inadequate reporting of original trials.

Several of the included reviews and trials were published before the current diagnostic criteria for CRPS (Harden 2010). This increases the risk that these studies included participants who would not

fulfil a diagnosis of CRPS under current diagnostic criteria. Although we aimed to include evidence on all CRPS subtypes and report results for each subtype separately, reviews did not always clearly distinguish between CRPS I and CRPS II. Additionally, few of the included reviews reported comprehensive demographic and clinical data on the included participants. These factors represent a source of clinical heterogeneity and make it difficult to establish for whom the evidence may be applicable.

The selection and reporting of outcome measures was inconsistent across RCTs and reviews, particularly between Cochrane and non-Cochrane reviews. Five non-Cochrane reviews failed to specify outcomes of interest and only two non-Cochrane reviews registered the selection of outcome measures before conducting the review. This increases the risk of selective outcome reporting (Stewart 2012) and makes it difficult to ascertain whether the absence of many of the outcomes of interest to this overview were missing in original trials, or simply not reported in reviews. Of the reviews that specified outcomes of interest to this overview, all selected pain intensity as the primary outcome. Few data were available for other overview outcomes such as quality of life and participant satisfaction with treatment. The definition and reporting of adverse events was inadequate, limiting our ability to make any firm conclusions regarding the safety of the included interventions. We also found the reporting of results to be poor. In many instances, results were reported narratively without providing quantitative data such as between-group estimates and their measures of precision. Without adequate reporting of such data, it is difficult to establish the clinical importance of many of the positive effects reported in this overview.

Quality of the evidence

At the review level, we identified important differences in the quality of Cochrane and non-Cochrane reviews. While the inclusion of non-Cochrane reviews ensured a more comprehensive summary of the published evidence, it also reduced the overall quality of evidence within this overview.

We used the AMSTAR 2 tool to assess the quality of included reviews. Four of five Cochrane reviews were judged as high quality due to their consistent and transparent methods used to search and select studies, perform analyses, and assess the risk of bias and certainty of evidence. In all instances, these methods were prespecified before the commencement of the review. We judged 10 of 12 non-Cochrane reviews as critically low quality, with most included reviews failing to satisfy all or most of the critical AMSTAR 2 criteria. Notably, only one non-Cochrane review (Orhurhu 2019) was judged to fully satisfy item 2 - "Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?". Failure to adhere to a prospectively developed protocol increases the risk of bias in the review (Shea 2017). That Cochrane reviews had better AMSTAR 2 ratings than non-Cochrane reviews is unremarkable considering Cochrane reviews have been demonstrated to have higher methodological rigour and more complete reporting than non-Cochrane reviews (Dosenovic 2018; Goldkuhle 2018; Page 2016). The low quality of the non-Cochrane reviews was striking and represents a body of evidence synthesis of limited utility for guiding CRPS care. The suboptimal review methods and reporting compound the already substantial limitations with the quality of the primary trial evidence in CRPS.

The included reviews assessed the risk of bias or methodological quality of included trials using a range of different assessment tools, limiting our ability to make comparative statements on individual domains across trials. The Cochrane ROB tool (Higgins 2011) was used in three of the five Cochrane reviews, but in only four of the seven non-Cochrane reviews published since its advent. Critically, three non-Cochrane reviews failed to conduct any assessment of risk of bias or methodological quality. We made two important observations regarding the risk of bias judgements using the Cochrane ROB tool across Cochrane and non-Cochrane reviews. First, the use of non-Cochrane risk of bias or methodological quality tools may have resulted in inappropriately positive quality ratings. For example, Cossins 2013 rated two small rTMS trials (Picarelli 2010; Pleger 2004) as 'high' quality using a 15-item methodological quality checklist (de Vet 1997), whereas the same two studies were rated at high overall risk of bias in a Cochrane review (O'Connell 2018). Second, when the Cochrane ROB tool was used in non-Cochrane reviews, we were not confident that it was applied appropriately. For example, Smart 2022 judged Bilgili 2016 at high risk of bias for random sequence allocation and blinding domains, whereas Duong 2018 judged Bilgili 2016 at low risk of bias for the same domains. While we only reported the results of Bilgili 2016 using data extracted from Smart 2022, it is possible that these inconsistencies were applied throughout Duong 2018, a review which contributed substantial data to this overview.

Use of the GRADE approach to assess the certainty of evidence was high for Cochrane reviews (four of five), but very low for non-Cochrane reviews (one of 12). This may in part be explained by the publication of several reviews before the advent of the GRADE system. We attempted to mitigate this issue by conducting additional GRADE assessments for reviews where they were missing. Across this overview, the highest certainty of evidence for any comparison was moderate, with the majority of comparisons judged as very low.

Potential biases in the overview process

We considered several biases during the overview processes and attempted to reduce them in several ways. This overview was conducted according to a published protocol (O'Connell 2011), and we have highlighted differences between the current version, previous version and published protocol of this overview. We used a comprehensive search strategy which was designed and implemented under expert guidance by the Cochrane Pain, Palliative and Supportive Care Review Group. While we have attempted to identify all eligible reviews using a comprehensive search strategy, it remains possible that we may have missed some key literature.

Two authors independently assessed the reviews for inclusion, extracted data and conducted GRADE and AMSTAR 2 assessments, resolving disagreements through recourse to a third reviewer, where necessary. As two of the included Cochrane reviews were authored by members of this overview team (O'Connell 2016: NOC, BMW; Smart 2022: KMS, MCF, BMW, NOC), there may have been a risk of potential bias with review and appraisal of this work. We were unable to reallocate all extraction tasks to members who were not authors on the original reviews, however no authors conducted AMSTAR 2 quality assessments for their own reviews.

Our application of GRADE judgements to comparisons where they were missing introduces an element of subjective judgement. It

was found to be particularly difficult because judgements were informed by data reported in the included reviews rather than the original studies, and because reviews assessed and reported study risk of bias or quality in different ways. We have tried to be consistent in our judgements across all comparisons but it should be recognised that these judgements are open to interpretation. The decision to downgrade twice for imprecision based on a sample size of less than 50 participants per arm may appear to be overly punitive. However, this is based on the observation that studies of this size are potentially more biased than those with 50 to 200 participants, which themselves are at risk of bias (Moore 2010).

In the current version of this overview, we did not reconduct analyses using trial report data where we identified inconsistencies or where reporting of effects was poor. While we acknowledge that doing this may have improved the accuracy of effect estimates, we are confident that such analyses would not have meaningfully changed any of the overview's conclusions.

Agreements and disagreements with other studies or reviews

We did not identify any published overviews of all interventions for treating pain and disability in adults with CRPS. The most up-to-date systematic review of all interventions for CRPS (Duong 2018) concluded that there is supporting evidence for bisphosphonates and short courses of oral steroids, and emerging evidence for a range of medical interventions, most notably ketamine, intravenous immunoglobulin, intrathecal administration of clonidine, adenosine and baclofen, and dorsal root ganglion stimulation, although the review authors reported that further confirmatory RCTs were warranted.

Our conclusions for the efficacy of bisphosphonates largely concur with those of Duong 2018, however, given the small number of total participants and significant heterogeneity in the included analysis from Chevreau 2017, we have graded this evidence as low certainty. Appropriate use of more stringent criteria to assess serious study limitations, such as the Cochrane ROB tool, may have downgraded the certainty of evidence for this comparison to very low. We note that the observed standardised mean difference for the pooled effect (-2.6) is considerably larger than effect sizes commonly seen in chronic pain trials and, as such, should be interpreted with caution. Accordingly, we would suggest that while the efficacy of bisphosphonates is promising according to these data, the current evidence is uncertain and requires further investigation. It is noteworthy that a series of unpublished industry-sponsored bisphosphonate trials (NCT02504008; NCT03530345; NCT03560986) have been terminated early for futility.

Our conclusion for oral steroids differs to that of Duong 2018, likely because their conclusion was partly based on positive effects on composite CRPS symptom scores rather than only specific pain or disability scales. Our overview only identified very low-certainty evidence of no effect of oral prednisone compared with placebo (Lukovic 2006), and very low-certainty evidence that continuing oral prednisolone therapy results in greater pain reductions than withdrawing oral prednisolone (Kalita 2016).

For ketamine, we found very low-certainty evidence of clinically important effects compared with placebo at post-intervention, but not short-term follow-up. Using updated GRADE criteria, we downgraded the certainty of evidence for this comparison from the previous version of this overview. It is remarkable that, despite no new published RCT evidence since 2009, CRPS has been reported as the most common indication for ketamine in pain clinics (Mangnus 2022b). That this widespread practice may have been largely informed by two RCTs with a combined 79 participants is alarming. Further RCTs are urgently needed to resolve uncertainties surrounding ketamine's medium- to long-term benefits, as well as efforts to improve active surveillance to collect ongoing safety data given the unknown harms of repeated dosing (Short 2018).

Since publication of Duong 2018, the promising effects of intravenous immunoglobulin have been tested in a large placebo-controlled RCT of 111 participants with longstanding CRPS (Goebel 2017). The observed benefits in Goebel 2010 were not replicated, with no differences found between immunoglobulin and placebo. These findings demonstrate the importance of replication studies and emphasise the inability of small exploratory trials to provide reliable evidence of efficacy.

In contrast to Duong 2018, we found no evidence of promise for intrathecal administration of clonidine, adenosine or baclofen. We did not identify placebo-controlled comparisons for these agents and based our conclusions on two comparative effectiveness trials (Rauck 2015; Van der Plas 2011). There was very low-certainty evidence of little to no between-group differences on pain intensity. We propose that a higher level of evidence is required to warrant further investigation and other interventions should be prioritised for future research.

Based on evidence from both their review and the previous version (Tran 2010), Duong 2018 concluded that there is no strong evidence to support the use of a range of pharmacological interventions including NSAIDs, magnesium, botulinum toxin A, lenalidomide, isosorbide dinitrate, mannitol, tadalafil, sarpogrelate, and gabapentin; and no evidence to support the use of IVRB using guanethidine, reserpine, droperidol, ketanserin, atropine, lidocaine-methylprednisolone, or ketorolac. Because most of the evidence for these interventions in this overview was derived from these reviews, our conclusions are broadly in agreement.

Duong 2018 concluded that dorsal root ganglion stimulation (DRGS) holds promise for refractory CRPS and recommended further confirmatory trials to validate its benefits. This conclusion was based on improvements in a composite efficacy and safety outcome compared with conventional spinal cord stimulation. Separate pain intensity scores were not reported and, as such, we cannot make comparisons for this outcome. While improvements in quality of life were observed at long-term follow-up, we found the certainty in evidence to be very low, and emphasise the difficulty of interpreting these positive effects in the absence of placebo-controlled trials. It is notable that a Cochrane review (O'Connell 2021) identified no trials testing DRGS against placebo in any chronic pain condition.

We found no up-to-date systematic reviews focusing on specific rehabilitation or physiotherapy interventions for CRPS with which to draw comparisons. A 2017 review of mirror therapy and graded motor imagery for CRPS (Méndez-Rebolledo 2017) reported that, while both interventions demonstrated consistent reductions in pain intensity and disability in CRPS I, the evidence was limited, owing primarily to small sample sizes and clinical heterogeneity. The review concluded that there is insufficient

evidence to recommend the use of these therapies over other CRPS I treatments. We would broadly concur with these conclusions and recommend that further trials be conducted.

AUTHORS' CONCLUSIONS

Implications for practice

For adults with CRPS

The evidence regarding the effectiveness of most interventions used to treat pain and disability in CRPS is very uncertain.

We found low-certainty evidence that, on average, treatment with bisphosphonates may reduce pain intensity compared with placebo, but is probably associated with an increased risk of experiencing an adverse effect.

We found moderate-certainty evidence that, on average, blocking the activity of the sympathetic nerves using lidocaine anaesthetic probably does not reduce pain intensity more than a placebo intervention, and low-certainty evidence that it may not be more effective than ultrasound.

We also found that other commonly used treatments such as ketamine infusions, spinal cord stimulation, graded motor imagery and mirror therapy may reduce pain intensity more than placebo or other active controls, however the evidence is very uncertain.

While there is a lack of evidence for adverse events, the risk of harm likely varies between invasive, drug and non-drug treatments and may be an may be an important consideration to guide the choice of management.

For clinicians

There is insufficient high-certainty evidence on which to base comprehensive clinical guidance on the management of CRPS. Current non-Cochrane systematic reviews are unlikely to provide an unbiased representation of the available RCT evidence.

We found moderate- or low-certainty evidence for only two placebo-controlled comparisons:

- There was low-certainty evidence bisphosphonates may reduce pain intensity post-intervention, and moderate-certainty evidence that they are probably associated with increased adverse events of any nature. The included studies used a range of bisphosphonates with different routes of administration, and were primarily used in early onset CRPS I. As such, it is unclear whether the observed effects are likely to apply to long-standing CRPS, or CRPS with associated neural tissue injury. Further investigations of this medicine class are warranted.
- There was moderate-certainty evidence that lidocaine local anaesthetic sympathetic blockade probably does not reduce pain intensity compared with placebo.

We found only low-certainty evidence for three effectiveness comparisons:

- compared with oral N-acetylcysteine, topical DMSO may not reduce pain intensity.
- compared with ultrasound of the stellate ganglion, lidocaine stellate ganglion may not reduce pain intensity.
- compared with continuous bupivacaine stellate ganglion block, continuous brachial plexus block may reduce pain intensity.

While there was evidence of efficacy or effectiveness for routinely used interventions for CRPS such as intravenous ketamine, spinal cord stimulation, graded motor imagery and mirror therapy, the very low-certainty of the evidence suggests that the true effects of these interventions are likely to be substantially different from the estimates of effect. These results should be interpreted with caution and do not reliably aid clinical decision-making. We did not identify any RCT evidence for commonly used pharmacological interventions such as tricyclic antidepressants or opioids.

While adverse event data are lacking for most included interventions, consideration of the probable risk of treatment-related harms may be important for guiding patient management. Based on findings from this overview, managing CRPS using an evidence-based approach will remain difficult until further larger, well-conducted trials are undertaken.

For policy-makers and funders

The available evidence relating to treatments for CRPS is very uncertain. Policy and funding decisions should not be made on the basis of findings from current non-Cochrane reviews due to their low methodological quality. There is insufficient evidence to support or refute the use of the majority of routinely used interventions for pain intensity and disability in CRPS. Funders might prioritise CRPS research calls that enable consortia of researchers to leverage funding for high-quality clinical trials that aim to meaningfully resolve key clinical uncertainties. Until such research is undertaken, clinical guidelines for the treatment of CRPS will continue to be informed largely by consensus.

Implications for research

Design of future systematic reviews

There is a clear need to improve the methodological quality of systematic reviews of treatments for CRPS. In planning for future reviews, authors should follow methodological guidance for systematic reviews outlined in the Cochrane Handbook (Higgins 2021). Careful consideration of the review Population, Intervention, Comparison(s), Outcome and Time (PICOT) is required when formulating the review question. Rather than limiting the scope of a review to a single CRPS subtype, authors should aim to include evidence on all CRPS subtypes, and report results separately. This will ensure no important evidence is excluded. In order to minimise duplication of reviews and reporting bias, methods should be established in a protocol prior to the conduct of the review and registered on open databases such as PROSPERO (Cashin 2021). To facilitate transparent, complete and accurate reporting of what was done, reviews should adhere to the PRISMA reporting guideline (Page 2021). Authors should clearly describe the included interventions in accordance with published guidance (Hoffmann 2017) in order to improve the usability of the review by clinicians, patients and policy makers.

Design of randomised trials

We have identified that there is very low-certainty evidence for most interventions used to treat pain and disability in CRPS. It is unlikely that further small, short-term studies testing poorly-defined interventions will meaningfully improve this uncertainty. There is an urgent need for adequately powered, high-quality

randomised controlled trials, tested over clinically-relevant time frames. There are many challenges to addressing this problem. Given the relatively low incidence of CRPS, it remains difficult to recruit adequate numbers into clinical trials. The best chance of solving this issue may be through multicentre, international collaborative research projects which recruit from much larger clinical populations. The use of telehealth trials could facilitate this. Recruitment targets may be more easily met through alterations to trial design parameters (Parmar 2016) and Bayesian approaches to increase statistical power (Partington 2022), and efficiency could be maximised by testing two or more interventions in a single factorial trial (Kahan 2022).

Future trials should use established diagnostic criteria (Harden 2010) and specify the type and aetiology of CRPS under investigation (Goebel 2021). Comprehensive reporting of participant characteristics, including those that stratify health opportunities and outcomes (O'Neill 2014), will help to assess the generalisability of findings. Trial interventions must be carefully selected based on major clinical uncertainty or rigorous pilot research. There is a critical need for industry-independent placebo-controlled replication trials of intravenous ketamine and bisphosphonates, and trials of routinely used pharmacological interventions such as tricyclic antidepressants and opioids. Trials testing pragmatic, multimodal models of functional restoration, such as those endorsed by clinical guidelines (Bruehl 2022), against minimal or no care should be also prioritised. Trialists should consider optimal strategies for reporting pain in clinical trials (Busse 2015) and measure outcomes specified in the core set for CRPS (Grieve 2017). There is also a clear need to improve the measurements and reporting of adverse events in the field. Trial reports should fully adhere to CONSORT guidance (Schulz 2010) and interventions should be described in sufficient detail to allow replication by using the TIDIER guidelines (Hoffmann 2014).

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The following people conducted the editorial process for this article:

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ADDITIONAL TABLES

Table 1. The Budapest diagnostic criteria for CRPS

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in three of the four following categories* • *Sensory*: reports of hyperaesthesia and/or allodynia • *Vasomotor*: reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry • *Sudomotor/oedema*: reports of oedema and/or sweating changes and/or sweating asymmetry • *Motor/trophic*: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign at time of evaluation in two or more of the following categories* • *Sensory*: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement) • *Vasomotor*: evidence of temperature asymmetry and/or skin colour changes and/or asymmetry • *Sudomotor/oedema*: evidence of oedema and/or sweating changes and/or sweating asymmetry • *Motor/trophic*: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

Table 1. The Budapest diagnostic criteria for CRPS *(Continued)*

4. There is no other diagnosis that better explains the signs and symptoms

*The Budapest research criteria increases specificity for research settings by requiring the presence of all four symptom categories and at least two sign categories

Table 2. Reasons for review exclusion

Reason for exclusion	Papers excluded
Ineligible study design	Aiyer 2018*; Bussa 2015*; De Souza 2015*; Dirckx 2012*; Dworkin 2013*; Friend 2022*; Galafassi 2021*; Jadad 1995*; Nagpal 2021*; Roche Bueno 2020*; Soin 2021*; Wang 2021**; Wertli 2014**; Żyluk 2018*
Insufficient CRPS exclusivity	Aamir 2020; Aiyer 2016; Andreae 2015; Balanaser 2022; Bies 2022; Birse 2012; Boychuk 2015; Boyd 2019; Brookes 2017; Buksnys 2020; Casale 2021; Chaparro 2012; Cooper 2017; Corrigan 2012; Datta Gupta 2022; David 2018; Deer 2020; Derry 2012a; Derry 2012b; Derry 2013; Derry 2014; Derry 2015a; Derry 2015b; Derry 2016; Derry 2017b; Derry 2019; Di Stefano 2021; Duarte 2020; Duehmke 2017; Dykukha 2021; Eccleston 2015; Finnerup 2015; Gallagher 2015; Gaskell 2014; Gaskell 2016; Gibson 2017; Hary 2022; Hearn 2012; Hearn 2014a; Hearn 2014b; Hoydonckx 2019; Iskedjian 2007; Jia 2022; Jiang 2022; Jin 2015; Ju 2017; Julian 2020; Jupudi 2021; Kapustin 2020; Knezevic 2020; Li 2015b; Liao 2017; Lunn 2014; Mailis-Gagnon 2004; Markman 2017; Martins de Andrade 2016; McNicol 2013; McNicol 2017; McParland 2021; Meng 2017; Mohiuddin 2021; Moisset 2020; Moore 2012; Moore 2015a; Moore 2015b; Moore 2015c; Mu 2017; Mücke 2018; Ney 2013; O'Connell 2010; Petzke 2016; Shi 2016; Shin 2021; Silvinato 2020; Singh 2017; Sommer 2020; Stannard 2016; Thieme 2016; Tremont-Lukats 2005; Vargas-Espinosa 2012; Wang 2017b; Wei 2019; Wiffen 2013a; Wiffen 2013b; Wiffen 2014a; Wiffen 2014b; Wiffen 2015; Wiffen 2016; Wiffen 2017; Zhou 2017; Wrzosek 2015
No novel coverage in addition to existing Cochrane reviews or other included reviews	Azari 2012; Brunner 2009; Chitneni 2021; Collins 2010; Connolly 2015; Daly 2009; Fabregat 2013; Gatzinsky 2021; Grabow 2003; Lu 2009; Matuschek 2017; Méndez-Rebolledo 2017; Nardone 2018; Oh 2015; Pearl 2020; Perez 2001; Rothgangel 2011; Selph 2011; Siongco 2020; Simpson 2009; Turner 2004; Van den Berg 2022; Visnjevac 2017
Previous version of already included review	Cepeda 2005; Moore 2011; Stanton 2013; Smart 2016; Straube 2010
Did not report outcomes relevant to this overview	Lin 2012; Packham 2018
Included randomised and non-randomised studies but did not report separately	Zhao 2018

*Not a systematic review that satisfied a judgement of 'Yes' on third AMSTAR criterion (Shea 2007)
**Excluded due to unclear network meta-analysis methodology and uninterpretable effect estimates

Table 3. List of interventions, reviews and trials included in the overview

Intervention	Review	Trials contributed and sample size (n)
Oral, intravenous and topical pharmacotherapy		
Bisphosphonates	Chauvineau 2005	Cohen 1998 (n = 14)
	Chevreau 2017	Manicourt 2004 (n = 40)

Table 3. List of interventions, reviews and trials included in the overview *(Continued)*

		Robinson 2004 (n = 27)
		Varenna 2000 (n = 32)
		Varenna 2013 (n = 82)
	Duong 2018	Eun Young 2016 (n = 21)
	Fassio 2022	Varenna 2021 (n = 78)
Botulinum toxin A	Duong 2018	Safarpour (n = 8)
Calcitonin	Tran 2010	Gobelet 1992 (n = 66)
		Gobelet 1986 (n = 24)
		Sahin 2006 (n = 35)
Corticosteroids	Duong 2018	Kalita 2016 (n = 58)
	Fischer 2010	Kalita 2006 (n = 60)
		Lukovic 2006 (n = 60)
Free radical scavengers	Fischer 2010	Goris 1987 (n = 20)
		Zuurmond 1996 (n = 30)
		Perez 2003 (n = 146)
	Fischer 2010	Perez 2008 (n = 41)
Gabapentin	Moore 2014 (Cochrane)	Van de Vusse 2004 (n = 58)
Immunoglobulin	Duong 2018	Goebel 2010 (n = 12)
Infliximab	Xu 2016	Dirckx 2013 (n = 13)
Isosorbide dinitrate	Duong 2018	Groeneweg 2009 (n = 24)
Lenalidomide	Duong 2018	Manning 2014 (n = 147)
NMDA receptor antagonists	Orhurhu 2019	Schwartzman 2009 (n = 60)
		Sigtermans 2009 (n = 19)
	Duong 2018	Fischer 2013 (n = 56)
		Van der Plas 2013 (n = 22)
	Cossins 2013	Gustin 2010 (n = NR)
NSAIDs	Duong 2018	Breuer 2014 (n = 20)
Sarpogrelate hydrochloride	Tran 2010	Ogawa 1998 (n = 30)
Tadalafil	Tran 2010	Groeneweg 2008 (n = 24)
Interventional procedures		

Table 3. List of interventions, reviews and trials included in the overview *(Continued)*

Neuraxial therapy		
Epidural clonidine	Tran 2010	Rauck 1993 (n = 26)
Intrathecal baclofen	Duong 2018	Van der Plas 2011 (n = 14)
Intrathecal clonidine	Duong 2018	Rauck 2015 (n = 20)
Intrathecal glycine	Duong 2018	Munts 2009 (n = 18)
Intrathecal methylprednisolone	Duong 2018	Munts 2010 (n = 10)
Intravenous regional blockade (IVRB)		
IVRB atropine	Tran 2010	Glynn 1993 (n = 30)
IVRB droperidol	Xu 2016	Kettler 1988 (n = 6)
IVRB guanethidine	Xu 2016	Blanchard 1990 (n = 21) Livingstone 2002 (n = 57) Ramamurthy 1995 (n = 60)
IVRB guanethidine/lidocaine/reserpine	Xu 2016	Rocco 1989 (n = 12)
IVRB ketanserin	Xu 2016	Bounameaux 1984 (n = 9) Hanna 1989 (n = 9)
IVRB lidocaine	Challapalli 2005 (Cochrane)	Wallace 2000 (n = 16)
IVRB lidocaine/ketorolac	Xu 2016	Eckmann 2011 (n = 12)
IVRB lidocaine/methylprednisolone	Fischer 2010	Taskaynatan 2004 (n = 22)
IVRB parecoxib/lidocaine/clonidine	Fassio 2022	Frade 2005 (n = 30)
Local anaesthetic sympathetic blockade (LASB)		
LASB	O'Connell 2016 (Cochrane)	Zeng 2003 (n = 60)
LASB lidocaine	O'Connell 2016 (Cochrane)	Aydemir 2006 (n = 25) Price 1998 (n = 7) Lim 2007 (n = 38) Nascimento 2010 (n = 43) Yoo 2012 (n = 42)

Table 3. List of interventions, reviews and trials included in the overview *(Continued)*

LASB botulinum toxin A/ bupivacaine	O'Connell 2016 (Cochrane)	Carroll 2009 (n = 9)
LASB bupivacaine	O'Connell 2016 (Cochrane)	Bonelli 1983 (n = 19) Toshniwal 2012 (n = 33)
LASB lidocaine/bupivacaine	O'Connell 2016 (Cochrane)	Rodriguez 2005 (n = 82)
LASB lidocaine/clonidine	O'Connell 2016 (Cochrane)	Freitas 2013 (n= 40)
LASB ropivacaine/triamcinolone	O'Connell 2016 (Cochrane)	Rocha 2014 (n = 36)
Sympathectomy	Straube 2013 (Cochrane)	Manjunath 2008 (n = 20)
Neuromodulation		
Repetitive transcranial magnetic stimulation	Cossins 2013	Pleger 2004 (n = NR) Picarelli 2010 (n = NR)
Spinal cord stimulation	Duong 2018	Deer 2017 (n= 146) Kriek 2017 (n = 40)
	Tran 2010	Kemler 2000 (n = 54) Kemler 2004 (n = NR) Kemler 2008 (n = NR)
Rehabilitation		
CO_2 and whirlpool baths	Smart 2022 (Cochrane)	Mucha 1992 (n = 40) Devrimsel 2015 (n = 60)
Electrophysical agents	Smart 2022 (Cochrane)	Askin 2014 (n = 45) Benedetti 2018 (n = 30) Bilgili 2016 (n = 30) Büyükturan 2018 (n = 42) Dimitrijevic 2014 (n = 50) Durmus 2004 (n = 40) Hazneci 2005 (n = 30)
Electro-acupuncture and massage	Smart 2022 (Cochrane)	Li 2012a (n = 120)
Exposure-based interventions	Smart 2022 (Cochrane)	Barnhoorn 2015 (n = 56)

Table 3. List of interventions, reviews and trials included in the overview *(Continued)*

		den Hollander 2016 (n = 46)
Fluidotherapy	Smart 2022 (Cochrane)	Ozcan 2019 (n = 32)
Graded motor imagery and mirror therapy	Smart 2022 (Cochrane)	Cacchio 2009a (n = 24) Cacchio 2009b (n = 48) Moseley 2004 (n = 13) Moseley 2006 (n = 37) Saha 2021 (n = 38) Sarkar 2017 (n = 30) Schreuders 2014 (n = 18) Strauss 2021 (n = 22) Vural 2016 (n = 30)
Manual lymphatic drainage	Smart 2022 (Cochrane)	Duman 2009 (n = 34) Uher 2000 (n = 40)
Multimodal physiotherapy	Smart 2022 (Cochrane)	Oerlemans 1999 (n = 135) Topcuoglu 2015 (n = 40)
Prism adaptation	Smart 2022 (Cochrane)	Halicka 2021 (n = 49)
Tactile discrimination	Smart 2022 (Cochrane)	Moseley 2009 (n = 10)
Virtual reality	Smart 2022 (Cochrane)	Hwang 2014 (n = 39) Jeon 2014 (n = 10) Lewis 2021 (n = 45)
Complementary and alternative therapies		
Acupuncture	Forouzanfar 2002	Fialka 1993 (n = 14) Kho 1995 (n = 28) Korpan 1999 (n = 14)
	Smith 2005	Ernst 1995 (n = 14)
	Peng 2018	Chai 2016 (n = 118) Chang 2005 (n = 80) Chen 2015 (n = 94) Gao 2016 (n = 100) Li 2012b (n = 60) Li 2015a (n = 92) Liang 2016 (n = 32)

Table 3. List of interventions, reviews and trials included in the overview *(Continued)*

		Liao 2006 (n = 90) Niu 2015 (n = 108) Shang 2008 (n = 80) Shen 2014 (n = 60) Sun 2012 (n = 60) Tie 2016 (n = 100) Wan 2013 (n = 120) Wang 2017a (n = 142) Wu 2014 (n = 200) Xu 2015 (n = 80) Zhao 2004 (n = 54) Zhang 2015 (n = 92) Zhong 2011 (n = 158)
	Forouzanfar 2002	Korpan 1999 (n = 14)
Qigong	Smith 2005	Wu 1999 (n = 26)
Relaxation therapy	Smith 2005	Fialka 1996 (n = 18)
Other interventions		
Occlusal splints	Cossins 2013	Fischer 2008 (n = NR)

CO_2: carbon dioxide
IVRB: intravenous regional blockade
LASB: local anaesthetic sympathetic blockade
NMDA: N-methyl D-aspartate
NR: not reported
NSAIDs: non-steroidal anti-inflammatory drugs

Table 4. Characteristics of included reviews

Review	Date of last search	Population	Interventions	Comparisons	Outcomes of interest specified?	Reported outcomes relevant to this overview
Cochrane reviews						
Challapalli 2005	May 2004 (search stabilised in 2020)	Participants of any age with neuropathic pain	Lidocaine or its analogs given parenterally or orally	Placebo or any active treatment	Yes	Pain intensity; pain relief; adverse events
Moore 2014	March 2014	Adult participants ≥ 18 years of age and above with neuropathic pain	Gabapentin	Placebo, no intervention, or any other ac-	Yes	Pain intensity; adverse events; serious adverse events

Table 4. Characteristics of included reviews *(Continued)*

				tive comparator		
O'Connell 2016	September 2015	CRPS in children or adults (diagnostic criteria not specified)	Selective sympathetic blockade with local anaesthetics	Placebo, no treatment, or alternative intervention	Yes	Pain intensity, adverse events
Smart 2022	July 2021	Adults ≥ 18 years of age, diagnosed with CRPS I or II using established or validated diagnostic criteria	Physiotherapy interventions employed either as standalone interventions or in combination	Placebo, no treatment, another intervention or usual care, or varying physiotherapy interventions compared with each other	Yes	Pain intensity; disability; health-related quality of life; patient global impression of change; adverse effects
Straube 2013	June 2013 (search stabilised in 2020)	Participants of any age, with any duration of neuropathic pain or CRPS (diagnostic criteria not specified)	Destructive surgical or chemical sympathectomy	Placebo (sham) or other active treatment, provided both participants and outcome assessors were blind to treatment group allocation	Yes	Pain relief; adverse events
non-Cochrane reviews						
Chauvineau 2005	2003	Participants with CRPS I or reflex sympathetic dystrophy (diagnostic criteria not specified)	Bisphosphonates	Not specified	No	Pain intensity; side effects
Chevreau 2017	2014	Adult participants with CRPS I according to Harden 2007 and Harden 2010 criteria	Bisphosphonates	Placebo	Yes	Pain; function; adverse events
Cossins 2013	February 2012	Adult participants with CRPS I or II (diagnostic criteria not specified)	Any intervention	Any comparison	Yes	Pain intensity
Duong 2018	August 2017	Participants with CRPS (diagnostic criteria not specified)	Any intervention	Any comparison	No	Pain intensity; disability; adverse effects; patient-reported global assessment of effect
Fassio 2022	June 2021	Adults with CRPS I according to Harden 2010, Galer 1998, Kozin 1981 or Veldman 1993 criteria	Pharmacological interventions	Placebo or other active treatments	Yes	Pain intensity; adverse events; serious adverse events

Table 4. Characteristics of included reviews *(Continued)*

Fischer 2010	December 2009	CRPS I (diagnostic criteria not specified)	Anti-inflammatory therapies	Any comparison	Yes	Pain, clinical improvement
Forouzanfar 2002	June 2000	RSD and CRPS I (diagnostic criteria not specified)	Any intervention	Any comparison	Yes	Pain intensity
Orhurhu 2019	December 2017	Subjects ≥ 18 years of age with chronic pain for ≥ 3 months	Ketamine	Placebo with or without conventional medical management	Yes	Pain intensity; adverse events
Peng 2018	July 2017	Participants aged ≥ 18 years of age with clinically confirmed shoulder-hand syndrome after stroke without complications (diagnostic criteria not specified)	Traditional manual acupuncture combined with rehabilitation	Placebo/sham acupuncture plus rehabilitation therapy or rehabilitation therapy alone	Yes	Pain intensity; function; activities of daily living
Smith 2005	November 2004	CRPS I (diagnostic criteria not specified)	Physiotherapeutic modalities	Any comparison	No	Pain intensity, disability; participant ratings of improvement; activities of daily living
Tran 2010	April 2009	CRPS I and II (diagnostic criteria not specified)	Any intervention	Any comparison	No	Pain intensity; disability; quality of life; participant ratings of improvement; adverse events
Xu 2016	February 2015	CRPS (diagnostic criteria not specified)	Intravenous therapies	Any comparison	No	Pain intensity; function; quality of life; adverse effects

CRPS: complex regional pain syndrome
RSD: reflex sympathetic dystrophy

Table 5. Results of AMSTAR 2 quality assessment

Review ID	1	2*	3	4*	5	6	7*	8	9*	10	11*	12	13*	14	15*	16	Overall confidence
Challapalli 2005**	+	P	-	P	+	-	+	P	P	-	+	+	-	+	+	+	Low
Chauvineau 2005	-	-	-	P	-	-	-	P	-	-	NA	NA	-	-	NA	-	Critically low
Chevreau 2017	+	-	-	-	+	+	-	-	-	-	+	-	+	-	+	+	Critically low
Cossins 2013	+	-	+	P	+	+	+	P	P	-	NA	NA	+	+	NA	+	Low
Duong 2018	-	-	+	-	+	+	+	P	+	-	NA	NA	-	-	NA	+	Critically low
Fassio 2022	+	P	-	-	+	-	+	-	+	-	+	-	-	+	-	+	Critically low
Fischer 2010	-	-	-	P	-	-	-	P	P	-	NA	NA	-	-	NA	-	Critically low
Forouzanfar 2002	-	-	-	-	+	-	-	-	P	+	NA	NA	-	+	NA	+	Critically low
Moore 2014**	+	+	-	P	+	+	+	P	P	+	+	+	+	-	+	+	High
O'Connell 2016**	+	+	-	+	+	+	+	P	+	+	NA	NA	+	+	NA	+	High
Orhurhu 2019	+	+	-	P	+	-	-	+	+	-	+	-	+	+	+	+	Low
Peng 2018	+	-	-	-	+	+	-	-	+	-	+	-	+	-	+	+	Critically low
Smart 2022**	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	High

Table 5. Results of AMSTAR 2 quality assessment *(Continued)*

Smith 2005	-	-	-	-	-	-	-	P	-	-	NA	NA	-	-	NA	-	Critically low
Straube 2013**	+	+	+	+	+	+	+	+	+	-	NA	NA	+	+	NA	+	High
Tran 2010	-	-	+	-	-	-	+	P	-	-	NA	NA	-	-	NA	+	Critically low
Xu 2016	-	-	-	-	+	+	-	P	-	-	NA	NA	-	-	NA	+	Critically low

*AMSTAR 2 critical domain; **Cochrane review' + = Yes; - = No; P = Partial yes; NA = No meta-analysis conducted

AMSTAR Items

1. Did the research questions and inclusion criteria for the review include the components of PICO?
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?*
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?*
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?*
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?*
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?*
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13. Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?*
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?*
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Table 6. Overview of reviews: Oral, intravenous and topical pharmacotherapy

Intervention and comparison	Contributing reviews	Relative effect	Number of participants (trials)	GRADE certainty of evidence	Comments
Anticonvulsants					
Gabapentin					
Oral gabapentin vs placebo	Moore 2014 (Cochrane)	**Pain intensity** GPE 'very much improved': RR 4.00, 95% CI 0.90 to 17.83; P = 0.07 **Adverse events** Any adverse event: RR 1.64, 95% CI 1.15 to 2.32 (higher for gabapentin) Somnolence: RR 4.72, 95% CI 1.45 to 15.35 (higher for gabapentin) Peripheral oedema: RR 0.31, 95% CI 0.03 to 2.93 Ataxia: RR 9.0, 95% CI 0.5 to 162.53	58 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and twice for imprecision
Anti-inflammatory therapies					
Corticosteroids					
Oral prednisolone vs oral piroxicam	Fischer 2010	**Disability** Barthel index: no significant between-group difference	60 (1)	Very low	Downgraded once for inconsistency and twice for imprecision
Continued oral prednisolone vs withdrawal of oral prednisolone	Duong 2018	**Pain intensity** VAS: mean (SD) 2.4 (1.0) vs 4.9 (2.1); P < 0.01) (in favour of continued oral prednisolone)	58 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and twice for imprecision

Table 6. Overview of reviews: Oral, intravenous and topical pharmacotherapy *(Continued)*

		Disability Bathel Index: no significant between-group difference Modified Rankin Scale: no significant between-group difference			
Oral prednisone vs placebo	Fischer 2010	**Pain intensity** VAS: no significant between-group difference	60 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and twice for imprecision
NSAIDs					
Intravenous parecoxib vs placebo	Duong 2018	**Pain intensity** No between-group difference	20 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and twice for imprecision
Free radical scavengers					
DMSO					
Topical DMSO vs placebo	Fischer 2010	**Pain intensity** VAS: significant between-group difference (in favour of DMSO)	30 (1)	Very low	Downgraded once for inconsistency and twice for imprecision
Topical DMSO vs oral N-acetylcysteine	Fischer 2010	**Pain intensity** No significant between-group difference	146 (1)	Low	Downgraded once for inconsistency and once for imprecision
Mannitol					
Intravenous mannitol vs placebo	Fischer 2010	**Pain intensity** VAS: no significant between-group difference	41 (1)	Very low	Downgraded once for inconsistency and twice for imprecision
Bisphosphonates					
Bisphosphonates vs placebo	Chevreau 2017 Fassio 2022	**Pain intensity** SMD: -2.6, 95% CI -1.8 to -3.4; P = 0.001; I^2 = 81%; 4 trials; n = 181 (in favour of bisphosphonates)	259 (5)	Low	Downgraded once for inconsistency and once for imprecision

Table 6. Overview of reviews: Oral, intravenous and topical pharmacotherapy *(Continued)*

		0 to 100 VAS: MD -21.80; 95% CI -30.28 to -13.32; 1 trial; n = 78 (in favour of bisphosphonates)			
	Chevreau 2017	**Adverse events** Any adverse event: RR 2.10, 95% CI 1.27 to 3.47 (higher for bisphosphonates)	181 (4)	Moderate	Downgraded once for imprecision
Intranasal pamidronate vs intranasal calcitonin	Chauvineau 2005	**Pain intensity** VAS: no significant between-group differences at post-intervention, short-term & medium-term	14 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and twice for imprecision
Calcitonin					
Intranasal calcitonin vs placebo	Tran 2010	**Pain intensity** No between-group difference	38 (1)	Very	Downgraded once for serious study limitations, once for inconsistency and twice for imprecision
Calcitonin + physiotherapy vs physiotherapy alone	Tran 2010	**Pain intensity** No between-group difference 1 trial Four-point pain scale: significant between-group difference (in favour of calcitonin + physiotherapy; 1 trial)	90 (2)	Very low	Downgraded once for serious study limitations, once for inconsistency and twice for imprecision
Intranasal calcitonin vs oral paracetamol	Tran 2010	**Pain intensity** No between-group difference	35 (1)	Very low	Downgraded once serious study limitations, once for inconsistency and twice for imprecision
Immunomodulators					
Infliximab					
Intravenous infliximab vs placebo	Xu 2016	**Pain intensity** No between-group difference	13 (1)	Very low	Downgraded once serious study limitations, once for inconsistency and twice for imprecision
Lenalidomide					

Table 6. Overview of reviews: Oral, intravenous and topical pharmacotherapy *(Continued)*

Oral lenalidomide vs placebo	Duong 2018	**Pain intensity** ≥ 30% responder rate: no between-group differences **Disability** Activity rating: no between-group difference	147 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and once for imprecision
NMDA receptor antagonists					
Ketamine					
Intravenous ketamine vs placebo	Orhurhu 2019	**Pain intensity** 0 to 10 NRS: post-intervention MD -2.38, 95% CI -3.53 to -1.23; I^2 = 34.9%; Tau^2 = 0.34; 2 trials, n = 79 (in favour of ketamine); medium term MD -0.55, 95% CI -1.50 to 0.39; I^2 = 0%; 2 trials, n = 79	79 (2)	Very low	Downgraded once for serious study limitations and twice for imprecision
Magnesium					
Intravenous magnesium vs placebo	Duong 2018	**Pain intensity** 11-point NRS: no between-group differences at post-intervention, short-term & medium-term	56 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and twice for imprecision
Memantine					
Memantine	Cossins 2013	**Pain intensity** VAS: significant between-group difference (in favour of memantine)	NR (1)	Very low	Downgraded once for inconsistency and twice for imprecision
Other pharmacological therapies					
Botulinum toxin A					
Intradermal/subcutaneous botulinum toxin A vs placebo	Duong 2018	**Pain intensity** BPI: no between-group difference	8 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and twice for imprecision

Table 6. Overview of reviews: Oral, intravenous and topical pharmacotherapy *(Continued)*

Isosorbide dinitrate					
Topical isosorbide dinitrate vs placebo	Duong 2018	**Pain intensity** No between-group difference **Disability** DASH: no between-group difference	24 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and twice for imprecision
Sarpogrelate hydrochloride					
Oral sarpogrelate hydrochloride + conventional care vs conventional care alone	Tran 2010	**Pain intensity** VAS: no between-group difference	30 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and twice for imprecision
Tadalafil					
Oral tadalafil vs placebo	Tran 2010	**Pain intensity** VAS: 15% vs 0% reduction, P = 0.004, (in favour of tadalafil)	24 (1)	Very low	Downgraded once serious study limitations, once for inconsistency and twice for imprecision

Unless specifically stated, comparisons refer to outcomes measured at the end of the intervention period.
BPI = Brief Pain Inventory
DASH = Disabilities of the Arm, Shoulder and Hand questionnaire
DMSO = dimethyl sulfoxide
GPE = Global Perceived Effect
MD = mean difference
NR = not reported
NRS = numeric rating scale
SMD = standardised mean ifference
RR = risk ratio
VAS = visual analogue scale

Table 7. Overview of reviews: Interventional procedures

Intervention and comparison	Contributing reviews	Relative effect	Number of participants (trials)	GRADE certainty of evidence	Comments
Neuraxial therapy					
Epidural pharmacological administration					

Table 7. Overview of reviews: Interventional procedures *(Continued)*

Epidural clonidine (300 µg and 700 µg) vs placebo	Tran 2010	**Pain intensity** VAS: significant between-group difference (in favour of both clonidine doses)	26 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and twice for imprecision
Epidural clonidine 300 µg vs epidural clonidine 700 µg	Tran 2010	**Pain intensity** VAS: no significant difference **Adverse events** Sedation: significant between-group difference (higher for 700 µg clonidine)	26 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and twice for imprecision
Intrathecal pharmacological administration					
Intrathecal baclofen 0.75 mg/mL^{-1} vs 3 mg/mL^{-1} infusions	Duong 2018	**Pain intensity** NRS: no between-group difference	14 (1)	Very low	Downgraded once for inconsistency and twice for imprecision
Intrathecal clonidine vs intrathecal adenosine	Duong 2018	**Pain intensity** > 30% responder rate: no between-group difference	20 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and twice for imprecision
Intrathecal glycine vs placebo	Duong 2018	**Pain intensity** NRS: no between-group difference **Disability** Radboud Skills Questionnaire: no between-group difference Walking Skills Questionnaire: no between-group difference	18 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and twice for imprecision

Table 7. Overview of reviews: Interventional procedures *(Continued)*

		Adverse events Any adverse event: no between-group difference			
Intrathecal methylprednisolone vs placebo	Duong 2018	**Pain intensity** NRS: no between-group difference	10 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and twice for imprecision
Intravenous regional blockade (IVRB)					
Atropine IVRB vs placebo	Tran 2010	**Pain intensity** NRS: no between-group difference	30 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and twice for imprecision
Droperidol IVRB vs placebo	Xu 2016	**Pain intensity** No between-group difference	6 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and twice for imprecision
Guanethidine IVRB vs placebo	Xu 2016	**Pain intensity** No between-group differences post-intervention (2 trials); increase in pain intensity in guanethidine group at medium-term (1 trial)	138 (3)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
		Adverse events Any adverse event: No between-group difference (1 trial) Vasomotor instability: significant between-group difference (higher for guanethidine IVRB; 1 trial)	117 (2)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
Ketanserin IVRB vs placebo	Forouzanfar 2002	**Pain intensity**	18 (2)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision

Table 7. Overview of reviews: Interventional procedures *(Continued)*

		No significant between-group difference (1 trial) VAS: significant between-group difference (in favour of ketanserin IVRB; 1 trial)			
Lidocaine IVRB vs placebo	Challapalli 2005 (Cochrane)	**Adverse events** Light-headedness: significant between-group difference (higher for lidocaine IVRB)	16 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and twice for imprecision
Methylprednisolone + lidocaine bier block vs placebo	Fischer 2010	**Pain intensity** VAS: no significant between-group difference	22 (1)	Very low	Downgraded once for inconsistency, and twice for imprecision
Guanethidine + lidocaine IVRB vs reserpine + lidocaine IVRB vs lidocaine IVRB alone	Xu 2016	**Pain intensity** No between-group difference	12 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and twice for imprecision
Parecoxib, lidocaine + clonidine IVRB vs lidocaine and clonidine IVRB vs intravenous parecoxib, lidocaine and clonidine	Xu 2016	**Pain intensity** Significant between-group difference (in favour of parecoxib, lidocaine and clonidine IVRB)	30 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and twice for imprecision
Local anaesthetic sympathetic blockade					
Lidocaine stellate ganglion block vs placebo	O'Connell 2016 (Cochrane)	**Pain intensity** VAS: no significant between-group difference	32 (2)	Moderate	Downgraded once for imprecision
Lidocaine stellate ganglion block vs stellate ganglion ultrasound	O'Connell 2016 (Cochrane)	**Pain intensity** VAS: no significant between-group difference	25 (1)	Low	Downgraded once for inconsistency and once for imprecision
Bupivacaine stellate ganglion block vs guanethidine IVRB	O'Connell 2016 (Cochrane)	**Pain intensity**	19 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and once for imprecision

Table 7. Overview of reviews: Interventional procedures *(Continued)*

		100 mm linear scale: no significant between-group difference			
Lidocaine + clonidine lumbar plexus sympathetic block vs lumbar plexus pulsed radiofrequency	O'Connell 2016 (Cochrane)	**Pain intensity** No significant between-group difference	40 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and once for imprecision
Lidocaine stellate ganglion block vs oral prednisone	O'Connell 2016 (Cochrane)	**Pain intensity** 0 to 3 scale hand pain: MD 0.00, 95% CI −0.35 to 0.35	38 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and once for imprecision
Lidocaine sympathetic block vs lidocaine + clonidine IVRB	O'Connell 2016 (Cochrane)	**Pain intensity** 0 to 10 VAS: no significant between-group difference	43 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and once for imprecision
Ropivacaine/triamcinolone thoracic sympathetic block vs subcutaneous ropivacaine/triamcinolone	O'Connell 2016 (Cochrane)	**Pain intensity** 0 to 10 BPI: post-intervention MD -1.25, 95% CI -3.20 to 0.70; long-term follow-up (MD -2.39, 95% CI -4.72 to -0.06 (in favour of sympathetic block)	36 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and once for imprecision
Continuous bupivacaine stellate ganglion block vs continuous bupivacaine brachial plexus block	O'Connell 2016 (Cochrane)	**Pain intensity** 0 to 10 scale: significant between-group difference in favour of continuous brachial plexus block	33 (1)	Low	Downgraded once for inconsistency and once for imprecision
Lidocaine image-guided vs lidocaine nonimage-guided stellate ganglion block	O'Connell 2016 (Cochrane)	**Pain intensity** 0 to 10 VAS: MD -0.58, 95% CI -1.51 to 0.35	42 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, once for imprecision, and once for indirectness
Stellate ganglion block + rehabilitation vs rehabilitation alone	O'Connell 2016 (Cochrane)	**Pain intensity** 0 to 10 VRS: MD 0.2, 95% CI -1.3 to 1.7	60 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency and once for imprecision.
Lidocaine and bupivacaine stellate ganglion block +	O'Connell 2016 (Cochrane)	**Pain intensity**	82 (1)	Very low	Downgraded once for serious study limitations,

Table 7. Overview of reviews: Interventional procedures *(Continued)*

conventional care vs conventional care alone		50% responder rate: ARR = 17%; NNTB = 6%			once for inconsistency and once for imprecision
Sympathectomy					
Percutaneous radiofrequency thermal lumbar sympathectomy vs phenol lumbar sympathetic neurolysis	Straube 2013	**Pain intensity** No significant between-group difference post-intervention or medium-term	20 (1)	Very low	Reasons for downgrading NR

Unless specifically stated comparisons refer to outcomes measured at the end of the intervention period.
ARR = absolute risk reduction
BPI = Brief Pain Inventory
IVRB = intravenous regional blockade
MD = mean difference
NNTB = number needed to treat for an additional beneficial outcome
NR = not reported
NRS = numeric rating scale
VAS = visual analogue scale
VRS = verbal rating scale

Table 8. Overview of reviews: Neuromodulation

Intervention and comparison	Contributing reviews	Relative effect	Number of participants (trials)	GRADE certainty of evidence	Comments
Neuromodulation					
Implanted spinal neuromodulation					
Standard, burst, 500 Hz and 1000 Hz SCS vs placebo	Duong 2018	**Pain intensity** Significant between-group differences (in favour of all SCS groups)	40 (1)	Very low	Downgraded once for inconsistency and twice for imprecision
SCS vs dorsal root ganglion stimulation	Duong 2018	**Adverse events** No between-group differences at long-term	146 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
SCS + physiotherapy vs physiotherapy alone	Tran 2010	**Pain intensity**	52 (2)	Very low	Downgraded once for serious study limitations, once for incon-

Table 8. Overview of reviews: Neuromodulation *(Continued)*

		VAS: mean (SD) 2.4 (2.5) vs 0.2 (1.4); P < 0.001) at medium-term; significant between-group differences at long-term (both in favour of SCS) **Disability** No between-group difference at medium-term			sistency and twice for imprecision
Non-invasive brain stimulation					
Repetitive transcranial magnetic stimulation vs placebo	Cossins 2013	**Pain intensity** Significant between-group differences post-intervention (2 trials); no significant between-group difference at medium-term (1 trial)	NR (2)	Very low	Downgraded once for inconsistency and twice for imprecision

Unless specifically stated comparisons refer to outcomes measured at the end of the intervention period.
MD = mean difference
NR = not reported
SCS = spinal cord stimulation
VAS: visual analogue scale

Table 9. Overview of reviews: Rehabilitation

Intervention and comparison	Contributing reviews	Relative effect	Number of participants (trials)	GRADE certainty of evidence	Comments
Sensory-motor training strategies					
Graded motor imagery (GMI)					
GMI vs standard care	Smart 2022 (Cochrane)	**Pain intensity** 0 to 100 VAS: post-intervention MD -14.45, 95% CI -23.02 to -5.87, P = 0.001; I^2 = 29%; two trials, n = 49; medium-term MD -21.00, 95% CI -31.17 to -10.83; 1 trial, n = 37 (both in favour of GMI) No between-group difference short-term (1 trial) **Disability**	68 (3)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision

Table 9. Overview of reviews: Rehabilitation *(Continued)*

		0 to 10 patient specific functional scale: post-intervention MD 1.87, 95% CI 1.03 to 2.71, P < 0.001; I^2 = 41%; 2 trials, n = 49; medium-term MD 2.30, 95% CI 1.12 to 3.48, P < 0.001; 1 trial, n = 37			
GMI vs waiting-list control	Smart 2022 (Cochrane)	**Pain intensity** 0 to 10 VAS: MD −0.58, 95% CI −1.94 to 0.78 **Adverse events** Increased swelling of the affected limb in 2 participants; increased pain in 12 participants (both occurring in GMI group)	22 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
Mirror therapy					
Mirror therapy vs placebo	Smart 2022 (Cochrane)	**Pain intensity** 0- to 100 VAS: 7/8 participants experienced reduced pain with mirror therapy vs 1/8 with placebo	24 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
Mirror therapy + stroke rehabilitation vs placebo mirror therapy + stroke rehabilitation	Smart 2022 (Cochrane)	**Pain intensity** 0 to 10 VAS: post-intervention MD -2.9, 95% CI -4.23 to -1.57, P < 0.001; medium-term MD -3.4, 95% CI -4.71 to -2.09; P < 0.001 (both in favour of mirror therapy) **Disability** 0 to 5 Wolf Motor Function: post-intervention 0-5 scale, MD -1.9, 95% CI -2.36 to -1.44; P < 0.001; medium-term MD -2.3, 95% CI -2.88 to -1.72; P < 0.001	48 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
Mirror therapy vs mental imagery	Smart 2022 (Cochrane)	**Pain intensity**	24 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and

Table 9. Overview of reviews: Rehabilitation *(Continued)*

		0 to 100 VAS: 7/8 participants experienced reduced pain with mirror therapy vs 2/8 with placebo			once for imprecision
Mirror therapy + stroke rehabilitation vs stroke rehabilitation alone	Smart 2022 (Cochrane)	**Pain intensity** 0 to 10 NRS: MD -1.40, 95% CI -2.26 to -0.54, P < 0.001; 1 trial (in favour of mirror therapy) 0 to 10 VAS: median within group change 0-10 VAS, 3 vs 1; 1 trial (in favour of mirror therapy) **Disability** 18 to 126 FIM: MD 21.95, 95% CI 9.71 to 34.19; P < 0.001; 1 study (in favour of mirror therapy) 0 to 14 Fugl-Meyer Assessment: median within-group change 3 vs 0; 1 study (in favour of mirror therapy)	68 (2)	Very low	Downgraded twice for serious study limitations, and once for imprecision.
Mirror visual feedback + medical management vs contrast baths + medical management	Smart 2022 (Cochrane)	**Pain intensity** 11-point NRS: MD -2.65, 95% CI -3.14 to -2.16; P < 0.001 (in favour of mirror visual feedback)	30 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
Mirror visual feedback + medical management vs contrast baths and exercise + medical management	Smart 2022 (Cochrane)	**Pain intensity** 11-point NRS: MD -2.60, 95% CI -3.08 to -2.12; P < 0.001 (in favour of mirror visual feedback)	30 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
Virtual reality					
Virtual body swapping with mental rehearsal vs 'watching movement only'	Smart 2022 (Cochrane)	**Pain intensity** 11-point pain scale: no between-group difference	39 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision

Table 9. Overview of reviews: Rehabilitation *(Continued)*

Virtual body swapping with mental rehearsal vs mental rehearsal only	Smart 2022 (Cochrane)	**Pain intensity** 11-point pain scale: no between-group difference	39 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
Virtual body swapping with mental rehearsal vs virtual body swapping alone	Smart 2022 (Cochrane)	**Pain intensity** No between-group difference	10 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
Virtual reality vs sham virtual reality	Smart 2022 (Cochrane)	**Pain intensity** 11-point NRS: MD 1.2; SMD 0.7 (measures of variance NR)	45 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
Tactile discrimination					
Four tactile discrimination training protocols compared with each other	Smart 2022 (Cochrane)	**Pain intensity** 100 mm VAS: no between-group differences **Adverse events** Increased pain during training	10 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
Prism adaptation					
Prism adaptation treatment vs placebo	Smart 2022 (Cochrane)	**Pain intensity** 11-point NRS: no between-group differences post-intervention and medium-term	49 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision.
Electrophysical agents					
Stellate ganglion ultrasound vs placebo	Smart 2022 (Cochrane)	**Pain intensity** 10 cm VAS: no between-group difference **Disability**	45 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision

Table 9. Overview of reviews: Rehabilitation *(Continued)*

		DASH: no between-group difference			
Stellate ganglion ultrasound vs TENS	Smart 2022 (Cochrane)	**Pain intensity** 0-10 VAS: MD 2.13, 95% CI 1.47 to 2.79; P < 0.001 (in favour of TENS)	30 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
Electromagnetic field therapy vs placebo	Smart 2022 (Cochrane)	**Pain intensity** 10 cm VAS: MD -2.2, 95% CI -1.99 to -2.41; P < 0.001; 1 trial; MD 1.6, 95% CI 0.83 to 2.37, P < 0.001; 1 trial (both in favour of electromagnetic field therapy); no between-group difference in 1 trial **Disability** 0 to 100 Maryland Foot Score: MD 14.4, 95% CI 11.36 to 17.44; P < 0.001; one study, n = 18 (in favour of electromagnetic field therapy) 0 to 100 DASH: MD -14.0 95% CI -4.41 to -23.59; P < 0.004; 1 study, n = 12 (in favour of electromagnetic field therapy) 0 to 100 Quick-DASH: 0-100, MD 2, 95% CI -3.91 to 7.91; one study **Adverse events** No between-group difference (1 study)	112 (3)	Very low	Downgraded once for serious study limitations, once for inconsistency
TENS vs placebo	Smart 2022 (Cochrane)	**Pain intensity** 10 cm VAS: MD -9, 95% CI -18.5 to 0.5; P = 0.074 (in favour of TENS) **Disability**	30 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision

Table 9. Overview of reviews: Rehabilitation *(Continued)*

		Duruöz Hand Index: MD -3.6, 95% CI -13.38 to 6.18; P = 0.48			
Laser therapy vs interferential therapy	Smart 2022 (Cochrane)	**Pain intensity** 0 to 100 VAS: MD -8.6, 95% CI -16.27 to -0.93; P = 0.03 (in favour of laser therapy) **Adverse events** No between-group difference	50 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
CO_2 bath therapy and exercise vs exercise alone	Smart 2022 (Cochrane)	**Pain intensity** Between-group difference in favour of CO_2 bath therapy	40 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
Whirlpool baths vs neuromuscular electrical stimulation	Smart 2022 (Cochrane)	**Pain intensity** 10 cm VAS: MD -0.65, 95% CI -1.03 to -0.27 ; P < 0.001 (in favour of whirlpool bath) **Adverse events** No between-group difference	60 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
Fluidotherapy + stroke rehabilitation vs stroke rehabilitation alone	Smart 2022 (Cochrane)	**Pain intensity** 10 cm VAS: no between-group difference **Disability** FIM: no between-group difference	32 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
Exposure-based interventions					
Pain exposure physical therapy	Smart 2022 (Cochrane)	**Pain intensity**	56 (1)	Very low	Downgraded once for serious study limitations, once for

Table 9. Overview of reviews: Rehabilitation *(Continued)*

apy vs usual physiotherapy		1-10 VAS: MD 0.61, 95% CI -0.70 to 1.92 at long-term			inconsistency, and once for imprecision
		Disability			
		0 to 100 DASH: MD 6.47, 95% CI -5.97 to 18.90 at long-term			
		0 to 40 Lower Limb Tasks Questionnaire: MD 5.11, 95% CI -0.45 to 10.68 at long-term			
Exposure in vivo vs usual physiotherapy	Smart 2022 (Cochrane)	**Pain intensity**	46 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
		0 to 10 NPS: MD -2.04 95% CI -3.01 to -1.07; P = 0.001 post-intervention; MD -2.82, 95% CI -4.18 to -1.46; P = 0.001 at medium-term (both in favour of exposure in vivo)			
		Disability			
		0 to 5 Radboud Skills Questionnaire: MD -1.08, 95% CI -1.60 to -0.56; P = 0.001 post-intervention; MD -1.30, 95% CI -0.92 to -1.69; P = 0.001 medium-term (both in favour of exposure in vivo)			
		0 to 10 Walking Ability Questionnaire: no between-group difference post-intervention; MD -3.62, 95% CI -6.78 to -0.47; P = 0.02 at medium-term (in favour of exposure in vivo)			
Multimodal physiotherapy					
Physiotherapy vs minimal care	Smart 2022 (Cochrane)	**Pain intensity**	135 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
		Between-group difference post-intervention; no between-group difference at long-term			
		Disability			

Table 9. Overview of reviews: Rehabilitation *(Continued)*

		5 to 50 Impairment Level Sum Score: MD -3.7, 95% CI -7.13 to -0.27, P = 0.03; long-term follow-up (in favour of physiotherapy) Radboud Skills Questionnaire: no between-group difference at long-term Modified Greentest: no between-group difference at long-term Radboud Dexterity Test: no between-group difference at long-term			
Physiotherapy vs occupational therapy	Smart 2022 (Cochrane)	**Pain intensity** No between-group difference at long-term **Disability** Impairment Level Sum Score: no between-group difference at long-term Radboud Skills Questionnaire: no between-group difference at long-term Modified Greentest: no between-group difference at long-term Radboud Dexterity Test: no between-group difference at long-term	135 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
Upper limb aerobic exercise + physiotherapy vs physiotherapy alone	Smart 2022 (Cochrane)	**Pain intensity** 10 cm VAS: MD -1.9, 95% CI -3.23 to -0.57; P < 0.005	40 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
Other physiotherapy-based interventions					
Manual lymphatic	Smart 2022 (Cochrane)	**Pain intensity**	74 (2)	Very low	Downgraded once for serious study

Table 9. Overview of reviews: Rehabilitation *(Continued)*

drainage therapy vs conventional care		No between-group difference			limitations, once for inconsistency, and once for imprecision
Electro-acupuncture and massage vs rehabilitation	Smart 2022 (Cochrane)	**Pain intensity** Pain on movement NRS: MD -1.70, 95% CI -2.09 to -1.31; P = 0.01 post-intervention; MD -1.40, 95% CI -1.78 to -1.02; P < 0.001 at short-term (both in favour of electro-acupuncture and massage) **Disability** Fugl-Meyer hand: no between-group difference post-intervention Fugl-Meyer upper limb no between-group difference at short-term **Adverse events** No between-group difference	120 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision

Unless specifically stated, comparisons refer to outcomes measured at the end of the intervention period.
CO_2 = carbon dioxide
DASH = Disabilities of the Arm, Shoulder and Hand questionnaire
FIM = Functional Independence Measure
GMI = graded motor imagery
MD = mean difference
NR = not reported
NPS = neuropathic pain scale
NRS = numeric rating scale
TENS = transcutaneous electrical nerve stimulation
VAS = visual analogue scale

Table 10. Overview of reviews: Complementary and alternative therapies and other interventions

Intervention and comparison	Contributing reviews	Relative effect	Number of participants (trials)	GRADE certainty of evidence	Comments
Complementary and alternative therapies					
Acupuncture					

Table 10. Overview of reviews: Complementary and alternative therapies and other interventions *(Continued)*

Acupuncture vs sham acupuncture	Forouzanfar 2002	**Pain intensity** VAS: no between-group differences (2 trials); significant between-group difference (in favour of acupuncture; 1 trial)	56 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and once for imprecision
Traditional manual acupuncture + rehabilitation vs rehabilitation alone	Peng 2018	**Pain intensity** VAS: MD 1.49, 95% CI 1.15 to 1.82; I^2 = 71%; Tau^2 = 0.17; 9 trials, n = 834 (in favour of manual acupuncture) **Disability** Fugl-Meyer Assessment: MD 8.42, 95% CI 6.74 to 10.10; I^2 = 94%; Tau^2 = 13.07; 20 trials, n = 1918 (in favour of manual acupuncture)	1918 (20)	Very low	Downgraded once for serious study limitations, once for inconsistency, once for imprecision and once for indirectness
Qigong					
Qigong vs placebo	Smith 2005	Pain intensity VAS: significant difference in number of participants with decreased pain (91% vs 36%; in favour of qigong)	26 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and twice for imprecision
Relaxation therapy					
Autogenic relaxation training + home treatment vs home treatment alone	Smith 2005	**Pain intensity** VAS: no between-group difference	18 (1)	Very low	Downgraded once for serious study limitations, once for inconsistency, and twice for imprecision
Other interventions					
Occlusal splints					
Occlusal splint vs control	Cossins 2013	**Pain intensity** NRS: no between-group difference	NR (1)	Very low	Downgraded once for inconsistency and twice for imprecision.

Unless specifically stated comparisons refer to outcomes measured at the end of the intervention period.
NRS = numeric rating scale
VAS = visual analogue scale

APPENDICES

Appendix 1. Search strategy Ovid MEDLINE

1 exp Complex Regional Pain Syndromes/

2 exp Neuralgia/

3 regional pain syndrome*.tw.

4 CRPS.tw.

5 (reflex and (sympathetic or neurovascular) and dystrophy).tw.

6 (RSD or RND).tw.

7 sudeck's atrophy.tw.

8 sudecks atrophy.tw.

9 algodystrophy.tw.

10 shoulder-hand syndrome*.tw.

11 causalgia.tw.

12 algoneurodystrophy.tw.

13 (neuropathic pain or neuralgia).tw.

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 (201110* or 201111* or 201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021* or 2022*).ed.

16 review.pt.

17 (medline or medlars or embase or pubmed or cochrane).tw,sh.

18 (scisearch or psychinfo or psycinfo).tw,sh.

19 cinahl.tw,sh.

20 ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.

21 (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.

22 (pooling or pooled or mantel haenszel).tw,sh.

23 (peto or dersimonian or der simonian or fixed effect).tw,sh.

24 (retraction of publication or retracted publication).pt.

25 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24

26 16 and 25

27 meta-analysis.pt.

28 meta-analysis.sh.

29 (meta-analys$ or meta analys$ or metaanalys$).tw,sh.

30 (systematic$ adj5 review$).tw,sh.

31 (systematic$ adj5 overview$).tw,sh.

32 (quantitativ$ adj5 review$).tw,sh.

33 (quantitativ$ adj5 synthesis$).tw,sh.

34 (methodologic$ adj5 review$).tw,sh.

35 (methodologic$ adj5 overview$).tw,sh.

36 (integrative research review$ or research integration).tw.

37 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36

38 26 or 37

BMJ Clinical Evidence search filter for MEDLINE used

Appendix 2. Search strategy Ovid Embase

1 exp Complex Regional Pain Syndrome/

2 exp Neuralgia/

3 regional pain syndrome*.tw.

4 CRPS.tw.

5 (reflex and (sympathetic or neurovascular) and dystrophy).tw.

6 (RSD or RND).tw.

7 sudeck's atrophy.tw.

8 sudecks atrophy.tw.

9 algodystrophy.tw.

10 shoulder-hand syndrome*.tw.

11 causalgia.tw.

12 algoneurodystrophy.tw.

13 (neuropathic pain or neuralgia).tw.

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 (201110* or 201111* or 201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021* or 2022*).dd.

16 exp review/

17 (literature adj3 review$).ti,ab.

18 exp meta analysis/

19 exp "Systematic Review"/

20 16 or 17 or 18 or 19

21 (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab.

22 RETRACTED ARTICLE/

23 21 or 22

24 20 and 23

25 (systematic$ adj2 (review$ or overview)).ti,ab.

26 (meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanal$).ti,ab.

27 24 or 25 or 26

28 14 and 15 and 27

BMJ Clinical Evidence search filter for Embase used

Appendix 3. Search strategy Cochrane Database of Systematic Reviews/DARE

#1 MeSH descriptor Complex Regional Pain Syndromes explode all trees

#2 MeSH descriptor Neuralgia explode all trees

#3 regional pain syndrome*

#4 CRPS

#5 (reflex and (sympathetic or neurovascular) and dystrophy)

#6 RSD or RND

#7 (sudeck's or sudecks) next atrophy

#8 algodystrophy

#9 shoulder-hand syndrome*

#10 causalgia

#11 algoneurodystrophy

#12 (neuropathic pain or neuralgia)

#13 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)

Appendix 4. Search strategy CINAHL

S18 S16 AND S17

S17 (TI (systematic* n3 review*)) or (AB (systematic* n3 review*)) or (TI (systematic* n3 bibliographic*)) or (AB (systematic* n3 bibliographic*)) or (TI (systematic* n3 literature)) or (AB (systematic* n3 literature)) or (TI (comprehensive* n3 literature)) or (AB (comprehensive* n3 literature)) or (TI (comprehensive* n3 bibliographic*)) or (AB (comprehensive* n3 bibliographic*)) or (TI (integrative n3 review)) or (AB (integrative n3 review)) or (JN “Cochrane Database of Systematic Reviews”) or (TI (information n2 synthesis)) or (TI (data n2 synthesis)) or (AB (information n2 synthesis)) or (AB (data n2 synthesis)) or (TI (data n2 extract*)) or (AB (data n2 extract*)) or (TI (medline or pubmed or psyclit or cinahl or (psycinfo not “psycinfo database”) or “web of science” or scopus or embase)) or (AB (medline or pubmed or psyclit or cinahl or (psycinfo not “psycinfo database”) or “web of science” or scopus or embase)) or (MH “Systematic Review”) or (MH “Meta Analysis”) or (TI (meta-analy* or metaanaly*)) or (AB (meta-analy* or metaanaly*))

S16 S14 AND S15

S15 EM 20111001-20221007

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 neuropathic pain or neuralgia

S12 algoneurodystrophy

S11 causalgia

S10 shoulder-hand syndrome*

S9 algodystrophy

S8 sudecks atrophy

S7 sudeck's atrophy

S6 RSD or RND

S5 (reflex and (sympathetic or neurovascular) and dystrophy)

S4 CRPS

S3 regional pain syndrome*

S2 (MH "Neuralgia+")

S1 (MH "Complex Regional Pain Syndromes+")

UTHealth CINAHL Filter used

Appendix 5. Search strategy PEDro

Abstract & Title: regional pain syndrome or CRPS or "reflex sympathetic dystrophy" or "reflex neurovascular dystrophy" or RSD or RND or "sudeck's atrophy" or "sudecks atrophy" or algodystrophy or shoulder-hand syndrome or causalgia or algoneurodystrophy or "neuropathic pain" or neuralgia

Problem: Pain

Topic: Chronic pain

Method: Systematic review

Published since: 2011

Appendix 6. Search strategy LILACS (Birme)

regional pain syndrome$ or CRPS or "reflex sympathetic dystrophy" or "reflex neurovascular dystrophy" or RSD or RND or "sudeck's atrophy" or "sudecks atrophy" or algodystrophy or shoulder-hand syndrome$ or causalgia or algoneurodystrophy or "neuropathic pain" or neuralgia [Words] and 2011 or 2012 or 2013 or 2014 or 2015 or 2016 or 2017 or 2018 or 2019 or 2020 or 2021 [Country, year publication] and review or meta-analysis [Publication type]

Appendix 7. Search strategy Epistemonikos

(title:((title:(regional pain syndrome*) OR abstract:(regional pain syndrome*)) OR (title:(CRPS OR RSD OR RND) OR abstract:(CRPS OR RSD OR RND)) OR (title:(algodystrophy) OR abstract:(algodystrophy)) OR (title:(shoulder-hand syndrome*) OR abstract:(shoulder-hand syndrome*)) OR (title:(causalgia OR algoneurodystrophy OR "neuropathic pain" OR neuralgia) OR abstract:(causalgia OR algoneurodystrophy OR "neuropathic pain" OR neuralgia)) OR (title:("reflex sympathetic dystrophy" OR "reflex neurovascular dystrophy") OR abstract:("reflex sympathetic dystrophy" OR "reflex neurovascular dystrophy"))) OR abstract:((title:(regional pain syndrome*) OR abstract:(regional pain syndrome*)) OR (title:(CRPS OR RSD OR RND) OR abstract:(CRPS OR RSD OR RND)) OR (title:(algodystrophy) OR abstract:(algodystrophy)) OR (title:(shoulder-hand syndrome*) OR abstract:(shoulder-hand syndrome*)) OR (title:(causalgia OR algoneurodystrophy OR "neuropathic pain" OR neuralgia) OR abstract:(causalgia OR algoneurodystrophy OR "neuropathic pain" OR neuralgia)) OR (title:("reflex sympathetic dystrophy" OR "reflex neurovascular dystrophy") OR abstract:("reflex sympathetic dystrophy" OR "reflex neurovascular dystrophy"))))

Appendix 8. Search results by source

2013 Version

DATABASE	Date of Search	Range of search	RESULTS
MEDLINE (OVID)	7 Oct 2011	Medline 1948 to Sep week 4 2011	417
Embase (OVID)	7 Oct 2011	1980 to 2011 week 39	1070
CDSR (*The Cochrane Library*)	7 Oct 2011	Issue 10 2011	331
DARE	7 Oct 2011	Issue 4 2011	98

(Continued)

CINAHL (EBsco)	10 Oct 2011	1982 to date of search	152
PEDro	10 Oct 2011	1929 to date	21
LILACS	11 Oct 2011	All years	103
NCDDR			defunct
		TOTAL	2192

2022 Version

DATABASE	Date of Search	Range of search	RESULTS
MEDLINE (OVID)	10 Oct 2022	Oct 2011 to 7 Oct 2022	1276
Embase (OVID)	10 Oct 2022	Oct 2011 to 7 Oct 2022	1732
CDSR (*The Cochrane Library*)	10 Oct 2022	Issue 10 of 12, 2022	80
CINAHL (EBsco)	10 Oct 2022	Oct 2011 to Oct 2022	1065
PEDro	10 Oct 2022	Oct 2011 to Oct 2022	20
LILACS	10 Oct 2022	2011 to Oct 2022	64
Epistemonikos	10 Oct 2022	Oct 2011 to 10 Oct 2022	70
Citation alerts	2022		3
		TOTAL	4310

Appendix 9. AMSTAR 2 assessment criteria

AMSTAR 2 is a 16-item critical appraisal tool to assist in identifying high quality systematic reviews. AMSTAR 2 is not designed to generate a summary score, but an overall rating based on weaknesses in 7 critical domains*.

1. Did the research questions and inclusion criteria for the review include the components of PICO?
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?*
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?*
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?*
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?*
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?*

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?*
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?*
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Ratings in overall confidence in the results of the review :

High (zero or one non-critical weakness): the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.

Moderate (more than one non-critical weakness): the systematic review has more than one weakness, but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.

Low (one critical flaw with or without non-critical weaknesses): the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.

Critically low (more than one critical flaw with or without non-critical weaknesses): the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

Appendix 10. Summary of low- and very low-certainty evidence results

Oral, intravenous and topical pharmacotherapy

There is low-certainty evidence that:

- Compared with placebo, bisphosphonates may reduce pain intensity
- Compared with oral N-acetylcysteine, topical DMSO may not reduce pain intensity

There is very low-certainty evidence that:

- Compared with placebo, oral prednisone, intravenous mannitol, botulinum toxin A, intranasal calcitonin, intravenous infliximab and intravenous parecoxib may not reduce pain intensity
- Compared with placebo, intradermal/subcutaneous botulnum toxin A may not reduce pain intensity or disability
- Compared with placebo, oral gabapentin may not reduce pain intensity and it may increase the risk of experiencing adverse events
- Compared with oral piroxicam, oral prednisone may not reduce disability
- Continuing treatment with oral prednisolone may reduce pain intensity more than discontinuing oral prednisolone
- Compared with placebo, oral prednisone may not reduce pain intensity
- Compared with intranasal calcitonin, intranasal pamidronate may not reduce pain intensity
- Compared with physiotherapy, calcitonin plus physiotherapy may have little to no effect on pain intensity
- Compared with oral paracetamol, intranasal calcitonin may not reduce pain intensity
- Compared with placebo, oral lenalidomide may not reduce pain intensity or disability
- Compared with placebo, topical isosorbide dinitrate may not reduce pain intensity or disability
- Compared with placebo, intravenous ketamine may reduce pain intensity
- Compared with placebo, intravenous magnesium may have no effect on pain intensity
- Compared with morphine plus placebo, memantine plus morphine may reduce pain intensity
- Compared with conventional care, oral sarpogrelate hydrochloride plus usual care may not reduce pain intensity
- Compared with placebo, oral tadalafil may reduce pain intensity

Interventional procedures

There is low-certainty evidence that:

- Compared with stellate ganglion ultrasound, lidocaine stellate ganglion may not reduce pain intensity
- Compared with continuous bupivacaine stellate ganglion block, continuous brachial plexus block may reduce pain intensity

There is very low-certainty evidence that:

- Compared with placebo, epidural clonidine may reduce pain intensity
- Compared with a slow intrathecal baclofen infusion, a fast intrathecal baclofen infusion may have no effect on pain intensity

- Compared with a 300µg epidural clonidine, 700µg epidural clonidine may have no effect on pain intensity and may increase the risk of sedation
- Compared with intrathecal clonidine, intrathecal adenosine may have no effect on pain intensity
- Compared with placebo, intrathecal glycine may have no effect on pain intensity, disability, or adverse events
- Compared with placebo, guanethdine IVRB may have no effect on pain intensity post-intervention but may reduce pain intensity at medium-term follow-up, and may have little to no effect on adverse events
- Compared with placebo, ketanserin IVRB may have little to no effect on pain intensity
- Compared with placebo, lidocaine IVRB may increase the incidence light-headedness
- Compared with each other, guantheidine plus lidocaine IVRB, reserpine plus lidocaine IVRB, and lidocaine IVRB protocols may have no effect on pain intensity
- Compared with IV parecoxib, lidocaine and clonidine, and IVRB with lidocaine and clonidine, IVRB with parecoxib, lidocaine and clonidine may reduce pain intensity
- Compared with guanethidine IVRB, bupivacaine stellate ganglion block may have no effect on pain intensity
- Compared with radiofrequency lumbar block, lidocaine and clonidine lumbar sympathetic block may have no effect on pain intensity
- Compared with oral prednisone, lidocaine stellate ganglion block may have no effect on pain intensity
- Compared with lidocaine and clonidine IVRB, lidocaine sympathetic block may have no effect on pain intensity
- Compared with subcutaneous ropivacaine and triamcinolone, thoracic sympathetic block using the same agents may have no effect on pain intensity
- Compared with lidocaine image-guided stellate ganglion block, lidocaine nonimage-guided stellate ganglion block may have no effect on pain intensity
- Compared with rehabilitation, stellate ganglion block plus rehabilitation may have no effect on pain intensity
- Compared with conventional care, lidocaine and bupivacaine stellate ganglion block plus conventional care may reduce pain intensity
- Compared with phenol lumbar sympathetic neurolysis, percutaneous radiofrequency thermal lumbar sympathectomy may not reduce pain intensity

Neuromodulation

There is very low-certainty evidence that:

- Compared with placebo, standard, burst and high frequency spinal cord stimulation may reduce pain intensity
- Compared with spinal cord stimulation, dorsal root ganglion stimulation may not increase the risk of adverse events
- Compared with physiotherapy, spinal cord stimulation plus physiotherapy may reduce pain intensity and may have no effect on disability at medium-term follow-up
- Compared with placebo, repetitive transcranial magnetic stimulation may reduce pain intensity post-intervention but may have no effect on pain intensity at medium-term follow-up

Rehabilitation

There is very low-certainty evidence that:

- Compared with placebo, mirror therapy and virtual reality may reduce pain intensity
- Compared with placebo, prism adaptation may have no effect on pain intensity
- Compared with standard care, graded motor imagery may reduce pain intensity and disability at post-intervention and medium-term follow-up, but may have no effect on pain intensity at short-term follow-up
- Compared with a waiting list control, graded motor imagery may have no effect on pain intensity
- Compared with mental imagery, mirror therapy may reduce pain intensity
- Compared with stroke rehabilitation, mirror therapy plus stroke rehabilitation may reduce pain intensity and improve function
- Compared with medical management plus contrast baths and medical management, contrast baths and exercise, mirror visual feedback plus medical management may improve pain intensity
- Compared with each other, four different tactile discrimination protocols may have no differential effects on pain intensity
- Compared with placebo, stellate ganglion ultrasound may not reduce pain intensity or disability
- Compared with TENS, stellate ganglion ultrasound may reduce pain intensity
- Compared with placebo, electromagnetic field therapy may reduce pain intensity and disability, but the evidence is conflicting
- Compared with placebo, TENS may have no effect on pain intensity and disability
- Compared with inferential therapy, laser therapy may reduce pain intensity
- Compared with exercise, CO_2 bath therapy may reduce pain intensity
- Compared with stroke rehabilitation, fluidotherapy plus stroke rehabilitation may have no effect on pain intensity or disability

- Compared with usual physiotherapy, pain exposure physical therapy may have no effect on pain intensity or disability
- Compared with usual physiotherapy, exposure in vivo may reduce pain intensity and disability
- Compared with minimal care, physiotherapy may reduce pain intensity post-intervention but may have no effect at long-term follow-up; and may reduce disability at long-term follow-up but the evidence is conflicting
- Compared with occupational therapy, physiotherapy may have no effect on pain intensity or disability
- Compared with physiotherapy, manual lymphatic drainage may have no effect on pain intensity
- Compared with rehabilitation, massage plus electro-acupuncture may reduce pain intensity, but may have no effect on disability

Complementary and alternative therapies and other interventions

There is very low-certainty evidence that:

- Compared with placebo, acupuncture and qigong may reduce pain intensity
- Compared with home treatment, autogenic relaxation plus home treatment may have no effect on pain intensity
- Compared with placebo, occlusal splints may have no effect on pain intensity

For all of the comparisons with very low-certainty evidence, we suggest this represents insufficient evidence to either support or refute the use of these interventions. Comparisons with low-certainty evidence should be treated with substantial caution.

WHAT'S NEW

Date	Event	Description
9 June 2023	New citation required but conclusions have not changed	Compared with the previous version of this overview, the current version included downgraded certainty in evidence for several interventions: ketamine, calcitonin, graded motor imagery, mirror therapy and multimodal physiotherapy. The current version also found moderate-certainty evidence that bisphosphonates are probably associated with an increased risk of adverse events of any nature.
9 June 2023	New search has been performed	This overview has been updated to include the results of a new search in October 2022. The overview now includes five Cochrane and 12 non-Cochrane systematic reviews, comprising data from 127 randomised controlled trials.

HISTORY

Protocol first published: Issue 11, 2011
Review first published: Issue 4, 2013

Date	Event	Description
15 December 2016	Review declared as stable	See Published notes.
15 July 2016	Amended	See Published notes.
17 June 2015	Review declared as stable	This review will be assessed for further updating in 2016.

CONTRIBUTIONS OF AUTHORS

MCF: conceived updates to methodology for the current version, collated the searches in collaboration with the PaPaS information specialist, applied eligibility criteria, assessed reviews, extracted and analysed data, judged the certainty in evidence using GRADE, interpreted the results, and led the write-up of the overview. MF will be responsible for identifying the need for a future update to this overview.

AGC: applied eligibility criteria, assessed reviews, extracted and analysed data, interpreted the results and contributed to the write-up of the overview.

BMW: contributed to protocol design, interpreted the results, and contributed to the write-up of the overview.
KMS: applied eligibility criteria, assessed reviews, extracted and analysed data, interpreted the results, and contributed to the write-up of the overview.

CB: applied eligibility criteria, assessed reviews, extracted and analysed data, interpreted the results, and contributed to the write-up of the overview.

LM: contributed to protocol design, provided statistical advice, interpreted the results, and contributed to the write-up of the overview.

GLM: contributed to protocol design, advised as a content expert on CRPS, reviewed the final list of reviews for possible omissions, interpreted the results, and contributed to the write-up of the overview.

JHM: contributed to protocol design, provided methodological advice, acted as third reviewer, interpreted the results and contributed to the write-up of the overview.

NOC: conceived and designed the protocol, conceived updates to methodology for the current version, applied eligibility criteria, assessed reviews, extracted and analysed data, judged the certainty in evidence using GRADE, interpreted the results, and contributed to the write-up of the overview.

DECLARATIONS OF INTEREST

NOC and BMW were authors of one included review (O'Connell 2016) and KMS, MCF, BM and NOC were authors of another included review (Smart 2022). Different authors (AGC, CB) conducted the AMSTAR 2 assessments for these reviews.

GLM was the lead author on three included studies (Moseley 2004; Moseley 2006; Moseley 2009) but was not involved in the data extraction process or writing of or interpretation of results for these trials. GLM has co-authored a textbook on the use of graded motor imagery in chronic pain, for which he receives author royalties.

MCF, AGC, BMW, GLM, JHM and NOC are involved in the conduct of a randomised controlled trial testing memantine and graded motor imagery for complex regional pain syndrome. At the time of writing this review, the trial is recruiting participants and is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12621000175875).

CB has an annual contract (Independent Contractor) to provide 12 hours of pain education lectures to pain and spine fellows at Kaiser Permanente. This position is not relevant nor a conflict to this title.

NOC is an author and PaPaS Co-ordinating editor. NOC had no input into the editorial decisions or processes for this overview.

SOURCES OF SUPPORT

Internal sources

- Australian Government Research Training Program, Australia

  Stipend for MCF
- Neuroscience Research Australia Top-up Scholarship, Australia

  Stipend for MCF
- Edward C Dunn Foundation Scholarship, Australia

  Stipend for MCF
- National Health and Medical Research Council Emerging Leader Fellowship, Australia

  Salary for AGC
- University of Notre Dame, Australia

  Salary for BW
- University College London, UK

  Salary for LM
- University of South Australia, Australia

  Salary for GLM

- Neuroscience Research Australia, Australia

  Salary for JM
- Brunel University, UK

  Salary for NOC

External sources

- National Institute for Health Research (NIHR), UK

  Cochrane Infrastructure funding to the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this updated overview, we made a number of changes compared with the protocol (O'Connell 2011) and the original version of the overview (O'Connell 2013):

- Background: this section has been updated in the current version of the overview to include recent information on CRPS diagnosis, pathophysiology and incidence.
- Searches: in the current version of this overview, we searched Epistemonikos but did not search the Database of Abstracts of Reviews of Effects (DARE), as it is no longer updated.
- Outcomes: in the current version of this overview, we grouped outcomes into post-intervention, short-term, medium-term and long-term follow-up periods, reporting only a single effect for each period.
- Assessment of methodological quality of included reviews: in the current version of this overview, we used the revised AMSTAR 2 instead of the original AMSTAR tool to assess the methodological quality of both Cochrane and non-Cochrane reviews.
- Assessment of the certainty of the evidence in included reviews: where reviews did not use GRADE to assess the certainty in evidence, we conducted these assessments ourselves using updated criteria compared with the previous version of this overview and the protocol (for a full description see Assessment of methodological quality of included reviews). We applied these judgements to all outcomes rather than only the primary outcomes, as done in the previous version of this overview.
- Interpretation of effects: in the current version of this overview, we interpreted minimally important between-group differences for pain intensity using OMERACT 12 recommendations.

INDEX TERMS

Medical Subject Headings (MeSH)

Bupivacaine; *Chronic Pain; *Complex Regional Pain Syndromes; Quality of Life; Systematic Reviews as Topic

MeSH check words

Adult; Humans