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REVIEW ARTICLE/BRIEF REVIEW

Treatment of complex regional pain syndrome: a review of the evidence

Traitement du syndrome de douleur régionale complexe: une revue des données probantes

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Abstract

Purpose *This narrative review summarizes the evidence derived from randomized controlled trials pertaining to the treatment of complex regional pain syndrome (CRPS).*

Source *Using the MEDLINE (January 1950 to April 2009) and EMBASE (January 1980 to April 2009) databases, the following medical subject headings (MeSH) were searched: "Complex Regional Pain Syndrome", "Reflex Sympathetic Dystrophy", and "causalgia" as well as the key words "algodystrophy", "Sudeck's atrophy", "shoulder hand syndrome", "neurodystrophy", "neuroalgodystrophy", "reflex neuromuscular dystrophy", and "posttraumatic dystrophy". Results were limited to randomized controlled trials (RCTs) conducted on human subjects, written in English, published in peer-reviewed journals, and pertinent to treatment.*

Principal findings *The search criteria yielded 41 RCTs with a mean of 31.7 subjects per study. Blinded assessment and sample size justification were provided in 70.7% and 19.5% of RCTs, respectively. Only biphosphonates appear to offer clear benefits for patients with CRPS. Improvement has been reported with dimethyl sulfoxide, steroids, epidural clonidine, intrathecal baclofen, spinal cord stimulation, and motor imagery programs, but further trials are required. The available evidence does not support the use of calcitonin, vasodilators, or sympatholytic and neuromodulative intravenous regional blockade. Clear benefits have not been reported with stellate/lumbar sympathetic blocks, mannitol, gabapentin, and physical/occupational therapy.*

Conclusions *Published RCTs can only provide limited evidence to formulate recommendations for treatment of CRPS. In this review, no study was excluded based on factors such as sample size justification, statistical power, blinding, definition of intervention allocation, or clinical outcomes. Thus, evidence derived from "weaker" trials may be overemphasized. Further well-designed RCTs are warranted.*

Résumé

Objectif *Ce compte-rendu narratif résume les données probantes dérivées d'études randomisées contrôlées portant sur le traitement du syndrome de douleur régionale complexe (SDRC).*

Source *Les termes MeSH suivants ont été recherchés dans les bases de données MEDLINE (janvier 1950 à avril 2009) et EMBASE (janvier 1980 à avril 2009): « Complex Regional Pain Syndrome », « Reflex Sympathetic Dystrophy », et « causalgia » ainsi que les mots-clés « algodystrophy », « Sudeck's atrophy », « shoulder hand syndrome », « neurodystrophy », « neuroalgodystrophy », « reflex neuromuscular dystrophy », et « posttraumatic dystrophy », soit : « syndrome de douleur régionale complexe », « dystrophie sympathique réflexe », et « causalgie », ainsi que les mots-clés « algodystrophie », « syndrome de Südeck », « syndrome épaule-main », « neurodystrophie », « neuro-algodystrophie », « dystrophie neuromusculaire réflexe » et « dystrophie post-traumatique », respectivement. Nous avons limité les résultats aux études randomisées contrôlées (ERC) réalisées chez l'humain, écrites en anglais dans des revues avec comités de pairs et portant sur le traitement.*

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Constatations principales *Les critères de recherche ont permis d'extraire 41 ERC avec en moyenne 31,7 sujets par étude. Une évaluation en aveugle et une justification de la taille d'échantillonnage étaient disponibles pour 70,7 % et 19,5 % des ERC, respectivement. Seuls les biphosphonates semblent procurer des bienfaits évidents aux patients souffrant de SDRC. On a rapporté une diminution de la douleur avec le diméthylsulfoxyde, les stéroïdes, la clonidine péridurale, le baclofen intrathécal, la stimulation de la moelle épinière, et les programmes d'imagerie motrice, mais d'autres études sont nécessaires. Les données probantes disponibles n'appuient pas l'utilisation de la calcitonine, de vasodilatateurs, ou de bloc régional intraveineux sympatholytique et neuromodulateur. On n'a pas rapporté de bénéfices clairs lors de l'utilisation de blocs sympathiques stellaires/lombaires, de mannitol, de gabapentine et du recours à la physiothérapie ou à l'ergothérapie.*

Conclusion *Les ERC publiées ne fournissent que des données limitées quant à la formulation de recommandations pour le traitement du SDRC. Dans ce compte-rendu, aucune étude n'a été exclue sur la base de facteurs tels que la justification de la taille de l'échantillonnage, la puissance statistique, la méthode en aveugle, la définition de l'attribution de l'intervention ou les devenirs cliniques. Dès lors, trop d'importance peut avoir été accordée aux données dérivées des études « plus faibles ». D'autres ERC bien conçues sont nécessaires.*

Introduction

First described more than 100 years ago, Complex Regional Pain Syndrome (CRPS) still remains a medical challenge today, with a natural history characterized by chronicity and relapses that can result in significant disability over time.[1] Women are affected more frequently than men, but the overall incidence is unknown. Fractures and surgical insult are often the precipitating events, but CRPS can also develop after a seemingly benign trauma. Adding to this confusion was the myriad of names used to describe the syndrome, such as "Reflex Sympathetic Dystrophy", "causalgia", "Sudeck's atrophy", "algodystrophy", "neurodystrophy", and "post-traumatic dystrophy". To standardize the taxonomy, the term CRPS was adopted in 1995 by the International Association for the Study of Pain (IASP).[2] This revision was deemed necessary because previous names, such as Reflex Sympathetic Dystrophy, were misleading. The underlying pathophysiology is poorly understood, and patients often do not respond to sympathetic blockade. Diagnostic criteria were also proposed by the IASP.[2] In contrast, treatment of CRPS remains a controversial topic. While the literature is replete with reports advocating the use of various clinical treatments for CRPS (from physiotherapy to spinal cord stimulation), the levels of supportive evidence are quite variable and sometimes limited. Accordingly, a literature search for level 1 evidence (from randomized controlled trials) was undertaken to determine the benefits associated with these therapeutic modalities. For the purpose of this review, no distinction was made between CRPS type 1 (formerly Reflex Sympathetic Dystrophy) and 2 (formerly causalgia).

Methods

Search strategy and selection criteria

The literature search for this review was conducted during the second week of April 2009 using the MEDLINE (January 1950 to the 2nd week of April 2009) and EMBASE (January 1980 to the 15th week of 2009) databases.

The following MeSH terms were searched: "Complex Regional Pain Syndrome", "Reflex Sympathetic Dystrophy", and "causalgia" as well as the key words "algodystrophy", "Sudeck's atrophy", "shoulder hand syndrome", "neurodystrophy", "neuroalgodystrophy", "reflex neuromuscular dystrophy", and "post-traumatic dystrophy". Results were limited to studies conducted on human subjects, written in English, and published in peer-reviewed journals. Only randomized controlled trials (RCTs) pertaining to the treatment of CRPS were considered for analysis. We excluded trials that investigated the impact of interventions on parameters measured *in vitro* (skin resistance, temperature, vasodilation, thresholds of pain to different stimuli, mapping of allodynic area) but did not assess the clinical response of patients. Furthermore, RCTs needed to deal exclusively with CRPS to be retained for analysis. We also excluded trials that enrolled a heterogeneous mix of patients suffering from CRPS and neuropathic pain (diabetic neuropathy, post herpetic neuralgia, phantom limb pain, trigeminal neuralgia, nerve root injury/radiculopathy, peripheral nerve injury/lesion/neuroma) or postsurgical pain (sustained after thoracotomy, mastectomy, inguinal hernia repair) and indiscriminately pooled results from all subjects. However studies that provided data specific to CRPS were included in this review. Randomized controlled trials (RCTs) published in the form of abstracts or correspondence were also excluded. After selecting the initial articles, we examined the reference lists as well as our personal files for additional material. No RCTs were excluded based on factors such as definition of intervention allocation or primary and secondary (clinical) outcomes. However, non-randomized studies, observational case

reports, and cohort studies were excluded to avoid potential biases introduced by institutional practices.

Results

Our search yielded 50 RCTs pertaining to the treatment of CRPS. Seven of these were excluded because they investigated treatments requiring consultants (acupuncturists, qi gong masters) or modalities (electromagnetic field, transcranial magnetic stimulation, occlusive splinting, and hyperbaric oxygen therapy) that are not readily available to most practitioners. One identified trial was excluded as it had recently been retracted;[A] another RCT was excluded because both groups received the same treatment (graded *in vivo* exposure) (Appendix 1). Eighteen of the remaining 41 RCTs studied pharmacological treatment (Table 1) and 18 investigated intravenous regional blockade or central and peripheral nerve blocks (Table 2). Spinal cord stimulation and adjuvant therapy were addressed in one and four studies, respectively (Tables 3 and 4). Overall, the quality of the 41 RCTs was variable. The average enrolment was 31.7 subjects per study. The IASP definition of CRPS was used in 30.0% of trials. Blinded assessment and sample size justification were provided in 70.7% and 19.5% of RCTs, respectively. The duration of CRPS prior to enrolment was provided in 70.7% of studies and varied from 50 days to 13 yr. Pain was the most common endpoint studied (78.1% of trials); patient follow up varied from two weeks to five years.

Pharmacological therapy

Calcitonin

Calcitonin has received considerable interest in the management of CRPS because of its analgesic properties through release of ß-endorphin as well as its inhibition of bone resorption.[3] To date, four RCTs have investigated the use of calcitonin in CRPS.

Bickerstaff *et al.*[3] randomized 38 patients with upper extremity CRPS to a four-week regimen of nasal calcitonin or placebo. The authors observed no differences between the two groups in terms of pain, hand volume, stiffness, grip strength, and vascular/sudomotor changes. Furthermore, radiographic, densitometric, and scintigraphic evaluations of the metacarpal bones were also similar. Gobelet *et al.*[4] randomized 24 patients suffering from hand or foot CRPS to physiotherapy alone (eight-week course) or the same physiotherapy regimen combined with a three-week course of subcutaneous calcitonin. At eight weeks, there were no intergroup differences in terms of pain, edema, range of motion, and fitness for work. Bone scintigraphy was also similar. In 66 patients diagnosed with wrist or ankle CRPS, Gobelet *et al.*[5] combined an intensive physiotherapy regimen (eight-week course) to a three-week course of nasal calcitonin or nasal placebo spray. At eight weeks, these authors noted decreased static and dynamic pain scores (using a four-point pain scale) in the treatment compared with the placebo group (0.45 ± 0.68 *vs* 0.69 ± 0.93; $P < 0.007$ and 0.77 ± 0.76 *vs* 1.22 ± 0.91; $P < 0.04$, respectively). Furthermore, range of motion was also greater in patients receiving calcitonin ($P < 0.04$). However, there were no differences between the two groups in terms of edema and ability to work. In 2006, Sahin *et al.*[6] enrolled 35 patients with upper extremity CRPS and provided them with an exercise and physical therapy program. In addition, the subjects were randomized to a two-month regimen of nasal calcitonin or oral paracetamol. At two months, Sahin *et al.*[6] observed no intergroup differences pertaining to pain, range of motion, allodynia, hyperalgesia, and trophic changes.

Biphosphonates

Bone demineralization often accompanies CRPS. This observation has prompted many authors to advocate treatment with biphosphonates, which are potent inhibitors of bone resorption.[7] To date, four RCTs have investigated the role of bisphosphonates in the treatment of CRPS.

In a study by Adami *et al.*,[7] 20 patients were randomized to receive a three-day course of intravenous alendronate or placebo. After two weeks of treatment, patients receiving alendronate presented significant improvements in pain, swelling, and range of motion compared with the control group (all $P < 0.01$). In light of these encouraging results, Manicourt *et al.*[8] randomized 39 patients with lower limb CRPS to an eight-week regimen of oral alendronate or placebo. Participants were excluded if they had received calcitonin one week prior to study entry; furthermore, they were encouraged to continue physical therapy and rehabilitation on a regular basis. At four, eight, and 12 weeks, participants receiving alendronate displayed better pain control and range of motion compared with controls (both $P < 0.05$). Moreover, edema was also improved with alendronate at four and eight weeks (both $P < 0.05$). In 2000, Varenna *et al.*[9] randomized 31 patients with CRPS to a ten-day course of intravenous clodronate or placebo. To assess efficacy, the authors used a visual analogue scale of pain (VAS, range 0-100), clinical global assessment (CGA, range 0-3), and an efficacy verbal score (EVS, range 0-3).

[A] The following article has been retracted: *Reuben SS, Rosenthal EA, Steinberg RB, Faruqi S, Kilaru PA*. Surgery on the affected upper extremity of patients with a history of complex regional pain syndrome: the use of intravenous regional anesthesia with clonidine. J Clin Anesth 2004; 16: 517-22.

Table 1 Randomized controlled trials pertaining to pharmacological treatment

Authors (year)	CRPS Defined According to IASP[2]	Blinded Assessment/ Sample Size Justification	Description	Number of Patients/ Groups	Primary Outcome and Duration of Follow up	Main Findings
Bickerstaff *et al.*[3] (1991)	N	N/N	Daily nasal calcitonin 400 units *vs* placebo for four weeks	38/2	Pain (dolorimetry ratio) until 12 weeks after start of treatment	No differences in pain, hand volume, stiffness, grip strength, vascular/ sudomotor changes. No differences in radiographic, densitometric, scintigraphic evaluation of metacarpa bones.
Gobelet *et al.*[4] (1986)	N	N/N	Daily subcutaneous calcitonin 100 units daily for three weeks combined with PT for eight weeks *vs* PT alone	24/2	Pain, edema, range of motion, and fitness for work until eight weeks after end of treatment	No difference.
Gobelet *et al.*[5] (1992)	N	Y/N	Nasal calcitonin 300 units daily *vs* placebo for three weeks in conjunction with PT for eight weeks	66/2	Pain until eight weeks after start of treatment	Calcitonin: better static/dynamic pain scores and range of motion at eight weeks. No differences in edema and ability to work.
Sahin *et al.*[6] (2006)	N	Y/N	Nasal calcitonin 200 mg daily *vs* oral paracetamol 1,500 mg daily in conjunction with PT for three weeks	35/2	Pain, range of motion, allodynia, hyperalgesia, trophic changes until two months after start of treatment	No difference.
Adami *et al.*[7] (1997)	N	Y/N	Alendronate 7.5 mg *iv* daily *vs* placebo for three days	20/2	Pain at two weeks after start of treatment	Alendronate: less pain and swelling, more range of motion.
Manicourt *et al.*[8] (2004)	Y	Y/Y	Alendronate 40 mg *po* daily *vs* placebo for eight weeks	39/2	Pressure tolerance (dolorimetric ratio) until 12 weeks after start of treatment	Alendronate: less pain, better pressure tolerance and mobility at four, eight, and 12 weeks. Alendronate: less edema at four and eight weeks.
Varenna *et al.*[9] (2000)	N	Y/N	Clodronate 300 mg *iv vs* placebo for ten days	31/2	Pain 40 days after end of treatment	Clodronate: less pain, improved global assessment (evaluated by investigator), and higher perceived efficacy (evaluated by patients).
Robinson *et al.*[10] (2004)	Y	Y/N	Palmidronate 60 mg *iv* as a single dose *vs* placebo	27/2	Pain after three months	Palmidronate: less pain, higher overall improvement (patient's assessment), and higher functional assessment scores.
Zuurmond *et al.*[11] (1996)	N	Y/N	50% DMSO cream daily *vs* placebo for two months	31/2	Pain and RSD score until two months after start of treatment	Similar reduction in RSD scores. Greater reduction in VAS scores with DMSO.
Geertzen *et al.*[12] (1994)	N	N/N	50% DMSO cream four times per day *vs* IVRB (twice per week) for three weeks	26/2	Score (based on pain, daily activities, edema, color, and ROM) until nine weeks after start of treatment	DMSO: greater improvement at seven and nine weeks.

Table 1 continued

Authors (year)	CRPS Defined According to IASP[2]	Blinded Assessment/ Sample Size Justification	Description	Number of Patients/ Groups	Primary Outcome and Duration of Follow up	Main Findings
Perez *et al.*[13] (2003)	N	Y/Y	50% DMSO cream four times per day *vs* NAC 600 mg *po* TID for 17 weeks	112/2	Impairment (ISS) until one year after start of treatment	No differences in ISS, disability and quality of life. Cold CRPS: greater improvement in ISS with NAC. Warm CRPS: greater improvement in SF-36 with DMSO.
Perez *et al.*[15] (2008)	N*	Y/Y	10% Intravenous mannitol in one litre of normal saline over four hours for five consecutive days *vs* placebo	41/2	Pain until nine weeks after start of treatment	No differences in pain, impairment, disability and handicap level.
Christensen *et al.*[16] (1982)	N	N/N	Prednisone 10 mg *po* TID *vs* placebo until clinical response or maximum of 12 weeks	23/2	Score (based on pain, edema, volar sweating, and finger-knitting ability) at end of treatment	Prednisone: better post treatment score.
Braus *et al.*[17] (1994)	N	N/N	Methylprednisolone 8 mg *po* QID for two weeks then taper dose for two weeks *vs* placebo in CRPS following stroke	34/2	SHS score until six months after end of treatment	Methylprednisolone: lower SHS score.
Kalita *et al.*[18] (2006)	N	N/Y	Prednisolone (40 mg *po* daily × two weeks then taper dose of 10 mg/week) *vs* piroxicam (20 mg *po*/day)	60/2	SHS score one month after start of treatment	Prednisolone: lower SHS score. No differences in Barthel Index (activities of daily living).
Van de Vusse *et al.*[19] (2004)	Y	Y/N	Gabapentin (600 mg daily × two days then 600 mg *po* BID × two days then 500 mg *po* TID × 17 days) *vs* placebo	46/2 (crossover study)	Pain (VAS) until eight weeks after randomization	No differences in VAS scores, NPS scores, mechanical allodynia. Gabapentin: improved global perceived effect and sensory deficit to mechanical stimulus. Gabapentin: more side effects.
Groeneweg *et al.*[20] (2008)	N*	Y/Y	Tadalafil 10 mg *po* daily × four weeks then 20 mg *po* daily × eight weeks *vs* placebo	24/2	Temperature change of the affected limb compared to the healthy extremity at end of study period	No differences in temperature change, muscular force and activity level. Tadalafil: greater reduction in pain.
Ogawa *et al.*[21] (1998)	N	N/N	Sarpogrelate 100 mg *po* TID and CT *vs* CT for three months	30/2	Pain (VAS) at the end of treatment	No difference in pain. Sarpogrelate: more patients report improvement in burning sensation.

BID = twice a day; CRPS = complex regional pain syndrome; CT = conventional treatment; DMSO = dimethyl sulfoxide; IASP = International Association for the Study of Pain; IVRB = intravenous regional block; ISS = impairment level sumscore; N = no; NAC = *N*-acetylcysteine; NPS = neuropathic pain scale; *po* = by mouth; PT = physiotherapy; QID = four times a day; RSD = reflex sympathetic dystrophy; SHS = shoulder hand syndrome; TID = three times a day; VAS = visual analogue scale; Y = yes; Yr = year

* CRPS diagnosed according to modified IASP definition[58]

Table 2 Randomized controlled trials pertaining to intravenous regional blockade and nerve blocks

Authors (year)	CRPS Defined According to IASP (2)	Blinded Assessment/ Sample Size Justification	Description	Number of Patients/ Groups	Primary Outcome/Duration of Follow up	Main Findings
Blanchard *et al.*[22] (1990)	N	Y/N	IVRB: guanethidine 20-30 mg in NS *vs* reserpine 0.5-1 mg in NS *vs* NS	21/3	Pain (VAS) until 12 weeks post IVRB	No difference.
Jadad *et al.*[23] (1995)	N	Y/N	IVRB: guanethidine 10-20 mg in NS *vs* guanethidine 30 mg in NS *vs* NS	9/3 (crossover study)	Pain (VAS) until one week post IVRB or until return of pain to its baseline level	No difference.
Livingstone *et al.*[24] (2002)	Y	Y/Y	IVRB: guanethidine 15 mg in 0.5% prilocaine 30 mL *vs* NS	56/2 (crossover study)	Pain (dolorimetry ratio) until one week post IVRB (short term) and until six months post Colles' fracture (long term)	No difference in pain. Guanethidine: more vasomotor instability at 15 weeks (color, sensitivity to changes in ambient temperature) and 30 weeks (temperature, swelling).
Kettler *et al.*[25] (1988)	N	Y/N	IVRB: droperidol 2.5 mg/heparin/NS *vs* heparin/NS	6/2	Pain (VAS) until two weeks post IVRB	No difference in pain. Droperidol: more adverse events (akithesia, dysphoria, nausea).
Hannah *et al.*[26] (1989)	N	Y/N	IVRB: two treatments with ketanserin 10-20 mg followed by two with placebo *vs* two treatments with placebo followed by two with ketanserin	9/2	Pain (VAS) until four weeks post IVRB	No difference in pain. Ketanserin: more adverse events (drowsiness, faintness, shakiness).
Glynn *et al.*[27] (1993)	N	Y/N	IVRB: atropine 0.6 mg in NS *vs* NS	30/2 (crossover study)	Pain (VAS) until one week post IVRB	No differences in VAS, pain relief, and mood.
Taskaynatan *et al.*[28] (2004)	N*	Y/N	IVRB: methylprednisolone 40 mg and 2% lidocaine 10 mL in NS *vs* NS, every week for three weeks.	22/2	Pain (VAS) one hour and 1.5 months post IVRB	No differences in pain, ROM, edema, and patient satisfaction.
Rocco *et al.*[29] (1989)	N	N/N	IVRB: guanethidine 20 mg in 0.5% lidocaine 50 mL *vs* reserpine 1.25 mg in 0.5% lidocaine 50 mL *vs* 0.5% lidocaine 50 mL	12/3 (crossover study)	Pain (VAS and personal log) until two years post treatment	No difference.
Ramamurthy *et al.*[30] (1995)	N	Y/N	IVRB: guanethidine 20 mg (upper limb) or 30 mg (lower limb) diluted in 0.5% lidocaine: one *vs* two *vs* four blocks	57/3	Pain (MPQ) until six months post treatment	No differences in pain, perceived effect, and ROM.
Bonelli *et al.*[31] (1983)	N	N/N	Four IVRBs: guanethidine 20 mg in heparin and NS *vs* eight stellate ganglion blocks: 0.5% bupivacaine 15 mL	19/2	Pain (VAS) until three months post treatment	No difference in pain. No differences in vasomotor disturbances, trophic changes, edema, and ROM at one and three months.
Hord *et al.*[32] (1992)	N	N/N	IVRB: bretylium 1.5 $mg \cdot kg^{-1}$ in 0.5% lidocaine 40-60 mL *vs* pure lidocaine	7/2 (crossover study)	Pain (pain relief scale) until the return of pain to $> 70\%$ of its baseline	Bretylium-lidocaine combination: longer analgesia.

Table 2 continued

Authors (year)	CRPS Defined According to IASP (2)	Blinded Assessment/ Sample Size Justification	Description	Number of Patients/ Groups	Primary Outcome/Duration of Follow up	Main Findings
Price *et al.*[33] (1998)	Y	Y/N	SGB or LSB: 1% lidocaine 15 mL for SGB and 1% lidocaine 15 mL plus 0.25% bupivacaine 10 mL for LSB *vs* NS	7/2 (crossover study)	Peak analgesic effect (VAS 30 min after injection) VAS until seven days post treatment	Similar peak analgesic effect. LA: longer analgesic duration.
Manjunath *et al.*[34] (2008)	N*	Y/N	LSB: TRF (two lesions at 80°C for 90 sec at L2, L3, and L4) *vs* neurolysis with 7% phenol 3 mL/level at L2, L3, and L4.	19/2	Pain (VAS, sharp pain, dull pain, surface pain, deep pain, intensity of pain, hot pain) until four months after treatment	No difference.
Haynsworth RF Jr *et al.*[35] (1991)	N	N/N	LSB: TRF (two lesions at 70°C for 120 sec at L2, L3, and L4) *vs* neurolysis with 6% phenol 3 mL/level at L2, L3, and L4	17/2	Duration of sympathectomy (temperature, sweat test performed bimonthly) until eight weeks after treatment	Phenol: longer duration.
Carroll *et al.*[36] (2009)	Y	Y/N	LSB: 0.5% bupivacaine 10 mL *vs* bupivacaine-BTA (75 units)	7/2 (crossover study)	Pain (VAS) until one month post treatment or return of pain to its baseline level	Bupivacaine - BTA: longer analgesic duration.
Tran *et al.*[37] (2000)	Y	Y/N	LSB: 2% lidocaine 3 mL with epinephrine (5 $\mu g \cdot mL^{-1}$) and 0.25% bupivacaine 15 mL: Iohexol (1.5 mL) *vs* NS	15/2	Pain (VAS) until one week after block	Iohexol: lower VAS scores one hour and the first morning after block. No differences afterwards. No differences in allodynia, percent of pain relief, and interference with daily activities.
Rauck *et al.*[38] (1993)	N	Y/N	Cervical or lumbar epidural for upper and lower limb CRPS, respectively: clonidine 300 µg *vs* 700 µg *vs* NS	26/3 (crossover study)	Pain (VAS, MPQ) until six hours post treatment	Clonidine: better analgesia than NS. No difference between the two clonidine doses. 300 µg clonidine: less sedation than 700 µg.
van Hilten *et al.*[39] (2000)	Y	Y/N	Intrathecal: baclofen 25 µg *vs* 50 µg *vs* 75 µg *vs* NS	7/4 (crossover study)	Dystonia (VAS) until eight hours after each injection	50 µg and 75 µg offer most reductions in dystonia. No difference between 25 µg and NS.

BTA = botulin toxin type A; CRPS = complex regional pain syndrome; IASP = International Association for the Study of Pain; IVRB = intravenous regional blockade; LSB = lumbar sympathetic block; MPQ = McGill pain questionnaire; N = no; NS = normal saline; ROM = range of motion; SGB = stellate ganglion block; TRF = thermal radiofrequency; VAS = visual analogue scale; Y = yes

* CRPS diagnosed according to modified IASP definition[58]

Table 3 Randomized controlled trials pertaining to spinal cord stimulation

Authors (year)	CRPS Defined According to IASP (2)	Blinded Assessment/ Sample Size Justification	Description	Number of Patients/ Group	Primary Outcome and Duration of Follow up	Main Findings
Kemler *et al.*[40-42] (2000)	N*	N/Y	SCS and PT *vs* PT alone	54/2	Pain (VAS), GPE, functional status, and quality of life until five years after start of treatment	SCS and PT: significant improvement in VAS and GPE at six months and two years. No differences in functional status and quality of life. SCS: 42% cumulative incidence of side effects at five years.

CRPS = complex regional pain syndrome; GPE = global perceived effect; IASP = International Association for the Study of Pain; N = no; PT = physiotherapy; SCS = spinal cord stimulation; VAS = visual analogue scale; Y = yes

* CRPS defined according to the IASP with two additional criteria: impaired function and symptomatology beyond the area of trauma

Forty days after treatment, subjects receiving clodronate displayed significantly improved VAS (22.3 ± 20.2 *vs* 56.4 ± 31.4; $P < 0.001$), CGA (0.9 ± 0.6 *vs* 1.9 ± 0.7; $P < 0.001$), and EVS scores (1.6 ± 0.7 *vs* 0.2 ± 0.4; $P < 0.001$) compared with controls. In 2004, Robinson *et al.*[10] randomized 27 patients to a single intravenous dose of palmidronate 60 mg or placebo. At the three-month evaluation, subjects who had received biphosphonates reported lower pain scores ($P = 0.043$), a greater overall improvement ($P = 0.026$), and higher functional assessment scores pertaining to physical function ($P = 0.047$).

Free radical scavengers

An excessive inflammatory reaction can lead to the overproduction of free radicals, resulting in the destruction of healthy tissue and possibly leading to CRPS. Thus, free radical scavengers have been proposed to curtail the disease process.[11] To date, three free radical scavengers (dimethyl sulfoxide, *N*-acetylcysteine [NAC], and mannitol) have been investigated for the treatment of CRPS.

In 1996, Zuurmond *et al.*[11] randomized 31 patients to a daily application of a fatty cream containing 50% dimethyl sulfoxide (DMSO) or a placebo. In addition, all subjects received physiotherapy. After two months of treatment, the authors observed that patients in the study group displayed a greater improvement in the Reflex Sympathetic Dystrophy score (based on the presence of pain, edema, decrease range of motion, altered colour and temperature, as well as use-dependent worsening of symptoms) (3 *vs* 4; $P < 0.01$). However, the reductions in subjective pain were similar for the two groups. In 26 patients with a new diagnosis for CRPS (<three months), Geertzen *et al.*[12] compared a three-week course of 50% DMSO to intravenous regional blockade with ismelin (twice a week for three weeks). Using a scoring system based on pain, disability, edema, colour, and range of motion, these authors observed a greater improvement at seven and nine weeks in subjects randomized to DMSO.

Subsequently, Perez *et al.*[13] compared 50% DMSO with NAC. One hundred twelve patients, who were recently diagnosed with CRPS (<one year) and did not undergo prior sympathectomy, were randomized to a 17-week course of 50% DMSO or NAC. All subjects also received paracetamol, naproxen, tramadol, and occupational and physical therapy. The primary outcome measurement was the Impairment Level SumScore (ISS), which incorporates pain, temperature, volume, and active range of motion of the affected extremity. Perez *et al.*[13] also assessed the effect of treatment on the disability level and the quality of life. After 17 weeks, no differences were found between the two groups. However, subgroup analysis revealed that patients with cold CRPS, defined as a –0.4°C difference between the affected and healthy extremity, showed a greater improvement in ISS with NAC compared with DMSO ($P = 0.04$). In contrast, subjects with warm CRPS, defined as a +0.4°C difference between the affected and healthy extremity, displayed more improvement in the quality of life with DMSO ($P = 0.001$). Follow up at 52 weeks again revealed no major differences between the two groups.

van Dieten *et al.*[14] performed a cost analysis using a pharmacoeconomic evaluation conducted in parallel to Perez *et al.*'s trial. Total costs were defined as the sum of direct costs within the healthcare system (visits to healthcare providers, prescribed medication, occupational devices, and home care), direct costs outside the healthcare system (travel expenses, costs of alternative treatment, over-the-counter medication, and family care), and indirect

Table 4 Randomized controlled trials pertaining to adjuvant therapy

Authors (year)	CRPS Defined According to IASP (2)	Blinded Assessment/ Sample Size Justification	Description	Number of Patients/ Groups	Primary Outcome and Duration of Follow up	Main Findings
Oerlemans *et al.*[43-45] (1999)	N	Y/N	PT *vs* OT *vs* CT	135/3	Pain (VAS and MPQ-DLV), ROM, impairment (GEPI rating and ISS), disability (Raboud Skills Questionnaire, modified Greentest, Raboud Dexterity Test), and handicap (SIP) until one year after inclusion in the study	No difference in VAS. At one year, fewer total and sensory words chosen on the MPQ-DLV by PT compared with OT (per protocol analysis). At one year, improved thumb ROM with PT compared with OT and CT (per protocol analysis). At one year, no differences in ISS and GEPI rating (per protocol analysis). At one year, no differences in Raboud Skills Questionnaire, modified Greentest, and SIP scores (per protocol analysis).
Lee *et al.*[47] (2002)	N	Y/Y	Six-week regimen of PT in children with LE CRPS: one *vs* three times per week	25/2	Pain (VAS) until six-12 months after end of treatment	No intergroup differences in VAS, gait, and stair climbing ability.
Moseley[48] (2004)	N*	Y/N	MIP *vs* conventional therapy for six weeks	13/2	Pain (NPS) until 12 weeks after start of treatment	MIP: decreased NPS scores and swelling at six and 12 months.
Moseley[49] (2005)	N*	Y/N	RecImMir *vs* ImRecIm *vs* RecMirRec for six weeks	20/3	Pain (NPS) until 12 weeks after start of treatment	RecImMir: greater decreases in NPS and task-specific NRS scores at 12 months.

CRPS = complex regional pain syndrome; CT = conventional therapy; GEPI = guides to the evaluation of permanent impairment; IASP = International Association for the Study of Pain; Im = imagined movements; ISS = impairment level sumscore; MIP = motor imagery program; Mir = mirror movements; N = no; MPQ-DLV = McGill pain questionnaire (Dutch Language Version); NPS = neuropathic pain scale; NRS = numerical rating scale; OT = occupational therapy; PT = physiotherapy; Rec = recognition of hand laterality; ROM = range of motion; VAS = visual analogue scale; Y = yes

* CRPS diagnosed according to modified IASP definition[58]

costs (absenteeism, loss of productivity). Over the course of the 52 weeks, van Dieten *et al.*[14] observed that DMSO resulted in lower total direct costs than NAC (2852 € *vs* 3934 €; $P < 0.05$).

Mannitol has also been investigated in the treatment of CRPS. Perez *et al.*[15] randomized 41 patients to receive 10% mannitol intravenously or placebo, each to be administered on five consecutive days. These authors found no intergroup differences in pain (assessed daily during nine weeks). Furthermore, the levels of impairment, disability, and handicap were also similar between the two groups at two, six, and nine weeks.

Steroids

Biopsy studies showing tissue inflammation in CRPS have led many authors to use steroids.[16] To date, three RCTs have investigated the role of steroids in the treatment of CRPS.

Christensen *et al.*[16] randomized 23 patients with upper extremity CRPS to prednisone or placebo. The medication was continued until a clinical response was obtained, but for no more than 12 weeks. Using a scale based on pain, edema, volar sweating, and finger-knitting ability, the authors observed 75% improvement rates of 100% and 20% in the treatment and control groups, respectively ($P < 0.01$). Braus *et al.*[17] enrolled 34 patients suffering from upper limb CRPS secondary to cerebral infarct. The subjects were randomized to a four-week course of methylprednisolone or placebo. After treatment, the steroid group presented a decreased shoulder-hand syndrome (SHS) score (based on pain/hyperalgesia, distal edema, and passive humeral abduction/external rotation). When patients in the placebo group were crossed over to the treatment arm, these benefits persisted. Furthermore benefits were still present at six months (SHS score $< 3/14$). Using a similar population, Kalita *et al.*[18] randomized 60 patients to a five-week course of prednisolone or piroxicam. After treatment, the prednisolone group displayed lower SHS scores (4.27 ± 2.83 *vs* 9.37 ± 2.89; $P < 0.001$). In both groups, no changes were detected in activities of daily living.

Gabapentin

Because neuropathic pain can be a prominent feature in CRPS, gabapentin, an anticonvulsant with proven analgesic effect in various neuropathic pain syndromes, has been investigated.[19]

van de Vusse *et al.*[19] undertook a double-blind randomized crossover study in 46 patients with long standing CRPS that was refractory to sympathetic blocks, mannitol infusions, and transcutaneous modulation. At first, the subjects were randomized to receive a three-week course of gabapentin or placebo. This was followed by a two-week washout period. Subsequently, the patients were crossed over. Overall, there were no differences in pain scores between treatment and control groups. However, using global perceived pain relief, more patients receiving gabapentin reported an improvement in pain control (43% *vs* 17% of patients; $P = 0.002$). Subjects receiving gabapentin also reported more side effects (dizziness, somnolence, lethargy) (all $P \leq 0.003$).

Tadalafil

During the chronic phase of CRPS, impaired microcirculation can lead to tissue hypoxia and metabolic tissue acidosis. Tadalafil is a vasodilator that inhibits phosphodiesterase 5, used to treat erectile dysfunction and pulmonary arterial hypertension.[20]

Groeneweg *et al.*[20] randomized 24 patients suffering from cold CRPS of a lower limb to a 12-week course of placebo or tadalafil. In addition, all subjects continued physiotherapy. After treatment, patients in the tadalafil group experienced a greater reduction in VAS scores (15% *vs* 0%; $P = 0.004$). However temperature changes, muscle strength, and activity level were similar between the two groups.

Sarpogrelate hydrochloride

Sarpogrelate hydrochloride, a selective 5-HT_2 antagonist, has been shown to improve peripheral blood circulation through inhibition of serotonin-induced platelet aggregation and vasoconstriction.[21]

Ogawa *et al.*[21] randomized 30 patients with CRPS to conventional treatment (sympathetic blocks, analgesics, antiepileptics, antidepressants, sedatives, physical therapy) or a three-month course of sarpogrelate combined with conventional therapy. At the end of treatment, no differences in pain were observed between the two groups. However, with sarpogrelate, a greater proportion of patients reported improvement in burning pain sensation (70% *vs* 0%; $P < 0.05$).

Interpretation

In all placebo-controlled RCTs, biphosphonates have been shown to decrease pain and swelling as well as to increase range of motion for patients with CRPS. In most trials pertaining to calcitonin, benefits associated with its administration were not detected. The effect of free radical scavengers may be drug dependent; while mannitol is no better than placebo, DMSO seems to provide a mild improvement in range of motion and vasomotor instability in patients with CRPS. Owing to its costs, NAC is best

reserved for a subgroup of patients with cold CRPS. A short course of oral steroids (prednisolone or methylprednisolone) may help with pain control, edema, and mobility in CRPS patients with or without cerebral infarcts. In light of the marginal benefits or limited supportive evidence, tadalafil, sarpogrelate, and gabapentin should be used with caution.

Intravenous regional blockade and nerve blocks

Intravenous regional blockade (IVRB)

Since CRPS has been traditionally associated with a dysfunction of the sympathetic nervous system, many authors have advocated treatment with sympathetic blockade, achieved using an IVRB consisting of local anesthetics, guanethidine (an inhibitor of the presynaptic release of norepinephrine), reserpine (an agent inhibiting norepinephrine synthesis and depleting norepinephrine stores), and/or droperidol (an alpha adrenergic antagonist). Ketanserin (a serotonin type 2 receptor antagonist) and atropine have also been used, although the beneficial effects with these agents were thought to occur through neuromodulation.

Currently, there are seven RCTs comparing IVRB therapy with placebo; another four RCTs compare various therapeutic agents for IVRB.

Randomized controlled trials comparing treatment with placebo

In 1990, Blanchard *et al.*[22] randomized 21 patients with CRPS to IVRB with guanethidine, reserpine, or normal saline (NS). Both guanethidine and reserpine were diluted in NS. Pain scores measured at weekly intervals during 12 weeks were not significantly different between the three groups. Subsequently, Jadad *et al.*[23] enrolled nine patients with CRPS who were known to be responsive to sympathectomy with guanethidine. In each subject, one low dose of guanethidine (10 and 20 mg for the upper and lower limb, respectively) diluted in NS, one high dose of guanethidine (30 mg for both upper and lower limbs) diluted in NS, and one dose of plain NS were tested on three occasions separated by intervals of one week. The order of the solutions was random. Jadad *et al.*[23] observed no intergroup differences in terms of pain intensity and relief, mood, and duration of analgesia. In 2002, Livingstone *et al.*[24] randomized 56 patients with upper extremity CRPS to IVRB with NS or guanethidine (diluted in 0.5% prilocaine). Based on the clinical response, further blocks, to a maximum of four, were administered at weekly intervals. Assessments (pain, vasomotor instability, digital tenderness, and stiffness) were carried out at 24 hr, 48 hr, and one week after each block. Compared with the control group, Livingstone *et al.*[24] found no benefits associated with guanethidine. In fact, long term analysis at 15 weeks revealed that patients receiving guanethidine were more likely to have persistent alterations in hand color ($P = 0.015$); the colour and temperature of their hands also exhibited more sensitivity to ambient thermal changes ($P = 0.003$). Moreover, at 30 weeks, more subjects complained of altered hand temperature (69% *vs* 14%; $P < 0.001$) and digital swelling ($P = 0.04$).

Although guanethidine is the most commonly used drug for IVRB, some authors have investigated alternative agents, such as droperidol, ketanserin, atropine, and methylprednisolone. Kettler *et al.*[25] enrolled six patients with CRPS who had previously obtained a significant but transient relief with a local anesthetic sympathetic block. The subjects were randomized to IVRB with droperidol/heparin/NS or placebo (heparin/NS). Pain was monitored daily. After two weeks, the procedure was repeated with the alternate solution. Droperidol was not associated with any analgesic benefits; however, in three patients, akithesia, dysphoria, or nausea occurred. Hanna *et al.*[26] randomized nine patients to a series of two IVRB with ketanserin followed by two IVRBs with placebo or vice versa. Treatments were provided at weekly intervals. No differences in pain scores were seen. However, ketanserin was associated with more drowsiness, faintness, and shakiness (all $P < 0.05$). In 1993, Glynn *et al.*[27] recruited 14 patients with CRPS that was confirmed by pain relief after a guanethidine IVRB. The subjects were randomized to IVRB with atropine diluted in NS or NS alone. Patients could receive up to two treatments at a weekly interval before crossing over to the alternate solution. There were no differences in pain, pain relief, and mood. Taskaynatan *et al.*[28] recruited 22 patients with upper limb CRPS who did not undergo sympathetic blockade in the prior month. Treatment was randomized to IVRB with methylprednisolone and 2% lidocaine (diluted in NS) or NS. A series of three treatment sessions was carried out at weekly intervals. Pain, range of motion, edema, and patient satisfaction, measured on each occasion one hour after tourniquet release, revealed no differences between the two groups. These variables were still similar at 1.5 months.

Randomized controlled trials comparing therapeutic modalities

Rocco *et al.*[29] recruited 12 patients with CRPS that presented temporary relief with either stellate or lumbar sympathetic block. IVRB was achieved using guanethidine diluted in 0.5% lidocaine, reserpine diluted in 0.5% lidocaine, or plain 0.5% lidocaine. Every subject underwent treatment with all three solutions in a randomized fashion at weekly intervals. Pain scores were evaluated over 90 min after each block, and patients maintained an hourly

pain log during the week following treatment. There were no differences between the three groups.

In 1995, Ramamurthy *et al.*[30] attempted to determine the optimal number of blocks for an IVRB with guanethidine. Fifty-seven patients with a recent history of CRPS (<three months), who had not undergone prior IVRB, were randomized to receive one, two, or four IVRBs. The blocks were carried out at four-day intervals using guanethidine diluted in 0.5% lidocaine. Pain, global evaluation (perceived improvement), and range of motion measured after each session and at one, three, and six months, were similar after one, two, or four blocks.

In 1983, Bonelli *et al.*[31] compared IVRB and stellate ganglion blockade. Nine patients were randomized to a series of four IVRBs with guanethidine performed every four days or to a sequence of eight stellate ganglion blocks (0.5% bupivacaine) carried out every other day. Although IVRB produced a greater increase in skin temperature and plethysmographic tracing 24 and 48 hr after the blocks, no intergroup differences in pain were observed at 15 min, one hour, 24 hr, 48 hr, 16 days, one month, and three months. Furthermore, at one and three months, there were no differences in vasomotor disturbances, trophic changes, edema, and range of motion.

In addition to guanethidine and reserpine, bretylium has also been used to treat CRPS. In 1992, Hord *et al.*[32] enrolled seven patients who had a history of temporary relief with stellate ganglion or sympathetic blocks. Each subject received two IVRB with bretylium (diluted in 0.5% lidocaine) and two IVRB with lidocaine. The sequence of treatments was randomized. A $> 30\%$ decrease in pain was considered clinically significant; therefore, when the patient's pain relief was less than 30%, the next IVRB was performed. Hord *et al.*[32] observed that IVRB with bretylium and lidocaine provided a longer analgesic duration than pure lidocaine (20 ± 17.5 days *vs* 2.7 ± 3.7 days; $P < 0.001$).

Stellate ganglion block (SGB) and lumbar sympathetic block (LSB)

The stellate and lumbar sympathetic ganglia are responsible for the sympathetic innervation of the upper and lower limb, respectively. Many authors have sought to interrupt these sympathetic pathways through local anesthetic blockade, chemical neurolysis, and/or radiofrequency neurotomy.

Price *et al.*[33] recruited four patients with upper extremity CRPS and three patients with lower extremity CRPS for whom they performed SGB and LSB, respectively. Each subject received one block with local anesthetics (1% lidocaine and 1% lidocaine/0.25% bupivacaine for SGB and LSB, respectively) and one with NS. The two blocks were separated by an interval of seven to ten days; the order was random. Thirty minutes after the injection, Price *et al.*[33] found no differences between the peak analgesic effects of the two groups. The duration of pain relief was greater with local anesthetics than NS (five days and 12 hr *vs* six hours; $P < 0.02$).

In 2008, Manjunath *et al.*[34] set out to compare phenol neurolysis and thermal radiofrequency of the lumbar sympathetic chain. Nineteen patients with lower limb extremity CRPS lasting more than six months, refractory to oral medications (gabapentin, amitryptiline, carbamazepine) but responsive to sympathetic blocks, were randomized to receive thermal radiofrequency or neurolysis with 7% phenol. Despite a reduction in pain scores compared with baseline, no intergroup differences were observed; follow up was carried out until four months. In a previous RCT ($n = 17$), Haynsworth *et al.*[35] also compared thermal radiofrequency (TRF) with phenol neurolysis for patients with lower extremity CRPS. The authors did not record the analgesic efficacy of either technique; however, they observed that sympathectomy (assessed by temperature and sweat test) was still present at eight weeks in 89% of patients in the phenol group compared with 12% in the TRF group ($P < 0.05$). The incidence of postsympathectomy neuralgia (11-33%) was not statistically different.

By preventing the release of acetylcholine from preganglionic sympathetic nerves, botulinum toxin type A (BTA) has been shown to induce a prolonged sympathetic block in animals.[36] Carroll *et al.*[36] recruited seven patients with lower limb CRPS lasting more than six months, refractory to two nonopioid medications but transiently responsive to a previous lumbar sympathectomy. Each subject received two LSBs consisting of bupivacaine or a combination of bupivacaine and BTA. The order was random and patients were eligible for the crossover injection one month after the disappearance of pain relief. Carroll *et al.*[36] found a longer duration of analgesia in the bupivacaine-BTA group (71 days *vs* < ten days; $P < 0.002$).

When performing LSB prior to LA injection, the needle tip's position is commonly verified with fluoroscopy and contrast agents. Tran *et al.*[37] set out to investigate if the latter affected the outcome of the block. Fifteen patients undergoing LSB for CRPS were randomized to receive iohexol or saline prior to the injection of LA. Over the course of the following week, these authors found no major differences between the two groups in terms of pain, allodynia, percent of relief from pain, and interference with daily activities.

Epidural clonidine

By reducing the sympathetic nervous activity, α2-adrenergic agonists administered in the epidural space may contribute to decreased pain in patients with CRPS.[38]

In 1993, Rauck *et al.*[38] enrolled 26 patients with CRPS that was no longer responsive to sympathetic blocks.

Cervical (C7-T1) and lumbar (L2-3) epidural catheters were inserted for upper and lower extremity CRPS, respectively. On consecutive days, patients received an epidural injection of clonidine 300 μg, clonidine 700 μg, or NS in random order. Throughout the study period (six hours), the authors found that pain (measured by VAS and the McGill Pain Questionnaire) was significantly improved in both treatment groups compared with placebo. There were no differences in analgesia between the two doses of clonidine. However, sedation scores were higher in patients receiving 700 μg ($P < 0.001$).

Intrathecal baclofen

The intrathecal administration of baclofen, a γ-aminobutyric acid – receptor (type B) agonist that inhibits sensory input to the spinal cord, has proven beneficial to some patients with dystonia.[39] Since CRPS can lead to dystonia and is often unresponsive to standard treatment, baclofen has been tried in CRPS.

In seven patients with dystonia, refractory to benzodiazepines, levodopa, antiepileptic drugs, botulinum toxin, mannitol, surgical/chemical sympathectomy, and oral baclofen, van Hilten *et al.*[39] inserted an intrathecal catheter and placed its tip at the T11-T12 level. Each subject received a daily bolus of baclofen (25, 50, or 75 μg) or NS in a randomized fashion. The authors observed that the 50 and 75 μg doses provided a significant decrease in dystonia compared with NS and 25 μg ($P < 0.05$).

Interpretation

In the setting of IVRB, the available evidence does not support the use of guanethidine, reserpine, droperidol, ketanserin, atropine, or lidocaine-methylprednisolone. Compared with placebo, local anesthetic agents prolong the duration of action but do not alter the peak effect of SGB and LSB. Two small studies (n = 7) suggest that combining local anesthetic agents with bretylium or botulinum toxin can increase the analgesic duration of IVRB and LSB, respectively. For LSB, although no analgesic differences were found between TRF and phenol neurolysis, the latter may result in longer lasting sympatholysis. Epidural clonidine (300 μg) and intrathecal clonidine (50-75 μg) constitute interesting alternatives for refractory lower limb CRPS and CRPS-related dystonia, respectively. However these neuraxial drugs require further investigation.

Spinal cord stimulation (SCS)

Spinal cord stimulation requires that an electrode be surgically placed in the epidural space at the level of the nerve roots innervating the painful area. An electrical current from the electrode induces paresthesiae, a sensation that suppresses pain. The current is supplied by a pulse generator that is located subcutaneously in the anterior abdominal wall. Patients can subsequently customize the intensity of the current by means of a device that uses radio-frequency transmission.[40] One RCT by Kemler *et al.*[40] studied the use of SCS in CRPS, while two subsequent studies from the same authors looked at the two- and five-year follow ups.[41,42]

Kemler *et al.*[40] recruited 54 patients suffering from CRPS for more than six months who had failed conventional treatment. Participants were randomized to SCS combined with standardized PT or PT alone. Allocation was done on a 2:1 basis in favour of the SCS group. For the latter, subjects first underwent trial lead placement. Those obtaining more than 50% improvement on VAS or more than six points on a seven-point global perceived effect (GPE) scale received permanent lead placement. The main outcome variables were the differences between pre-randomization measurements and those at six months for the VAS, GPE, functional measurements, and quality of life indicators. Thirty-six patients were recruited to the SCS/PT group; 24 proceeded to permanent lead placement. Eighteen patients were allocated to the PT only group. Using an intent-to-treat analysis, changes in VAS favoured the SCS/PT group at six months (-2.4 ± 2.5 *vs* $+0.2 \pm 1.4$; $P < 0.001$). Furthermore, the percentage of patients achieving a GPE score of 6/7 or higher was 36% for the SCS/PT group and 6% for the PT group ($P = 0.01$). No differences were found for the changes in functional status and quality of life.

At two years, the SCS/PT group continued to have statistically better results (VAS and GPE).[41] However, at five years, there were no statistical differences in any of the measured variables.[42]

Over the five-year study period, 42% of patients with SCS experienced at least one complication, with 72% of adverse events occurring during the first two years. The most common complication was pulse generator failure, followed by lead displacement and need to revise the pulse generator pocket.[40-42]

Interpretation

In patients with CRPS, SCS can provide significant pain reduction for up to two years. However, this effect may be lost between the second and fifth year of treatment. Furthermore SCS appears to have no impact on functional status or quality of life. During the first two years, SCS is also associated with a 72% rate of complications (most commonly generator failure, lead displacement, and need to revise the pulse generator pocket). Thus, in light of the adverse events and costs, further RCTs are needed to support the use of spinal cord stimulation.

Adjuvant therapy

Physiotherapy (PT) and occupational therapy (OT)

In 1999, Oerlemans *et al.*[43] set out to investigate the role of PT and OT in the treatment of CRPS. They recruited 135 patients suffering from upper limb CRPS, which was present for less than one year and had not been treated with prior sympathectomy. After receiving free radical scavengers (DMSO or NAC), vasodilators (verapamil, ketanserine, or pentoxifylline), and trigger point injections, subjects were randomized to PT, OT, or control therapy (CT). The treatment sessions were continued until no further progress could be achieved or until their cessation did not result in a recurrence of symptoms. Their intensity and frequency were adjusted to individual patient needs. Goals for PT included improving pain control and increasing coping mechanisms. For OT, the authors tried to reduce the inflammatory symptoms, support the limb in the most functional position, normalize sensibility, and improve function for daily activities. After one year, Oerlemans *et al.*[43] observed that there were no significant differences in the decrease of pain (VAS scores) for all three groups. However, using a per-protocol analysis, scrutiny of the dimensions of pain (as assessed by the McGill Pain Questionnaire, Dutch Language Version) revealed that patients in the PT group selected fewer total and sensory words to describe their pain compared with their OT counterparts (all P values < 0.05). Compared with OT and CT, PT also provided improved active range of motion of the thumb at one year ($P < 0.05$).

Subsequently, Oerlemans *et al.*[44] calculated the impairment rating in all three groups one year after their inclusion in the study. The impairment rating was performed according to the American Medical Association's *Guides to the Evaluation of Permanent Impairment* and included active range of motion, two-point discrimination, and grip strength. No significant differences were found between the three groups.

In the third publication based on the collected data, Oerlemans *et al.*[45] then set out to compare the levels of impairment, disability, and handicap. In terms of impairment, the authors observed no differences in ISS at one year. In terms of disability, the Raboud Skills Questionnaire and modified Greentest could not detect any differences between the three groups. The level of handicap, assessed by sickness impact profile (SIP) scores, was also similar.

In the final study, the same group of authors proceeded to calculate the cost-effectiveness of adjuvant PT and OT.[46] Total calculated costs included medical, non medical, and loss of productivity costs. The incremental cost-effectiveness ratios (ICER) were calculated by first obtaining the mean difference in effectiveness between end-of-study and baseline measures. The total medical costs were then divided by the latter. When the authors examined the ICER for SIP, both PT and OT proved to be more costly and less effective than CT. For the Greentest, compared with CT, OT yielded an ICER of 992 Netherland guilders (NLG) per point of effectiveness; again, PT was more costly and less effective. Physiotherapy and OT both provided an improvement in ISS compared with controls, and PT was more cost efficient than OT (184 NLG/point *vs* 1152 NLG/point, respectively).

The optimal frequency of PT sessions was examined by Lee *et al.*[47] The authors recruited 28 children, aged eight to 17 yr and suffering from lower extremity CRPS, who had not received sympathetic blocks or more than two sessions of physiotherapy. Cognitive-behavioural therapy (relaxation training, deep breathing exercises, biofeedback, and guided imagery) was provided to all subjects. They were subsequently randomized to receive PT at a frequency of one or three times a week for six weeks. The PT program was individualized to each patient and included transcutaneous electrical nerve stimulation, progressive weight bearing, tactile desensitization, massage, as well as contrast baths. At the short term (six weeks to three months after treatment) and long term follow ups (six to 12 months after treatment), no intergroup differences were noted in terms of outcomes related to pain and functionality. Furthermore, a phone interview (conducted at a mean of 133 weeks) also revealed no differences pertaining to pain, function (ambulation), CRPS recurrence, activity level (participation in sports), and school attendance.

Motor imagery program (MIP)

Moseley[48] recruited 13 patients who developed CRPS after a wrist fracture and randomized them to a MIP or to continue their ongoing (conventional) treatment. The MIP incorporated recognition of hand laterality (subjects were presented with pictures of right and left hands and asked to identify the correct side), imagined hand movement (subjects were presented pictures of a hand in different positions and asked to imagine moving their own hand to adopt the posture shown), as well as mirror movements (subjects placed both hands into a box with a mirror separating the two compartments and, while moving both hands, were asked to watch the reflection of the unaffected hand in the mirror). Each stage lasted two weeks, and subjects were required to perform the tasks hourly from 8 a.m. to 8 p.m. No restrictions were placed on the conventional treatment. Six and twelve weeks after the completion of treatment, patients in the MIP group presented less pain and decreased swelling (both $P < 0.05$). The beneficial effects of treatment were replicated when the controls crossed over to the MIP group.

In a follow-up study, Moseley[49] randomized 20 patients to receive MIP in three different sequences: recognition of laterality/imagined movements/mirror movements

(RecImMir), imagined movements/recognition of laterality/imagined movements (ImRecIm), and recognition of laterality/mirror movements/recognition of laterality (RecMirRec). At 12 weeks, the author found that the RecImMir group experienced a greater decrease in pain and an increase in functionality compared with the other two groups (both $P < 0.05$).

Interpretation

Due to contradictory results, the benefits pertaining to PT and OT remain unclear. In adults, the optimal frequency of PT has not been determined. In children, weekly and triweekly PT sessions yield similar results when combined with cognitive-behavioural therapy. The optimal type of PT has not been elucidated. Motor imagery seems to offer promising results but further trials are required to validate its use.

Limitations

For practical reasons, a decision was taken to limit this review to RCTs published in the English language. Although such a restriction may constitute a methodological limitation, we believe that its impact on the paper's conclusions is small. Expansion of our search criteria (using the same databases and time periods) to languages other than English only yielded an additional eight RCTs.[50-57] In this review, no attempt was made to produce a meta-analysis. In our view, given the wide array of therapeutic modalities used for CRPS, patient enrolment would have been insufficient for many treatments to support a systematic pooling of data. We also made no distinction between CRPS type 1 and type 2; except for the documented presence of nerve injury, both entities appear to be clinically similar.[2] Finally, no RCT was excluded based on factors such as sample size justification, statistical power, blinding, definition of intervention allocation, or clinical outcomes. This may represent a limitation to our review, as it may serve to overemphasize evidence derived from "weaker" RCTs. Most importantly, we cannot exclude the possibility that trials that lacked sample size justification, provided limited enrolment, and found no difference between study groups were inadequately powered to answer the question they sought to investigate.

Table 5 Randomized controlled trials comparing treatment with control

Therapeutic modality	Total number of RCTs comparing treatment with control	Number of RCTs with positive findings*
Biphosphonates	4	4
DMSO	1	1
Steroids (in CRPS patients with cerebral infarct)	1	1
Steroids (in CRPS patients without cerebral infarct)	1	1
Epidural clonidine	1	1
Intrathecal baclofen	1	1
Motor imagery program	1	1
Spinal cord stimulation	1	1¶
Calcitonin	4	1
Sympatholytic IVRB (lidocaine/methylprednisolone, guanethidine, reserpine, bretylium, droperidol)	5	0
Neuromodulative IVRB (atropine, ketanserin)	2	0
Vasodilator (tadalafil, sarpogrelate)	2	0
Stellate ganglion/lumbar sympathetic block	1	0
Mannitol	1	0
Gabapentin	1	0
Physical therapy	1	0
Occupational therapy	1	0

* A RCT with positive findings is defined as a trial comparing treatment with control that demonstrates improved primary outcomes in the treatment group. RCTs comparing different therapeutic modalities are not included in this table

¶ Beneficial effects were observed from zero to two years but not from two to five years

RCT = randomized controlled trial; DMSO = dimethyl sulfoxide; CRPS = complex regional pain syndrome; IVRB = intravenous regional blockade

Conclusions

In terms of pharmacological treatment, oral and intravenous biphosphonates, but not calcitonin, have been proven to reliably decrease pain and swelling as well as increase range of motion in patients with CRPS. For free radical scavengers, topical DMSO constitutes the best option. However, its beneficial effects appear to be mild. A short course of oral steroids may be indicated for CRPS patients with or without cerebral infarcts. Limited benefits or supportive evidence suggest that tadalafil, sarpogrelate, and gabapentin should be used with caution.

In the setting of IVRB, the available evidence does not support the use of guanethidine, reserpine, droperidol, ketanserin, atropine, or lidocaine-methylprednisolone. Compared with placebo, local anesthetic agents prolong the duration of action but do not alter the peak effect of stellate and lumbar sympathetic blocks. Epidural and intrathecal clonidine constitute interesting alternatives for refractory lower limb CRPS and CRPS-related dystonia, respectively, but these neuraxial drugs require further investigation. Two small studies suggest that combining local anesthetic agents with bretylium or botulinum toxin can increase the analgesic duration of IVRB and LSB, respectively.

Considering the high incidence of side effects, limited analgesic duration, and costs, further studies are required to support the use of spinal cord stimulation. The benefits derived from adjunctive PT and OT remain unclear. Further trials are required to validate the use of motor imagery programs.

In summary, only biphosphonates appear to offer clear benefits for patients with CRPS. Improvement has been reported with dimethyl sulfoxide, steroids (in CRPS with or without cerebral infarcts), epidural clonidine, intrathecal baclofen, spinal cord stimulation, and motor imagery programs; further trials are required to confirm these findings. The available evidence does not support the use of calcitonin, vasodilators, or sympatholytic and neuromodulative intravenous regional blockade. Clear benefits have not been reported with stellate/lumbar sympathetic blocks, mannitol, gabapentin, and physical/occupational therapy, and further studies are required (Table 5).

Caution should be exercised when interpreting the limited data available in the literature on CRPS. Many issues regarding these therapeutic modalities remain unresolved; thus, they require elucidation through well-designed and meticulously conducted RCTs. Future trials should use uniform diagnostic criteria for CRPS; sample size justification and blinded assessment should be systematically implemented. Furthermore, the duration of CRPS prior to enrolment and the length of follow up need to be rigorously controlled. Study endpoints should include pain relief but also reversal of trophic changes and improvement of functionality (range of motion). Lastly, most studies have thus far focused on single or dual therapeutic modalities; the role of multimodal therapy warrants investigation.

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Appendix

See Table 6.

Table 6 Randomized controlled trials not included in the review

Study	Description	Reason for non inclusion
Reuben *et al.*[A] (2004)	IVRB: Lidocaine and clonidine *vs* lidocaine and NS	Article retracted because of fabricated data.
De Jong *et al.*[59] (2005)	Graded exposure *in vivo*	Similar treatment for both study groups (only timing was different)
Kho[60] (1995)	Traditional *vs* sham acupuncture	Treatment not commonly used.
Korpan *et al.*[61] (1999)	Traditional *vs* sham acupuncture	Treatment not commonly used.
Wu *et al.*[62] (1999)	Qi emission/instruction: qigong master *vs* sham master	Treatment not commonly used.
Durmus *et al.*[63] (2004)	Pulsed electromagnetic field treatment *vs* placebo	Treatment not commonly used.
Kiralp *et al.*[64] (2004)	Hyperbaric *vs* normal oxygen therapy	Treatment not commonly used.
Pleger *et al.*[65] (2004)	Repetitive transcranial magnetic cortical stimulation *vs* placebo	Treatment not commonly used.
Fischer *et al.*[66] (2008)	Occlusal splint *vs* no stomatognathic intervention	Treatment not commonly used.

IVRB = intravenous regional blockade; NS = normal saline

References

1. *Sharma A*, *Agarwal S*, *Broatch J*, *Raja SN*. A web-based cross-sectional epidemiological survey of complex regional pain syndrome. Reg Anesth Pain Med 2009; 34: 110-5.
2. *Stanton-Hicks M*, *Janig W*, *Hassenbusch S*, *Haddox JD*, *Boas R*, *Wilson P*. Reflex sympathetic dystrophy: changing concepts and taxonomy. Pain 1995; 63: 127-33.
3. *Bickerstaff DR*, *Kanis JA*. The use of nasal calcitonin in the treatment of post-traumatic algodystrophy. Br J Rheumatol 1991; 30: 291-4.
4. *Gobelet C*, *Meier JL*, *Schaffner W*, *Bischof-Delaloye A*, *Gerster JC*, *Burckhardt P*. Calcitonin and reflex sympathetic dystrophy syndrome. Clin Rheumatol 1986; 5: 382-8.
5. *Gobelet C*, *Waldburger M*, *Meier JL*. The effect of adding calcitonin to physical treatment on reflex sympathetic dystrophy. Pain 1992; 48: 171-5.
6. *Sahin F*, *Yilmaz F*, *Kotevoglu N*, *Kuran B*. Efficacy of salmon calcitonin in complex regional pain syndrome (type 1) in addition to physical therapy. Clin Rheumatol 2006; 25: 143-8.
7. *Adami S*, *Fossaluzza V*, *Gatti D*, *Fracassi E*, *Braga V*. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. Ann Rheum Dis 1997; 56: 201-4.
8. *Manicourt DH*, *Brasseur JP*, *Boutsen Y*, *Depreseux G*, *Devogelaer JP*. Role of alendronate in therapy for posttraumatic complex regional pain syndrome type 1 of the lower extremity. Arthritis Rheum 2004; 50: 3690-7.
9. *Varenna M*, *Zucchi F*, *Ghiringhelli D*, *et al.* Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. A randomized, double blind, placebo controlled study. J Rheumatol 2000; 27: 1477-83.
10. *Robinson JN*, *Sandom J*, *Chapman PT*. Efficacy of pamidronate in complex regional pain syndrome type I. Pain Med 2004; 5: 276-80.
11. *Zuurmond WW*, *Langendikj PN*, *Bezemer PD*, *Brink HE*, *De Lange JJ*, *van Loenen AC*. Treatment of acute reflex sympathetic dystrophy with DMSO 50% in a fatty cream. Acta Anaesthesiol Scand 1996; 40: 364-7.
12. *Geertzen JH*, *de Bruijn H*, *de Bruijn-Kofman AT*, *Arendzen JH*. Reflex sympathetic dystrophy: early treatment and psychological aspects. Arch Phys Med Rehabil 1994; 75: 442-6.
13. *Perez RS*, *Zuurmond WW*, *Bezemer PD*, *et al*. The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study. Pain 2003; 102: 297-307.
14. *van Dieten HE*, *Perez RS*, *van Tulder MW*, *et al.* Cost effectiveness and cost utility of acetylcysteine versus dimethyl sulfoxide for reflex sympathetic dystrophy. Pharmacoeconomics 2003; 21: 139-48.
15. *Perez RS*, *Pragt E*, *Geurts J*, *Zuurmond WW*, *Patijn J*, *van Kleef M*. Treatment of patients with complex regional pain syndrome type I with mannitol: a prospective, randomized, placebo-controlled, double-blinded study. J Pain 2008; 9: 678-86.
16. *Christensen K*, *Jensen EM*, *Noer I*. The reflex dystrophy syndrome response to treatment with systemic corticosteroids. Acta Chir Scand 1982; 148: 653-5.
17. *Braus DF*, *Krauss JK*, *Strobel J*. The shoulder-hand syndrome after stroke: a prospective clinical trial. Ann Neurol 1994; 36: 728-33.
18. *Kalita J*, *Vajpayee A*, *Misra UK*. Comparison of prednisolone with piroxicam in complex regional pain syndrome following stroke: a randomized controlled trial. QJM 2006; 99: 89-95.
19. *van de Vusse AC*, *Stomp-van den Berg SG*, *Kessels AH*, *Weber WE*. Randomised controlled trial of gabapentin in complex regional pain syndrome type 1 [ISRCTN84121379]. BMC Neurol 2004; 4: 13.
20. *Groeneweg G*, *Huygen FJ*, *Niehof SP*, *et al.* Effects of tadalafil on blood flow, pain, and function in chronic cold complex regional pain syndrome: a randomized controlled trial. BMC Musculoskelet Disord 2008; 9: 143.
21. *Ogawa S*, *Suzuki H*, *Shiotani M*, *et al.* A randomized clinical trial of sarpogrelate hydrochloride for neuropathic pain in patients with post-herpetic neuralgia and reflex sympathetic dystrophy. Pain Clinic 1998; 11: 125-32.
22. *Blanchard J*, *Ramamurthy S*, *Walsh N*, *Hoffman J*, *Schoenfeld L*. Intravenous regional sympatholysis: a double-blind comparison of guanethidine, reserpine, and normal saline. J Pain Symptom Manage 1990; 5: 357-61.
23. *Jadad AR*, *Carroll D*, *Glynn CJ*, *McQuay HJ*. *Intravenous regional sympathetic* blockade for pain relief in reflex sympathetic dystrophy: a systematic review and a randomized, double-blind crossover study. J Pain Symptom Manage 1995; 10: 13-20.
24. *Livingstone JA*, *Atkins RM*. Intravenous regional guanethidine blockade in the treatment of post-traumatic complex regional pain syndrome type 1 (algodystrophy) of the hand. J Bone Joint Surg Br 2002; 84: 380-6.
25. *Kettler RE*, *Abram SE*. Intravenous regional droperidol in the management of reflex sympathetic dystrophy: a double-blind, placebo-controlled, crossover study. Anesthesiology 1988; 69: 933-6.
26. *Hanna MH*, *Peat SJ*. Ketanserin in reflex sympathetic dystrophy. A double-blind placebo controlled cross-over trial. Pain 1989; 38: 145-50.
27. *Glynn CJ*, *Stannard C*, *Collins PA*, *Casale R*. The role of peripheral sudomotor blockade in the treatment of patients with sympathetically maintained pain. Pain 1993; 53: 39-42.
28. *Taskaynatan MA*, *Ozgul A*, *Tan AK*, *Dincer K*, *Kaylon TA*. Bier block with methylprednisolone and lidocaine in CRPS type I: a randomized, double-blinded, placebo-controlled study. Reg Anesth Pain Med 2004; 29: 408-12.
29. *Rocco AG*, *Kaul AF*, *Reisman RM*, *Gallo JP*, *Lief PA*. A comparison of regional intravenous guanethidine and reserpine in reflex sympathetic dystrophy. A controlled, randomized, double-blind crossover study. Clin J Pain 1989; 5: 205-9.
30. *Ramamurthy S*, *Hoffman J*. Intravenous regional guanethidine in the treatment of reflex sympathetic dystrophy/causalgia: a randomized, double-blind study. Guanethidine Study Group. Anesth Analg 1995; 81: 718-23.
31. *Bonelli S*, *Conoscente F*, *Movilia PG*, *Restelli L*, *Francucci B*, *Grossi E*. Regional intravenous guanethidine vs. stellate ganglion block in reflex sympathetic dystrophies: a randomized trial. Pain 1983; 16: 297-307.
32. *Hord AH*, *Rooks MD*, *Stephens BO*, *Rogers HG*, *Fleming LL*. intravenous regional bretylium and lidocaine for treatment of reflex sympathetic dystrophy: a randomized, double-blind study. Anesth Analg 1992; 74: 818-21.
33. *Price DD*, *Long S*, *Wilsey B*, *Rafii A*. Analysis of peak magnitude and duration of analgesia produced by local anesthetics injected into sympathetic ganglia of complex regional pain syndrome patients. Clin J Pain 1998; 14: 216-26.
34. *Manjunath PS*, *Jayalakshmi TS*, *Dureja GP*, *Prevost AT*. Management of lower limb complex regional pain syndrome type 1: an evaluation of percutaneous radiofrequency thermal lumbar sympathectomy versus phenol lumbar sympathetic neurolysis- a pilot study. Anesth Analg 2008; 106: 647-9.
35. *Haynsworth RF Jr*, *Noe CE*. Percutaneous lumbar sympathectomy: a comparison of radiofrequency denervation versus phenol neurolysis. Anesthesiology 1991; 74: 459-63.
36. *Carroll I*, *Clark JD*, *Mackey S*. Sympathetic block with botulinum toxin to treat complex regional pain syndrome. Ann Neurol 2009; 65: 348-51.

37. *Tran KM*, *Frank SM*, *Raja SN*, *El-Rahmany HK*, *Kim LJ*, *Vu B*. Lumbar sympathetic block for sympathetically maintained pain: changes in cutaneous temperatures and pain perception. Anesth Analg 2000; 90: 1396-401.
38. *Rauck RL*, *Eisenach JC*, *Jackson K*, *Young LD*, *Southern J*. Epidural clonidine treatment for refractory reflex sympathetic dystrophy. Anesthesiology 1993; 79: 1163-9.
39. *van Hilten BJ*, *van de Beek WJ*, *Hoff JI*, *Voormolen JH*, *Delhaas EM*. Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. N Engl J Med 2000; 343: 625-30.
40. *Kemler MA*, *Barendse GA*, *van Kleef M*, *et al.* Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. N Engl J Med 2000; 343: 618-24.
41. *Kemler MA*, *De Vet HC*, *Barendse GA*, *Van Den Wildenberg FA*, *Van Kleef M*. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy; two years' follow-up of the randomized controlled trial. Ann Neurol 2004; 55: 13-8.
42. *Kemler MA*, *De Vet HC*, *Barendse GA*, *Van Den Wildenberg FA*, *Van Kleef M*. Effect of spinal cord stimulation for chronic complex regional pain syndrome type I: five-year final follow-up of patients in a randomized controlled trial. J Neurosurg 2008; 108: 292-8.
43. *Oerlemans HM*, *Oostendorp RA*, *de Boo T*, *Goris RJ*. Pain and reduced mobility in complex regional pain syndrome I: outcome of a prospective randomised controlled clinical trial of adjuvant physical therapy versus occupational therapy. Pain 1999; 83: 77-83.
44. *Oerlemans HM*, *Goris JA*, *de Boo T*, *Oostendorp RA*. Do physical therapy and occupational therapy reduce the impairment percentage in reflex sympathetic dystrophy? Am J Phys Med Rehabil 1999; 78: 533-9.
45. *Oerlemans HM*, *Oostendorp RA*, *de Boo T*, *van der Laan L*, *Severens JL*, *Goris JA*. Adjuvant physical therapy versus occupational therapy in patients with reflex sympathetic dystrophy/complex regional pain syndrome type I. Arch Phys Med Rehabil 2000; 81: 49-56.
46. *Severens JL*, *Oerlemans HM*, *Weegels AJ*, *van t' Hof MA*, *Oostendorp RA*, *Goris RJ*. Cost-effectiveness analysis of adjuvant physical or occupational therapy for patients with reflex sympathetic dystrophy. Arch Phys Med Rehabil 1999; 80: 1038-43.
47. *Lee BH*, *Scharff L*, *Sethna NF*, *et al.* Physical therapy and cognitive-behavioral treatment for complex regional pain syndromes. J Pediatr 2002; 141: 135-40.
48. *Moseley GL*. Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial. Pain 2004; 108: 192-8.
49. *Moseley GL*. Is successful rehabilitation of complex regional pain syndrome due to sustained attention to the affected limb? A randomised clinical trial. Pain 2005; 114: 54-61.
50. *Perrigot M*, *Bergego C*, *Hocini A*, *Pierrot-Deseilligny E*. Algodystrophic syndrome in hemiplegia. Clinical and therapeutic study (French). Ann Med Interne (Paris) 1982; 133: 544-8.
51. *Friez L*, *Pere G*, *Breuillard P*, *Meignan S*. Comparison of treatment with griseofulvin, beta blockers and calcitonin in 55 cases of post-traumatic algoneurodystrophies (French). Rev Rhum Mal Osteoartic 1982; 49: 857-60.
52. *Cherot A*, *Amor B*. Treatment of algodystrophy. A randomized study of 95 cases with 3 treatments: calsyn 100, visken, grisefuline and penthonium (French). Rev Rhum Mal Osteroartic 1983; 50: 95-7.
53. *Gobelet C*. The role of calcitonin in the treatment of algoneurodystrophy (French). Schweiz Rundsch Med Prax 1986; 75: 7-9.
54. *Kotzki N*, *Pelissier J*, *Dusotoit C*, *et al.* Preventive processes of shoulder-hand syndrome in bedridden hemiplegic patients: evaluation of three processes (French). Ann Réadaptation Méd Phys 1991; 34: 351-5.
55. *Riou C*, *Daoudi Y*, *Langlais F*, *Pawlotsky Y*, *Cheverry C*. Can algodystrophy be prevented by thyrocalcitonin? (French). Rev Chir Orthop Reparatrice Appar Mot 1991; 77: 208-10.
56. *Uher EM*, *Vacariu G*, *Schneider B*, *Fialka V*. Comparison of manual lymph drainage with physical therapy in complex regional pain syndrome, type I. A comparative randomized controlled therapy study (German). Wien Klin Wochenschr 2000; 112: 133-7.
57. *Tabak Y*, *Entok E*, *Tascioglu F*, *et al.* The efficacy of intranasal salmon calcitonin in the treatment of reflex sympathetic dystrophia (Turkish). J Rheum Med Rehab 2004; 15: 234-40.
58. *Bruehl S*, *Harden RN*, *Galer BS*, *et al.* External validation of IASP criteria for complex regional pain syndrome and proposed research diagnostic criteria. International Association for the Study of Pain. Pain 1999; 81: 147-54.
59. *de Jong JR*, *Vlaeyen JW*, *Onghena P*, *Cuypers C*, *den Hollander M*, *Ruijgrok J*. Reduction of pain-related fear in complex regional pain syndrome type I: the application of graded exposure in vivo. Pain 2005; 116: 264-75.
60. *Kho KH*. The impact of acupuncture on pain in patients with reflex sympathetic dystrophy. Pain Clinic 1995; 8: 59-61.
61. *Korpan MI*, *Dezu Y*, *Schneider B*, *Leitha T*, *Fialka-Moser V*. Acupuncture in the treatment of posttraumatic pain syndrome. Acta Orthop Belg 1999; 65: 197-201.
62. *Wu WH*, *Bandilla E*, *Ciccone DS*, *et al.* Effects of qigong on late-stage complex regional pain syndrome. Altern Ther Health Med 1999; 5: 45-54.
63. *Durmus A*, *Cakmak A*, *Disci R*, *Muslumanoglu L*. The efficiency of electromagnetic field treatment in complex regional pain syndrome type I. Disabil Rehabil 2004; 26: 537-45.
64. *Kiralp MZ*, *Yildiz S*, *Vural D*, *Keskin I*, *Ay H*, *Dursun H*. Effectiveness of hyperbaric oxygen therapy in the treatment of complex regional pain syndrome. J Int Med Res 2004; 32: 258-62.
65. *Pleger B*, *Janssen F*, *Scwenkreis P*, *Volker B*, *Maier C*, *Tegenthoff M*. Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. Neurosci Lett 2004; 356: 87-90.
66. *Fischer MJ*, *Reiners A*, *Kohnen R*, *et al.* Do occlusal splints have an effect on complex regional pain syndrome? A randomized, controlled proof-of-concept trial. Clin J Pain 2008; 24: 776-83.