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REVIEW ARTICLE/BRIEF REVIEW

Treatment of complex regional pain syndrome: an updated systematic review and narrative synthesis

Traitement du syndrome douloureux régional complexe : étude systématique actualisée et synthèse narrative

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Abstract

Purpose *Although multiple treatments have been advocated for complex regional pain syndrome (CRPS), the levels of supportive evidence are variable and sometimes limited. The purpose of this updated review is to provide a critical analysis of the evidence pertaining to the treatment of CRPS derived from recent randomized-controlled trials (RCTs).*

Source *The MEDLINE, EMBASE, Psychinfo, and CINAHL databases were searched to identify relevant RCTs conducted on human subjects and published in English between 1 May 2009 and 24 August 2017.*

Principal findings *The search yielded 35 RCTs of variable quality pertaining to the treatment of CRPS. Published trials continue to support the use of bisphosphonates and short courses of oral steroids in the setting of CRPS. Although emerging evidence suggests a therapeutic role for ketamine, memantine, intravenous immunoglobulin, epidural clonidine, intrathecal clonidine/baclofen/adenosine, aerobic exercise, mirror therapy, virtual body swapping, and dorsal root ganglion stimulation, further confirmatory RCTs are warranted. Similarly, trials also suggest an expanding role for peripheral sympathetic blockade (i.e., lumbar/thoracic sympathetic, stellate ganglion, and brachial plexus blocks).*

Conclusions *Since our prior systematic review article (published in 2010), 35 RCTs related to CRPS have been reported. Nevertheless, the quality of trials remains variable. Therefore, further research is required to continue investigating possible treatments for CRPS.*

Résumé

Objectif *Bien que de nombreux traitements aient été préconisés pour le syndrome douloureux régional complexe (SDRC), les niveaux de preuve en leur faveur sont variables et parfois limités. L'objectif de cette étude actualisée est de fournir une analyse critique des données probantes ayant trait au traitement du SDRC à partir d'essais cliniques randomisés récents.*

Source *Des recherches ont été menées dans les bases de données MEDLINE, EMBASE, Psychinfo et CINAHL pour l'identification des essais cliniques randomisés pertinents menés chez l'homme et publiés en anglais entre le 1er mai 2009 et le 24 août 2017.*

Constatations principales *La recherche a identifié 35 essais cliniques randomisés de qualité variable en rapport avec le traitement du SDRC. Les essais publiés continuent à soutenir l'emploi des bisphosphonates et des traitements de courte durée de corticostéroïdes par voie orale dans le cadre du SDRC. Bien que de nouvelles données probantes suggèrent que certains traitements (kétamine, mémantine, immunoglobulines IV, clonidine par voie péridurale, clonidine/baclofène/adénosine par voie intrathécale, activité physique aérobique, thérapie par le miroir, l'échange de corps virtuel et la stimulation du ganglion de la racine postérieure) peuvent jouer un rôle*

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thérapeutique, une confirmation par de nouveaux essais cliniques randomisés reste nécessaire. Les essais suggèrent également un plus grand rôle pour le bloc sympathique périphérique (c'est-à-dire, blocs sympathiques lombaires/thoraciques, bloc du ganglion cervico-thoracique et du plexus brachial).

Conclusions *Depuis notre précédente revue systématique (publiée en 2010), 35 essais cliniques randomisés en rapport avec le SDRC ont été publiés. Néanmoins, la qualité de ces essais reste variable. De la recherche supplémentaire est donc nécessaire pour continuer à évaluer les traitements possibles du SDRC.*

First described more than a century ago, complex regional pain syndrome (CRPS) remains a contemporary medical challenge with a natural history characterized by chronicity and relapses that can result in significant disability over time.[1] Fractures and surgical insult constitute common precipitating events but CRPS can also develop after a seemingly benign trauma. Although multiple treatments have been advocated for CRPS, the levels of supportive evidence are variable and sometimes limited. In 2010, we published a systematic review summarizing the evidence derived from randomized-controlled trials (RCTs) in an attempt to determine the benefits associated with these therapeutic modalities.[2] In the 2010 review article, we concluded that only bisphosphonates appear to offer clear benefits for patients with CRPS and that multiple knowledge gaps exist. For instance, although improvement had been reported following the administration of steroids, epidural clonidine, intrathecal baclofen, spinal cord stimulation (SCS), and motor imagery programs, further trials were required to confirm these findings. During the last eight years, numerous subsequent studies have appeared in the literature. Thus, the primary purpose of this updated review is to provide a critical analysis of the recent evidence pertaining to the treatment of CRPS derived from RCTs published between May 2009 and August 2017.

Methods

Search strategy and selection criteria

An updated literature search was conducted by two authors (S.D. and D.Q.T.) on 24 August 2017 using the MEDLINE, Psychinfo, and CINAHL databases. The latter were queried from their inception until 24 August 2017. Because this review article serves as an update to the one published in 2010, we elected to use the same (previously published) search strategy.[2] The terms "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" were searched. Results were limited to studies conducted on human subjects, written in English, and published in peer-reviewed journals. Only RCTs pertaining to the treatment of CRPS were considered for analysis. For the purpose of this review, no distinction was made between CRPS type 1 (formerly reflex sympathetic dystrophy) and 2 (formerly causalgia). Trials that investigated the impact of prophylactic interventions were excluded and RCTs published only as abstract or correspondence were not included in our subsequent analysis. After selecting the initial articles, we examined their reference lists and the SCOPUS Cochrane database of systematic reviews for additional material. No RCTs were excluded based on factors such as definition of intervention allocation or primary and secondary outcomes. Nevertheless, non-randomized studies, observational case reports, and cohort studies were excluded to avoid potential biases introduced by institutional practices.[2]

Data extraction was carried out by coauthors S.D. and D.B. (pharmacologic therapy), K.J.T. and D.B. (adjuvant therapy), R.J.F. and D.B. (intravenous and peripheral sympathetic blockade), and D.Q.T. and D.B. (neuraxial therapy). Information recorded included the year of publication, the definition of CRPS used by the study, the duration of CRPS prior to patient enrolment, the method of randomization, the study's sample size, the presence of blinded assessment, the definition of the primary outcome, and sample size justification. All data entry was then confirmed and verified by three coauthors (S.D., D.B., and D.Q.T.).

For each trial, validity was further explored by using the Cochrane Database Tool for assessing risk of bias. Relevant information was collected by two coauthors (D.B. and D.Q.T.). Six domains were evaluated including: adequacy of sequence generation, allocation concealment, and blinding (of participants, personnel and outcome assessors); how incomplete outcome data were addressed; selective outcome reporting; and other sources of bias (e.g., study design issues, early trial termination, baseline imbalance in study groups). Subsequently, each domain result was categorized as "yes" (green), indicating a low risk of bias, "no" (red), indicating a high risk of bias, and "unclear" (yellow), indicating an unknown risk of bias. This information was then presented as risk of bias summaries (Figs. 1, 2, 3, 4, and 5).

Results

Our initial search criteria yielded 41 RCTs. Of these, five were excluded because they referred to the contribution of non-anesthesia providers (e.g., acupuncturists) or employed techniques that are not commonly used (e.g., manual lymphatic drainage, low-level laser therapy, transcranial stimulation). Another trial was excluded because it did not analyze data belonging to the placebo group (Appendix). Of the remaining 35 RCTs, 14 studied pharmacologic treatment (Table 1), four investigated neuraxial blocks (Table 2), and three addressed spinal cord/dorsal root ganglion stimulation (Table 3). Intravenous/peripheral sympathetic blocks and adjuvant therapy were investigated by eight and six studies, respectively (Tables 4 and 5).

	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Free of selective outcome reporting	Free of other potential threats to validity	Treatment investigated
Breuer 2014 **(18)**	+	+	+	+	?	−	IV parecoxib vs. placebo
Finch 2009 **(21)**	+	+	+	?	?	?	Topical ketamine vs. placebo
Fischer 2013 **(19)**	+	+	+	+	?	?	IV magnesium vs. placebo
Goebel 2010 **(27)**	+	+	+	+	?	+	IVIG vs. placebo
Groeneweg 2009 **(28)**	+	+	+	+	−	?	Topical ISDN vs. placebo
Gustin 2010 **(24)**	?	+	+	?	?	?	PO memantine vs. placebo
Kalita 2016 **(17)**	+	?	−	+	?	+	PO prednisolone vs. no treatment
Manning 2014 **(26)**	+	+	+	+	?	?	PO lenalidomide vs. placebo
Safarpour 2010 **(25)**	?	?	+	+	+	−	SC&ID botulinum toxin A vs. placebo
Schwartzman 2009 **(22)**	?	?	+	+	?	?	IV ketamine vs. placebo
Sigtermans 2009 **(23)**	+	+	?	?	?	?	IV ketamine vs. placebo
van der Plas 2013 **(20)**	+	+	+	+	+	?	IM magnesium vs. placebo
Varenna 2013 **(8)**	+	+	+	+	+	?	IV neridronate vs. placebo
Eun Young 2016 **(9)**	?	−	?	?	?	?	IV pamidronate vs. PO prednisolone

Fig. 1 Risk of bias summary of randomized controlled trials pertaining to pharmacologic treatment of CRPS published between May 2009 and August 2017. CRPS = complex regional pain syndrome; IM = intramuscular; ISDN = isosorbide di-nitrate; IV = intravenous; IVIG = intravenous immunoglobulin; PO = *per os*; SC&ID = subcutaneous and intradermal

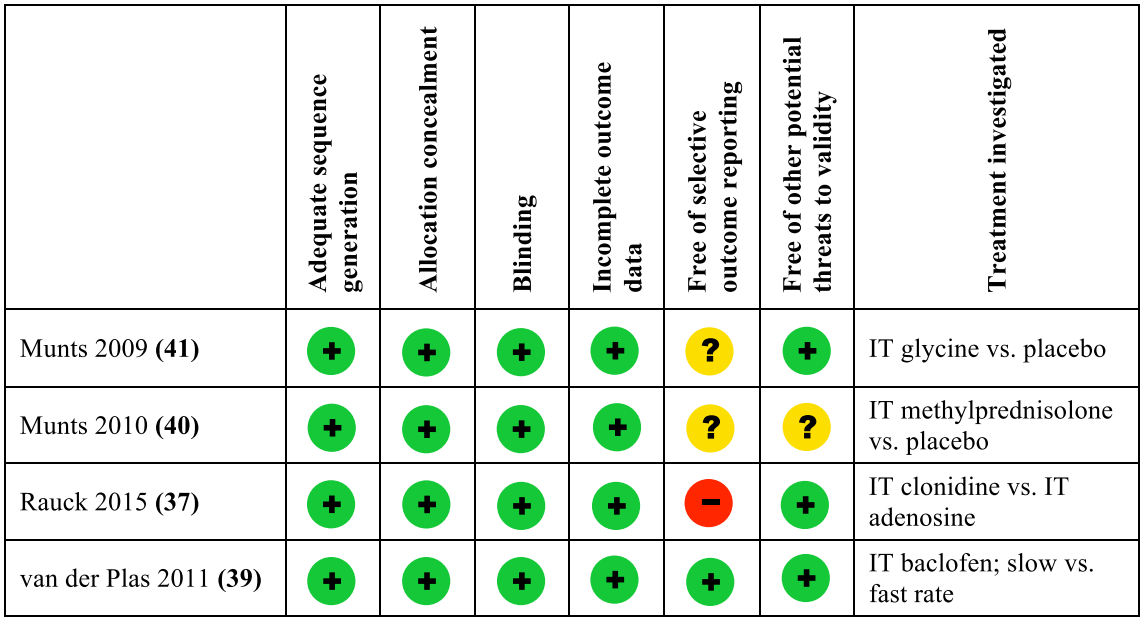

Fig. 2 Risk of bias summary of randomized controlled trials pertaining to neuraxial treatment of CRPS published between May 2009 and August 2017. CRPS = complex regional pain syndrome; IT = intrathecal

Overall the quality of the RCTs was quite variable. In many trials, the information presented was insufficient to properly assess all types of bias (Figs. 1, 2, 3, 4, 5). Nevertheless, studies pertaining to neuraxial therapy seemed to be display fewer sources of potential bias (Fig. 2). The average (range) patient enrolment in each report was 35.2 (8-147) subjects per study. The latest definition of CRPS (i.e., using the "Budapest criteria") recommended by the International Association for the Study of Pain[3] was employed by 19 (54%) of the trials reviewed. Sample size justification was provided in 20 (57%) RCTs. The average (or median) duration of CRPS prior to enrolment was recorded in 28 (80%) studies and varied between 52 days and 12.5 years. Pain constituted the most common primary endpoint (63% of trials) and the study assessment period varied between 30 min and 12 months after treatment.

Pharmacologic therapy

Bisphosphonates

Because bone demineralization often accompanies CRPS, bisphosphonates, which inhibit bone resorption, have been advocated for therapy.[4] In our previous review article,[2] we found that the four RCTs (combined $n = 117$) comparing bisphosphonates to placebo prior to 2009 displayed remarkably consistent results.[4-7] For example, three-day and eight-week courses of intravenous and oral alendronate, respectively, provided significant improvements in pain and range of motion at two, four, eight, and 12 weeks.[4,5] Moreover, compared with placebo, edema was also decreased at four and eight weeks.[5] Similarly, a ten-day course of intravenous clodronate resulted in improved pain and clinical global assessment as well as efficacy scores 40 days after treatment.[6] The benefits derived from bisphosphonates were even manifest after a single 60 mg-dose of intravenous pamidronate. The latter resulted in lower pain scores, greater overall improvement, and higher functional assessment scores of physical function at the three-month evaluation.[7]

Since the prior review article,[2] two additional RCTs have investigated the use of bisphosphonates for CRPS.[8,9] In the first trial, Varenna *et al.*[8] showed that, compared to placebo, a ten-day intravenous infusion (100 mg qid every third day) of neridronate, an amino-bisphosphonate structurally similar to alendronate and pamidronate, resulted in lower pain scores at 20 and 40 days. Furthermore, at day 40, compared with placebo, the neridronate group displayed a greater proportion of patients with a reduction in pain scores of $\geq$ 50% (73.2% *vs* 32.5%, respectively; $P = 0.0003$), lower edema, less pain with passive motion, as well as a lower incidence of both allodynia (15% *vs* 50%; $P < 0.0001$) and hyperalgesia (12.5% *vs* 61.1%; $P = 0.0027$). In the second trial, Eun Young *et al.*[9] compared a six-day regimen of intravenous pamidronate (60 mg tid every other day) with a two-week tapering course of oral prednisolone in hemiplegic stroke patients with CRPS. These authors found that prednisolone provided greater reductions in wrist circumference

compared with palmidronate at one, two, and four weeks but palmidronate provided a greater decrease in pain scores at one and two weeks.[9]

Calcitonin

In addition to its inhibitive effect on bone resorption, calcitonin may be beneficial in CRPS because of possible ß-endorphin-mediated analgesia.[10] Prior to 2009, four RCTs (combined $n = 165$) had investigated the use of calcitonin for upper and lower limb CRPS. Compared to placebo or standard control therapies (e.g., physiotherapy and paracetamol), neither oral nor intranasal calcitonin provided significant benefits in terms of pain, edema, trophic changes, stiffness, grip, or radiographic/densitometric/scintigraphic evaluation.[10-13] Since 2009, no further RCTs have investigated the therapeutic role of calcitonin for CRPS.

Steroids

Biopsy studies showing evidence of tissue inflammation in CRPS have prompted several authors to investigate the use of steroids for analgesia.[14-16] In the previous review article,[2] we reported that, prior to 2009, three RCTs had evaluated the role of steroids in the treatment of CRPS. In 23 patients suffering from upper limb CRPS, Christensen *et al.*[14] observed that, compared to placebo, (oral) prednisone resulted in higher improvement rates of pain, edema, volar sweating, and finger-knitting ability. In patients suffering from CRPS due to cerebral infarct, Braus *et al.*[15] observed a lower Shoulder-Hand Syndrome (SHS) score (based on pain/hyperalgesia, distal edema, and passive humeral abduction/external rotation) after a four-week course of oral methylprednisolone compared with placebo. In a similar patient population, Kalita *et al.*[16] compared five-week courses of prednisolone versus piroxicam. These authors found that, compared to piroxicam, the prednisolone group displayed significantly lower mean SHS scores after treatment.

In the last eight years, only one RCT has investigated the therapeutic role of steroids in CRPS. Kalita *et al.*[17] studied 58 subjects afflicted with CRPS after cerebral infarct. All patients received a two-week course of oral prednisolone (40 mg) followed by a regimen tapered to 10 mg at day 30. The 52 responders (defined as patients with a two-point improvement in CRPS score) were then randomized to continued treatment (10 $mg \cdot day^{-1}$ for another month) or no treatment. Kalita *et al.*[17] found that, after one month, the study group displayed lower mean [standard deviation (SD)] CRPS [2.7 (0.8) *vs* 5.8 (2.5); $P < 0.01$] and lower mean (SD) visual analogue scale (VAS) [2.4 (1.0) *vs* 4.9 (2.1); $P < 0.01$] scores. Nevertheless, no intergroup differences were detected in the Barthel Index of daily activity[17] and the modified Rankin Scale for functional recovery.[17] In the control group, after one month without treatment, 50% of subjects experienced deterioration in the CRPS score by more than two points. Interestingly, resumption of prednisolone resulted in a 77% rate of improvement over the following month.[17]

Non-steroidal anti-inflammatory drugs

In 2014, Breuer *et al.* hypothesized that selective cyclo-oxygenase-2 (COX-2) inhibition would lead to a reduction in peripheral sensitization and normalization of mechanical pain thresholds to blunt pressure i.e., the pressure point

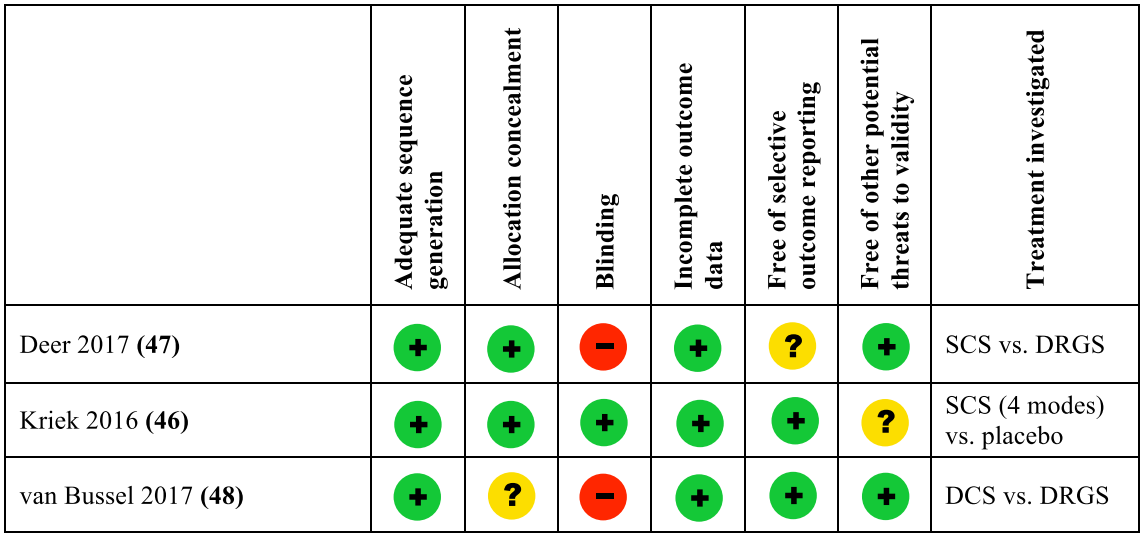

Fig. 3 Risk of bias summary of randomized controlled trials pertaining to spinal cord or dorsal root ganglion stimulation for CRPS published between May 2009 and August 2017. CRPS = complex regional pain syndrome; DCS = dorsal column stimulation; DRGS = dorsal root ganglion stimulation; SCS = spinal cord stimulation

threshold (PPT).[18] These authors randomized 20 in-hospital patients with upper limb CRPS to a two-day regimen of intravenous parecoxib (40 mg bid) or normal saline. Unfortunately, they were unable to show significant differences in terms of PPT or standardized quantitative sensory testing (QST). Furthermore, pain scores and finger circumference remained unchanged in both groups.[18]

N-methyl-D-aspartate (NMDA) receptor antagonist

Peripheral and central sensitizations have been proposed as mechanisms in the development and maintenance of CRPS. In the neural sensitization cascade, cytokines, substance P, and calcitonin gene-related peptide can lead to the release of glutamate in the central nervous system. In turn, glutamate activates dormant NMDA receptors, which promote calcium influx into the synaptic cleft thereby increasing the efficiency of synaptic pain signal transmission. Thus, the activation of NMDA receptors may play a crucial role in the development of central sensitization as well as spontaneous pain and hyperalgesia.[19]

In the central nervous system, magnesium can function as an NMDA receptor antagonist thereby stabilizing abnormal neural excitation. In 2013, Fischer *et al.*[19] randomized 56 patients afflicted with CRPS to a five-day course of intravenous magnesium (70 $mg \cdot kg^{-1}$ over four hours per day) or saline. No intergroup differences were found in terms of Impairment Level Sum Scores and pain (11-point BOX scale) at one, three, six, and 12 weeks after the start of treatment. The same year, van der Plas *et al.*[20] investigated the benefits of intramuscular magnesium in patients with dystonia caused by CRPS. Subjects were randomized to a three-week course of intramuscular magnesium (escalating daily doses of 1,000 to 2,000 mg) or saline. After a one-week washout period, they underwent the alternate treatment; no intergroup differences in dystonia were found.[20] Nevertheless, these results should be interpreted with caution as van der Plas *et al.*[20] terminated the trial prematurely (after enrolling only 22 out of a planned 40 patients) because of difficulty with recruitment.

The anesthetic agent, ketamine, possesses potent non-competitive NMDA receptors blocking properties.[21] In

	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Free of selective outcome reporting	Free of other potential threats to validity	Treatment investigated
Askins 2014 **(60)**	+	+	+	?	?	−	LDHF US; 2 intensities vs. placebo
de Oliveira Rocha 2014 **(56)**	+	+	+	+	?	?	TSB vs. subcutaneous injection
Eckmann 2011 **(50)**	+	+	+	+	+	?	IVRB with lidocaine and 4 different doses of ketorolac
Freitas 2014 **(57)**	+	?	+	?	?	?	LSB vs. PRF
Meier 2009 **(55)**	+	?	+	+	?	+	LSB vs. IV LA
Nascimiento 2010 **(51)**	?	?	+	+	?	+	IVRB vs. 2 different doses of clonidine for SGB
Toshniwal 2012 **(59)**	+	+	−	+	?	?	SGB vs. ICBPB
Yoo 2012 **(58)**	?	?	?	+	?	+	SGB; US vs. landmarks

Fig. 4 Risk of bias summary of randomized controlled trials pertaining to sympathetic blocks for CRPS published between May 2009 and August 2017. CRPS = complex regional pain syndrome; ICBPB = infraclavicular brachial plexus block; IV LA = intravenous local anesthetics; IVRB = intravenous regional block; LDHF US = low-dose high frequency ultrasound; LSB = lumbar sympathetic block; PRF = pulse radiofrequency; SGB = stellate ganglion block; TSB = thoracic sympathetic block; US = ultrasound

2009, Finch *et al.*[21] investigated the benefits of topical ketamine in 20 subjects suffering from CRPS. These authors randomized subjects to a 10% ketamine or placebo cream application over the affected area. After a one-week washout period, patients were crossed over to the alternate group. Finch *et al.*[21] observed that, 30 min after application, topical ketamine resulted in decreased allodynia (to light brushing) and hyperalgesia (to punctate stimulation). Unfortunately, because assessments were only carried out at 30 min, the duration of these benefits remains unknown. In a separate study, Schwartzman *et al.*[22] investigated the benefits of a ten-day regimen of intravenous ketamine (with the dose incrementally increased to 0.35 $mg{\cdot}kg^{-1}{\cdot}hr^{-1}$ without exceeding 25 $mg{\cdot}hr^{-1}$) infused over four hours each day. Although these authors found that, compared to placebo, intravenous ketamine resulted in significant decreases in overall pain and certain pain parameters (e.g., pain in the most affected area, burning pain, pain with light touch) as well as night awakenings, their results should be interpreted with caution, as they halted patient recruitment after recruiting only 19 patients (out of a planned 40 subjects) in part because statistical significance had been reached for many outcomes.[22] To date, the largest trial (n = 60) investigating the benefits of ketamine in the setting to CRPS was conducted by Sigtermans *et al.*[23] In 2009, these authors randomized subjects to a four-day infusion of intravenous ketamine (1.2-7.2 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$) *vs* normal saline, titrated according to pain relief and the presence of side effects. Pain scores were then assessed weekly through the 12th week. Sigtermans *et al.*[23] reported consistently lower pain scores in the ketamine group until week 11. Unfortunately, these benefits appeared short lasting, as pain scores were comparable between the two groups towards the end of treatment (week 12). Furthermore, ketamine resulted in a higher incidence of nausea, vomiting, and psychomimetic side effects. Moreover, no intergroup differences were found in terms of use of the affected limb, walking ability, range of motion, threshold for touch, and temperature/volume of the affected limb.[23]

In 2010, Gustin *et al.*[24] enrolled 20 patients afflicted with CRPS to physiotherapy and morphine combined with a 49-day regimen of memantine (escalating doses from 5-40 mg) or placebo. Although patients randomized to the control group did report a decrease in static pain compared to baseline, only subjects receiving memantine displayed improvements in pain with movement, mood, and disability.

	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Free of selective outcome reporting	Free of other potential threats to validity	Treatment investigated
Barnhoorn 2015 **(65)**	+	+	?	+	+	−	Conventional PT vs. PEPT
Bilgili 2016 **(67)**	+	+	+	?	?	?	CT vs. CT + TENS
Cacchio 2009 **(70)**	?	?	+	+	?	+	CT vs. CT + MT
Jeon 2014 **(72)**	?	?	?	?	?	?	VBS video with active vs. passive participation
Pervane Vural 2015 **(71)**	+	?	+	+	?	+	CT vs. CT + MT
Topcuoglu 2015 **(66)**	+	?	+	+	?	?	CT vs. CT + aerobic exercise

Fig. 5 Risk of bias summary of randomized controlled trials pertaining to adjuvant therapy for CRPS published between May 2009 and August 2017. CRPS = complex regional pain syndrome; CT = conventional therapy; MT = mirror therapy; PEPT = pain exposure physical therapy; PT = physical therapy; TENS = transcutaneous electrical nerve stimulation; VBS = virtual body swapping

Table 1 Randomized-controlled trials in CRPS of pharmacologic treatment published between May 2009 and August 2017

Authors (yr)	CRPS defined according to IASP (Budapest criteria)/ duration of CRPS prior to treatment	Sample size justification	Description	Number of patients/groups	Primary outcome	Main findings
Varenna *et al.* (2013)[8]	Y/ NA	Y	Neridronate (100 mg *iv* QID every third day for 10 days) *vs* placebo in patients with CRPS of the hand or foot	76/2	Comparative change in VAS pain scores 40 days after the first infusion	Neridronate: lower VAS scores at day 20 and 40 At 40 days, neridronate group displayed a higher proportion of patients with $\geq$ 50% decreases in VAS scores, lower edema scores, and less pain with passive motion At 40 days, neridronate group displayed lower incidence of allodynia (15% *vs* 50%) and hyperalgesia (12.5% *vs* 61.1%)
Eun Young *et al.* (2016)[9]	Y/ 51.6 (26.6) days	N	IV pamidronate (60 mg TID) every other day during 6 days *vs* PO prednisolone (1 $mg \cdot kg^{-1}$) tapered over 2 weeks in patients with CRPS post stroke	21/2	Not defined/4 weeks after the end of treatment	Palmidronate: lower VAS scores compared with prednisolone at 1 and 2 weeks Prednisolone: greater decrease in wrist circumference compared with pamidronate at 1, 2, and 4 weeks No intergroup differences in finger circumference
Kalita *et al.* (2016)[17]	N/ 9.5 (5.7) weeks	Y	Patients with CRPS post stroke get 40 mg prednisolone PO for 2 weeks followed by a tapering dose to 10 mg at day 30 Responders are randomized to 10 mg *vs* no prednisolone for 1 month	52/2	CRPS scale/ 1 month	At 1 month, 10-mg group displayed lower mean (SD) CRPS scores [2.7 (0.8) *vs* 5.8 (2.5)] and VAS scores [2.4 (1.0) *vs* 4.9 (2.1)] No intergroup differences in BI and mRS scores
Breuer *et al.* (2014)[18]	Y/ 5.5 [4-36] months	Y	IV parecoxib (40 mg BID for 2 days) *vs* placebo	20/2	Pressure pain threshold after treatment	No intergroup differences in post-treatment pressure pain threshold or quantitative sensory testing No changes in pain or finger circumference

Table 1 continued

Authors(yr)	CRPS defined according to IASP (Budapest criteria)/ duration of CRPS prior to treatment	Sample size justification	Description	Number of patients/groups	Primaryoutcome	Main findings
Fischer *et al.* (2013)[19]	N/ 10.5 [5.0-26.8] months	Y	Intravenous magnesium (70 mg·kg^{-1} over 4 hr) for 5 consecutive days *vs* placebo	56/2	ISS and BOX-11 scale at 1, 3, 6, and 12 weeks after the start of treatment	No intergroup differences using ISS and BOX-11 scale Magnesium: compared with baseline, improvement in MPQ at 6 weeks and perceived job participation at 12 weeks
van der Plas (2013)[20]	N/ 11.5 [IQR = 6–16] yr	Y	Intramuscular magnesium (twice a day) for 3 weeks (escalating daily doses from 1000-2000 mg) *vs* placebo Crossover after 1-week period	22/ Crossover trial	Change in BFM scores after 3 weeks	No intergroup differences in the change in dystonia, as measured by BFM, BADS, and NRS No intergroup differences in myoclonus (UMRS), tremor (TRGRS), and function Magnesium: improved pain (NRS) scores, higher proportion of patients improving on CGI
Finch *et al.* (2009)[21]	N/ 18 months [2 months-19.2 yr]	N	Topical ketamine 10% *vs* placebo cream on the dorsum of the affected hand or foot. Crossover after 1-week period	20/ Crossover trial	Not defined/30 min after the application of the cream	Topical ketamine: decreased allodynia to light brushing and hyperalgesia to punctate stimulus No differences in terms of pain and touch threshold before and after treatment
Schwartzman *et al.* (2009)[22]	Y/ 6.6 (5.8) yr	Y	4-hr daily infusion of IV ketamine (incrementally increased until 0.35 mg·kg^{-1}·hr^{-1} without exceeding 25 mg·hr^{-1}) *vs* saline over the course of 10 days	19/2	Overall pain	Ketamine: decrease in overall pain and some pain parameters (pain in most affected area, burning pain, pain with light touch) as well as night awakenings compared with baseline Ketamine: compared with baseline, no differences in quantitative sensory testing, temperature, allodynia, pressure/ heat/cold evoked pain, quality of life testing

Table 1 continued

Authors(yr)	CRPS defined according to IASP (Budapest criteria)/ duration of CRPS prior to treatment	Sample size justification	Description	Number of patients/groups	Primaryoutcome	Main findings
Sigtermans *et al.* (2009)[23]	N/ 7.4 [0.1-31.9] yr	Y	4.2-day infusion of IV ketamine (1.2-7.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) *vs* saline, titrated according to pain relief and presence of side effects	60/2	Pain scores assessed weekly until week 12 (week 1 = the start of treatment)	Ketamine: lower pain scores until week 11, higher incidence of nausea/ vomiting/ psychomimetic effects No intergroup differences in terms of analgesia at week 12 No intergroup differences in use of affected limb, walking ability, range of motion, threshold for touch, temperature/ volume of the affected limb, blood pressure, and liver function tests
Gustin *et al.* (2010)[24]	N/ 16.0 (10.3) months	N	Physiotherapy and 56-day regimen of oral morphine with 49-day regimen of memantine (escalating doses from 5-40 mg) *vs* placebo	20/2	NA	Memantine: compared with baseline, improvement in static/dynamic pain, mood (evaluated by Center for Epidemiologic Studies Depression Scale), and disability (evaluated by Pain Index) Placebo: no improvement in dynamic pain, mood, or disability
Safarpour e*t al.* (2010)[25]	Y/ Mean duration of allodynia = 5.5 [range = 1–20] yr	N	Botulinum toxin A 5 U/ site (half subcutaneous/half intradermal) over 10-40 sites *vs* placebo	8/2	Improvement in pain (Brief Pain Inventory), pain days (Clinical Pain Impact Questionnaire) and quantitative sensory testing at 3 weeks and 2 months	No intergroup differences
Manning *et al.* (2015)[26]	Y/ Duration $\geq$ 1 yr	Y	Lenalidomide 10 $mg \cdot day^{-1}$ *vs* placebo during 12 weeks	147/2	Therapeutic response (defined as a $\geq$ 30% improvement in pain scores compared with baseline) at 12 weeks	No intergroup differences in rates of therapeutic response (16.1%) No intergroup differences in the change from baseline in terms of daily sleep assessment, Short-Form MPQ, activity rating, and allodynia at week 12

Table 1 continued

Authors(yr)	CRPS defined according to IASP (Budapest criteria)/ duration of CRPS prior to treatment	Sample size justification	Description	Number of patients/groups	Primaryoutcome	Main findings
Goebel *et al.* (2010)[27]	Y/ Between 6 and 30 months	Y	IVIG 0.25 $g \cdot kg^{-1} \cdot day^{-1}$ for 2 days *vs* placebo Crossover after 28-daywashout period	12/ Crossover trial	Pain intensity measured between day 6 and day 19 after the start of the infusion	IVIG: lower pain scores during treatment period and higher incidence of patient-reported improvement
Groeneweg *et al.* (2009)[28]	N/ 51.5 (37.5) months (ISDN group) 45.5 (29.6) months (placebo group)	N	ISDN *vs* placebo ointment 4 times a day during 10 weeks in patients with cold CRPS of the hand	24/2	Temperature of the hand at the end of treatment (10 weeks)	No intergroup differences in hand temperature, levels of NO and ET-1, pain and activity level (DASH and ULAM)

BADS = Barry-Albright Dystonia Scale; BI = Barthel Index; BID = twice a day; BFM = Burke-Fahn-Marsden Dystonia Rating Scale; CGI = Clinical Global Impression Scale; CRPS = complex regional pain syndrome; DASH = Disability of the Arm, Shoulder and Hand questionnaire; IASP = International Association for the Study of Pain; IQR = interquartile range; ISS = Impairment Level Sum Score; ISDN = isosorbide dinitrate; IV = intravenously; IVIG = intravenous immunoglobulin; MPQ = McGill Pain Questionnaire; mRS = modified Rankin Scale; N = no; NA = information not available; NO = nitric oxide; NRS = numerical rating scale; PO = per os; QID = four times a day; SF-36 = Short Form Health Survey; TRGRS = Tremor Research Group Rating Scale; U = unit; ULAM = upper limb activity monitor; UMRS = Unified Myoclonus Rating Scale; VAS = visual analogue scale; Y = yes

Unless otherwise indicated, the duration of CRPS prior to treatment is expressed as mean (SD) or median [range]

Botulinum toxin A (BoNT-A)

Botulinum toxin A is purported to provide analgesia by decreasing peripheral sensitization (through the inhibition of pain neurotransmitters), central sensitization (through the inhibition of muscle spindles discharge), and central perception of pain (through the blocking of retrograde axonal transport).[25] In 2010, Safarpour *et al.*[25] randomized eight patients afflicted with allodynia and CRPS to BoNT-A (five units/site, half subcutaneously and half intradermally, over ten to 40 sites) or placebo. At both three weeks and two months after treatment, these authors found no intergroup differences in variables assessed by the Brief Pain Inventory (BPI), Clinical Pain Questionnaire, McGill Pain Questionnaire (MPQ), QST, and Patient Satisfaction Scale. Furthermore, study patients found BoNT-A injections extremely painful and were unwilling to undergo similar treatment even if the latter were efficacious.[25]

Lenalidomide

Elevated plasmatic levels of pro- and anti-inflammatory cytokines found in CRPS patients suggest a therapeutic role for non-steroidal immune-modulating agents such as lenalidomide, a thalidomide derivative with a decreased potential for toxicity. In 2014, Manning *et al.*[26] randomized 147 patients afflicted with CRPS to a 12-week course of lenalidomide (10 $mg \cdot day^{-1}$) or placebo. At the end of the treatment period, the authors found no intergroup differences in therapeutic responses (defined as a 30% improvement in pain scores compared with baseline) or changes from baseline in terms of daily sleep assessment, Short-Form MPQ, activity rating, and allodynia.[26]

Intravenous immunoglobulin (IVIG)

Evidence of immune activation in patients afflicted with CRPS has prompted some authors to administer IVIG, an agent purported to reduce peripheral and central glia-mediated neuro-immune activation.[27] In 2010, Goebel *et al.*[27] enrolled 12 subjects with CRPS refractory to conventional treatment. Patients were initially randomized to a two-day course of IVIG (0.25 $g \cdot kg^{-1} \cdot day^{-1}$ for two days) or placebo. Subsequently, after a 28-day washout period, they were crossed over to the other group. In this small trial, Goebel *et al.*[27] reported lower pain scores during active treatment with IVIG.

Table 2 Randomized-controlled trials of CRPS to neuraxial treatment published between May 2009 and August 2017

Authors (yr)	CRPS defined according to IASP (Budapest Criteria)/ duration of CRPS prior to treatment	Sample size justification	Description	Number of patients/groups	Primary outcome	Main findings
Rauck *et al.* (2015)[37]	Y/ 5 [2.3-15] yr	Y	First visit: IT clonidine (100 μg) *vs* adenosine (2 mg) Second visit (1 week later): alternate treatment (90% chances) *vs* normal saline (10% chances)	20/ Crossover trial	Success: proportion of patients with > 30% decrease in pain (compared with baseline) 2 hr after treatment	No intergroup differences in success, patient-reported global assessment of effect, and reduction in areas of allodynia and hyperalgesia Clonidine: greater reduction in pain scores (compared with baseline) and greater decrease in blood pressure
van der Plas (2011)[39]	N/ 12.5 [IQR = 8.0–16.3] yr	Y	IT baclofen fixed daily dose: infusion at fast rate (concentration = 0.75 mg/mL) *vs* slow rate (concentration = 3 $mg{\cdot}mL^{-1}$) during 2 weeks After the first treatment and 1 week of open administration (3 $mg{\cdot}mL^{-1}$), the alternate concentration/rates infused during 2 weeks	14/ Crossover trial	Change in NRS score for pain and dystonia between baseline and end of 2-week infusion period	No intergroup differences in terms of self-reported changes in NRS score for pain or dystonia No intergroup differences in dystonia (as assessed by an investigation using the BFM scale) No intergroup differences in patient preference (as assessed by PPQ) No intergroup differences in symptomatic improvement (as assessed by GIS) Fast rate: more adverse events (e.g., headache, chorea, nausea, hallucinations, amnesia, drowsiness, light-headedness)
Munts *et al.* (2010)[40]	N/ 4.5 (2.2) yr	Y	IT methyprednisolone (60 mg) *vs* normal saline	10/2	Change in pain intensity NRS at 6 weeks	No intergroup differences in change in pain intensity NRS scores No intergroup differences in pain (as assessed by the McGill questionnaire) Methyprednisolone group: worsening myoclonus (as assessed by the UMRS) No intergroup differences in movement disorder (as assessed by the BFM scale and TGRGS) No intergroup differences in symptomatic improvement (as assessed by patient and clinician GIS)

Table 2 continued

Authors (yr)	CRPS defined according to IASP (Budapest Criteria)/ duration of CRPS prior to treatment	Sample size justification	Description	Number of patients/groups	Primary outcome	Main findings
Munts *et al.* (2009)[41]	N/ 9 [IQR = 5–7] yr	N	IT catheter tip positioned in midthoracic region Patients randomized to 4-week course of glycine (starting at 8 $mg \cdot day^{-1}$ for the first week and incrementally increased by 8 $mg \cdot week^{-1}$) *vs* normal saline After a 1-week tapering dose (3 equal doses reductions separated by an interval of 48 hr) and a 1-week washout period, the alternate treatment was infused for 4 weeks	18/ Crossover trial	NA/ Outcomes assessed at the end of treatment (4^{th} week)	No intergroup differences in pain (as assessed by the NRS and MPQ) No intergroup differences in movement disorder (as assessed by the BFM scale, UMRS, and TGRGS) No intergroup differences in activity level (as assessed by the Radboud and walking ability questionnaires) No intergroup differences in adverse events No intergroup differences in symptomatic improvement (as assessed by patient and clinician GIS)

BFM = Burke-Fahn-Marsden; CRPS = complex regional pain syndrome; GIS = global impression scale; IASP = International Association for the Study of Pain; IQR = interquartile range; IT = intrathecal; MPQ = McGill Pain Questionnaire; N = no; NA = information not available; NRS = numeric rating scale; PPQ = patient preference questionnaire; TRGRS = Tremor Research Group Rating Scale; UMRS = unified myoclonus rating scale; Y = yes

Unless otherwise indicated, the duration of CRPS prior to treatment is expressed as mean (SD) or median [range]

Isosorbide dinitrate (ISDN)

Long-standing CRPS can result in impaired microcirculation and decreased temperature of the affected limb. A nitric oxide donor, such as ISDN, could potentially promote endothelium-derived vasodilation.[28] In 2009, Groeneweg *et al.*[28] randomized 24 patients afflicted with "cold" CRPS of the hand to topical ISDN or placebo treatment. The ointments were applied four times daily over a period of ten weeks. At the end of the treatment period, the authors observed no intergroup differences in skin temperature, pain, activity level, or levels of nitric oxide and endothelin 1 (extracted from blister fluid).[28]

Free radical scavengers

In theory, an excessive inflammatory reaction can lead to the overproduction of free radicals, resulting in the destruction of healthy tissue and potentially contributing to CRPS. Thus, free radical scavengers (i.e., mannitol, dimethyl sulfoxide, *N*-acetylcysteine) have been advocated to curtail the pathologic process.[29] Prior to 2009, free radicals had been investigated with mixed results. Although intravenous 10% mannitol provided minimal benefits,[30] daily application of a fatty cream containing 50% dimethyl sulfoxide (DMSO) for two months resulted in a greater improvement in Reflex Sympathetic Dystrophy scores compared with placebo.[29] Furthermore, a three-week course of DMSO 50% provided a greater improvement in terms of pain, disability, edema, colour, and range of motion than intravenous regional blockade with ismelin.[31] In contrast, Perez *et al.*[32] found minimal differences between DMSO 50% and *N*-acetylcysteine in terms of pain, temperature, volume, active range of motion of the affected extremity, disability level, and the quality of life after 17 weeks of treatment. Since 2009, no RCT has investigated the therapeutic role of free radical scavengers in CRPS patients.

Other pharmacologic agents (gabapentin, tadalafil, and sarpogrelate hydrochloride)

In our prior review article,[2] we reported that gabapentin, tadalafil, and sarpogrelate hydrochloride had received some interest for the treatment of CRPS. Because neuropathic pain can be a prominent feature in CRPS, gabapentin, an anticonvulsant with a proven analgesic effect in various neuropathic pain syndromes, has been investigated as a

Table 3 Randomized-controlled trials pertaining to spinal cord or dorsal root ganglion stimulation for CRPS published between May 2009 and August 2017

Authors (yr)	CRPS defined according to IASP (Budapest Criteria)/ duration of CRPS prior to treatment	Sample size justification	Description	Number of patients/ groups	Primary outcome	Main findings
Kriek *et al.* (2017)[46]	Y/ 3 [IQR = 1–5] yr	Y	2-Week periods of sham (placebo) SCS *vs* burst stimulation *vs* stimulation with 40 Hz *vs* 500 Hz *vs* 1000 Hz 2-week treatments separated by 2-day washout cycles	29/ Crossover trial	VAS, MPQ, GPE	Compared with placebo, all treatment groups show improved pain (VAS scale) and satisfaction (GPE): no intergroup differences among treatment modalities No differences in improvement between control, burst, and 1200-Hz groups 48% patients prefer standard (40 Hz) stimulation
Deer *et al.* (2017)[47]	Y/ average durations of chronic pain = 6.8 and 7.5 yr for SCS and DRGS group, respectively	Y	SCS *vs* DRG stimulation	105/2	Success: defined as $\geq$ 50% reduction in VAS pain score (compared with baseline) and absence of neurostimulation-induced adverse events in trial period and at 3 months	DRGS: higher success rates, greater interference, activity and affective scales (Brief Pain Inventory), less postural variation in perceived paresthesia intensity throughout the study period (3, 6, 9, 12 months) DRGS: lower incidence of paresthesia in non-painful areas, greater improvements in mood (i.e. total mood, tension, depression, confusion), greater improvements in the physical component score, general health and social functioning scales of the SF-36 No intergroup differences in patient satisfaction and adverse events
van Bussel *et al.* (2017)[48]	Y/NA	N	Dorsal column stimulation *vs* DRGS for knee CRPS 1-Week treatment periods separated by 2-day washout period	12/ Crossover trial	Patient's preferred treatment	More patients preferred DRGS than dorsal column stimulation (83% *vs* 17%)

CRPS = complex regional pain syndrome; DRGS = dorsal root ganglion stimulation; GPE = global perceived effect; IASP = International Association for the Study of Pain; IQR = interquartile range; IT = intrathecal; MPQ = McGill Pain Questionnaire; N = no; SCS = spinal cord stimulation; NA = information not available; SF-36 = Short-Form-36; VAS = visual analogue scale; Y = yes

Unless otherwise indicated, the duration of CRPS prior to treatment is expressed as mean (SD) or median [range]

Table 4 Randomized-controlled trials pertaining to sympathetic blocks for CRPS published between May 2009 and August 2017

Authors (yr)	CRPS defined according to IASP (Budapest criteria)/duration of CRPS prior to treatment	Sample size justification	Description	Number of patients/groups	Primary outcome	Main findings
Eckmann *et al.* (2011)[50]	Y/ 9.9 (5.4) months	N	Patients with lower extremity CRPS received IVRB using 50 mL of 0.5% lidocaine with 0, 30, 60, or 120 mg of ketorolac at 1-week intervals	10/ crossover trial	NRS score at 1 week	No significant changes found at 1 week compared with baseline in any of the groups
Nascimento *et al.* (2010)[51]	N/NA	Y	Patients with upper limb CRPS received IVRB (70 mg of lidocaine and 30 μg of clonidine) *vs* stellate ganglion block (70 mg of lidocaine) *vs* stellate ganglion block (70 mg of lidocaine and 30 μg of clonidine) weekly during 4 weeks	43/3	VAS scores	No intergroup differences in VAS scores and duration of analgesia
Meier *et al.* (2009)[55]	N/ 9 [2-72] months	Y	Pediatric patients with lower limb CRPS Lidocaine 1% (0.1 mL·kg^{-1} and a maximum of 6 mL) injected in a paravertebral catheter placed adjacent to the lumbar sympathetic chain *vs* the same volume administered intravenously	23/Crossover trial	Difference in measures of spontaneous and evoked pain before and 30 minutes after injection	Lidocaine injected via the paravertebral catheter produced significant reductions in allodynia to brush and pinprick temporal summation, as well as verbal pain score compared with intravenous injection. No carry-over effect was seen at 12 hours
de Oliveira Rocha *et al.* (2014)[56]	Y/ 22.7 (26.3) months (block group) 21 (21.6) months (control group)	Y	Patients with CRPS of the upper extremity TSB at T2 using 10 mL of 0.375% ropivacaine and 100 mg of triamcinolone *vs* same solution injected SC	29/2	Average pain score derived from the BPI at 1 and 12 months	No intergroup differences at 1 month TSB: lower average pain scores at 12 months
Freitas *et al.* (2014)[57]	N/NA	N	Patients with CRPS of the lower extremity. Lumbar sympathetic block (15 mL of lidocaine 2% and clonidine 100 μg per level) *vs* PRF (3 cycles of 120 sec at 42°C) at L2-3 and L3-4	39/2	NA	No intergroup differences in VAS scores, pain quality at 24 hours, 7 days, and 2, 4, and 6 months No intergroup differences in Rand-SF 36

Table 4 continued

Authors(yr)	CRPS defined according to IASP (Budapest criteria)/duration of CRPS prior to treatment	Sample size justification	Description	Number of patients/groups	Primaryoutcome	Main findings
Yoo *et al.* (2012)[58]	Y/ NA	N	Patients with CRPS of the upper extremity post stroke. Ultrasound-guided stellate ganglion block with 5 mL of 0.5% lidocaine *vs* landmark-based technique using 10 mL of 0.5% lidocaine	42/2	Pain intensity (VAS) and hand volume measured pre-block, at 2 and 4 weeks	US group: lower VAS core at 2 and 4 weeks No intergroup difference in hand volume
Toshniwal *et al.* (2012)[59]	Y/ 8.8 (4.4) months (continuous stellate group) 9.3 (2.8) months (continuous infraclavicular group)	N	Patients with CRPS of the upper extremity. Continuous stellate ganglion block *vs* infraclavicular brachial plexus block for 7 days	30/2	NPSS, edema score and range of motion measured for 4 weeks after end of infusion	Both groups improved significantly in all measures compared with baseline during the follow-up period. Significant NPSS differences in favor of the infraclavicular group were only found during the first 12 hr
Askin *et al.* (2014)[60]	N/ 0.5 Watts·cm^{-2}: 57 [38-156] days 3 Watts/cm^2: 62 [25-161] days Control group: 70.5 [15-161] days	N	Patients with CRPS of the upper extremity Low dose high frequency US applied percutaneously to the cervical sympathetic chain at C7, 5 min·day^{-1} for 20 sessions. Intensity of 0, 0.5 *vs* 3 watts·cm^{-2}	40/3	NA	No intergroup differences

BPI = Brief Pain Inventory; CRPS = complex regional pain syndrome; IASP = International Association for the Study of Pain; IV = intravenously; IVRB = intravenous regional block; N = no; NA = information not available; NPSS = neuropathic pain score; NRS = numerical rating scale; PRF = pulsed radiofrequency; Rand SF 36 = Rand Short Form Health Survey-36; SC = subcutaneous; TSB = thoracic sympathetic block; US = ultrasound; VAS = visual analogue scale; Y = yes

Unless otherwise indicated, the duration of CRPS prior to treatment is expressed as mean (SD) or median [range]

Table 5 Randomized-controlled trials pertaining to adjuvant therapy for CRPS published between May 2009 and August 2017

Authors (yr)	CRPS defined according to IASP (Budapest criteria)/ duration of CRPS prior to treatment	Sample size justification	Description	Number of patients/ groups	Primary outcome	Main findings
Barnhoorn *et al.* (2015)[65]	Y/ 7.2 (4.1) months	Y	Conventional PT *vs* PEPT	56/2	ISS-RV (includes VAS, MPQ, AROM and skin temperature) measured at 3, 6, 9 months	No intergroup differences
Topcuoglu *et al.* (2015)[66]	Y/ 81.4 (36.3) days (conventional rehabilitation group) 75.3 (29.3) days (aerobic exercise group)	N	Conventional rehabilitation (i.e., TENS, cold-pack, retrograde massage, contrast bath, analgesics) *vs* conventional rehabilitation + aerobic exercise (30 min, 5 days·week^{-1})	40/2	Improvement in VAS scores and CRPS determinants (hyperesthesia, allodynia, dynamic pain, hand edema, range of motion of shoulder/wrist)	Aerobic exercise: significant decrease in hyperalgesia, metacarpal joint tenderness, sweating, hand pain at rest/during exercise during the day/at night, shoulder pain during the daytime/upon movement
Bilgili *et al.* (2016)[67]	N/NA	N	Standard treatment (i.e., contrast bath/whirlpool bath/exercise program) alone *vs* combined with TENS for a total of 15 sessions	30/2	NA	TENS: greater improvement in pain scores (measured by VAS and LANSS) and edema compared with baseline than standard treatment alone No intergroup differences in ROM or functional capacity (grip strength)
Cacchio *et al.* (2009)[70]	N/ 2.6 (1.5) months (control group) 2.8 (1.3) months (MT group)	Y	Conventional post CVA therapy (neurorehabilitation techniques, OT, ± speech therapy) (5 days·week^{-1}, 1 hr·day^{-1} for 4 weeks) without *vs* with MT 30 minutes/day (weeks 1, 2) and 1 hr·day^{-1} (weeks 3, 4)	48/2	Decrease in self-reported pain at rest and upon shoulder movement (forward flexion) and allodynia at 1 week after treatment	MT: decreased pain and allodynia at 1 week and 6 months MT: improved function (measured using the functional ability and performance time in the Wolf Motor Function Test and quality of movement item in the motor activity log) at 1 week and 6 months
Pervane Vural *et al.* (2016)[71]	N/ NA (duration of CVA = 120-180 days)	Y	Conventional post CVA rehabilitation (neurodevelopmental facilitation techniques, PT, OT, ± speech therapy) (2-4 hr·day^{-1}, 5 days·week^{-1} for 4 weeks) without *vs* with MT (30 min·day^{-1})	30/2	Post-treatment pain (VAS score)	MT: greater improvements in VAS, FIM-motor, FMA-wrist, FMA-hand scores and shorter hospital stay than conventional rehabilitation No intergroup differences in MAS scores

Table 5 continued

Authors (yr)	CRPS defined according to IASP (Budapest criteria)/ duration of CRPS prior to treatment	Sample size justification	Description	Number of patients/ groups	Primary outcome	Main findings
Jeon (2014)[72]	Y/ 52 [33-120] months	N	Virtual body swapping video with the patient only watching the video *vs* reproducing and mentally rehearsing the posture	10/2	NA	No intergroup differences in pain Treatment group: less body disturbance perception (evaluated by modified BDPQ)

AROM = active range of motion; BMT = best medical therapy; BPDQ = body perception disturbance questionnaire; BPI-sf = Brief Pain Inventory (short form); CRPS = complex regional pain syndrome; CVA = cerebral vascular accident; DASH = Disability of the Shoulder and Hand Questionnaire; FIM = functional independence measure; FMA = Fugl-Meyer Assessment; GMI = graded motor imagery; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale; ISS-RV = Impairment Level Sum Score-Restricted Version; LANSS = Leeds Assessment of Neuropathic Signs and Symptoms; MAS = Modified Ashworth Scale; MPQ = McGill Pain Questionnaire; MT = mirror therapy; NA = information not available; OT = occupational therapy; PEPT = pain exposure physical therapy; PIQ = Pain Impact Questionnaire; PT = physical therapy; ROM = range of motion; TENS = transcutaneous electrical nerve stimulation; VAS = visual analogue scale

Unless otherwise indicated, the duration of CRPS prior to treatment is expressed as mean (SD) or median [range]

possible therapeutic modality. In a crossover study (n = 46), patients with long-standing CRPS were randomized to a three-week course of gabapentin or placebo. After a two-week washout period, they received the alternate treatment (or placebo). No intergroup differences were found in pain scores. Although more patients receiving gabapentin reported an improvement in pain control (using global perceived pain relief), they also experienced more adverse events (dizziness, somnolence, lethargy).[33]

During the chronic phase of CRPS, impaired microcirculation can lead to tissue hypoxia and metabolic tissue acidosis. Thus, tadalafil, a vasodilator (through phosphodiesterase 5 inhibition), which has been previously used to treat erectile dysfunction and pulmonary arterial hypertension, was investigated by Groeneweg *et al*.[34] These authors randomized 24 patients suffering from cold CRPS to a 12-week course of tadalafil or placebo. After treatment, patients in the tadalafil group experienced a greater reduction in pain (15% *vs* 0%; P = 0.004). Nevertheless, temperature changes, muscle strength, and activity level remained similar between the two groups.[34]

Sarpogrelate hydrochloride, a selective 5-hydroxy-tryptamine$_2$ antagonist, has been shown to improve peripheral blood circulation through inhibition of serotonin-induced platelet aggregation and vasoconstriction.[35] Ogawa *et al*.[35] 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 intergroup differences were found in terms of pain control. Nevertheless, a greater proportion of patients randomized to sarpogrelate reported improvement in burning pain (70% *vs* 0 %; $P < 0.05$). Because only modest therapeutic benefits have been associated with gabapentin, tadalafil, and sarpogrelate, no RCT has further investigated the role of these agents for CRPS management since 2009.

Interpretation

Since 2009, 14 RCTs have investigated various pharmacologic agents for the treatment of CRPS. The new evidence continues to support the use of bisphosphonates and a short course of oral steroids. Although emerging evidence seems to support the administration of ketamine, memantine, and IVIG, these findings require further validation because of the small number of trials and limited enrolment per trial. More importantly, the benefits associated with (intravenous) ketamine may not exceed the period of infusion and can result in nausea, vomiting, and psychomimetic side effects, thereby limiting its usefulness for outpatient management. The evidence published since 2009 does not support the use of non-steroidal anti-inflammatory agents, magnesium, BoNT-A, lenalidomide, and ISDN ointment.

In the prior review article,[2] we concluded that calcitonin provides no therapeutic benefits. Furthermore, because of the limited supportive evidence or marginal benefits, we advised that mannitol, tadalafil, sarpogrelate, and gabapentin should be employed with caution. Moreover, we detected only a mild improvement in range of motion and vasomotor instability with DMSO. In the last eight

years, no RCT has been carried out to refute (or confirm) these previous conclusions.

Neuraxial therapy

Epidural clonidine

By reducing the sympathetic nervous activity, α_2-adrenergic agonists administered in the epidural space may contribute to decreasing pain.[36] In our prior review article,[2] we reported that one small RCT (n = 26) had investigated the administration of epidural clonidine in patients with refractory CRPS.[36] On consecutive days, subjects received an epidural injection of clonidine 300 μg, clonidine 700 μg, or normal saline in random order. The authors reported that, compared to placebo, pain was significantly improved in both treatment groups throughout the study period (six hours). Although no analgesic differences were detected between the two doses of clonidine, sedation scores were higher in patients receiving 700 μg.[36] Since 2009, no RCT has investigated the therapeutic role of epidural clonidine for CRPS.

Intrathecal clonidine and adenosine

In 2015, Rauck *et al.*[37] compared the therapeutic benefits of intrathecal clonidine and adenosine for CRPS with hyperalgesia. They randomized 20 patients with lower limb CRPS to 100 μg of intrathecal clonidine or 2 mg of intrathecal adenosine. One week later, subjects received the alternate treatment. Rauck *et al.*[37] found no differences in success rates (defined as $>$ 30% decreases in pain compared with baseline, two hours after treatment), patient-reported global assessments of effect, or reductions in areas of allodynia or hyperalgesia. Nevertheless, clonidine resulted in a greater reduction in blood pressure.

Intrathecal baclofen

Complex regional pain syndrome can lead to dystonia, which is often unresponsive to standard treatment. 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.[38] Prior to 2009, only one small crossover RCT (n = 7) had investigated the benefits of intrathecal baclofen in patients with CRPS-related dystonia. van Hilten *et al.*[38] observed that, compared with saline and 25 μg, administration of 50 μg and 75 μg of baclofen resulted in decreased dystonia.

In 2011, van der Plas *et al.*[39] proceeded to investigate the optimal infusion strategy for intrathecal baclofen. They randomized 14 patients with CRPS-related dystonia to a slow (baclofen concentration = 3 $mg{\cdot}mL^{-1}$) *vs* fast (baclofen concentration = 0.75 $mg{\cdot}mL^{-1}$) infusion rate during two weeks. The cumulative daily dose of baclofen was identical in both study groups. After the first treatment and after one week of open administration (3 $mg{\cdot}mL^{-1}$), the alternate concentration/rate was infused for another two weeks. van der Plas *et al.*[39] detected no intergroup differences in self-reported changes in pain or dystonia, patient preference, or symptomatic improvement at the end of the two-week treatment period. Nevertheless, the fast-infusion group reported a higher incidence of adverse events (e.g., headache, chorea, nausea, hallucinations, amnesia, drowsiness, light-headedness).[39]

Intrathecal steroids

In light of the demonstrated benefits associated with parenteral administration of steroids,[14-17] Munts *et al.*[40] set out to investigate the role of intrathecal steroids in the management of CRPS. These authors speculated that steroid injection directly into the subarachnoid space would help curtail central sensitization. Thus, they randomized ten patients afflicted with CRPS to intrathecal administration of methylprednisolone (60 mg) or normal saline. At six weeks, Munts *et al.*[40] were unable to detect intergroup differences in terms of pain, dystonia, tremor, symptomatic improvement, or adverse events. In fact, myoclonus (as assessed by the Unified Myoclonus Rating Scale)[40] was worse in the methylprednisolone group.

Intrathecal glycine

Because glycinergic neurotransmission may play an important inhibitory role in the processing of sensory and motor information, intrathecal glycine has been investigated as a potential therapeutic agent in patients suffering from CRPS with dystonia. Munts *et al.*[41] placed an intrathecal catheter in 18 subjects and randomized them to a four-week course of glycine (starting at 8 $mg{\cdot}day^{-1}$ for the first week and incrementally increased by 8 $mg{\cdot}week^{-1}$) or normal saline. After a one-week tapering regimen (three equal dose reductions separated by an interval of 48 hr) and a one-week washout period, patients received the alternate treatment. At four weeks, Munts *et al.*[41] found no intergroup differences in terms of pain, movement disorder, symptomatic improvement, or adverse events.

Interpretation

Since 2009, four RCTs have investigated the benefits of intrathecal agents for the management of CRPS. While

intrathecal clonidine and adenosine constitute promising options for CRPS with hyperalgesia, further confirmatory RCTs are required. The optimal doses of epidural clonidine and intrathecal baclofen as well as the optimal infusion strategy for intrathecal baclofen warrant further investigation. The available literature does not support the intrathecal use of steroids or glycine. To complicate matters further, of the agents investigated, only baclofen has been officially approved for neuraxial use by the Federal Food and Drug Administration and Health Canada. Thus, the administration of neuraxial clonidine, adenosine, steroids, or glycine should be considered off-label use for now.

Spinal cord and dorsal root ganglion stimulation

Spinal cord stimulation requires the surgical or percutaneous placement of an electrode into the epidural space at the level of the nerve roots innervating the painful area. An electrical current originates from the electrode and is supplied by a pulse generator located in a subcutaneous pocket. The latter can be positioned in various locations (e.g., gluteal, anterior abdominal, axillary, paravertebral). The electrical current induces paresthesias and enables the suppression of pain.[42] Purported mechanisms of action include inhibition of the hyperexcitable central neural circuitry, decrease in the efferent sympathetic output, and antidromic-activated release of vasoactive substances.[43]

In our 2010 review article,[2] we reported that prior to 2009 only one RCT had investigated the use of SCS in CRPS. In 2000, Kemler *et al.*[42] recruited 54 patients suffering from refractory CRPS and randomized them to SCS combined with standardized physiotherapy or physiotherapy alone. At six months, Kemler *et al.*[42] observed that changes in pain scores favoured the SCS/ physiotherapy group. Furthermore, the percentage of patients achieving a global perceived effect (GPE) score of 6/7 or higher was 36% for the SCS/PT group and 6% for the PT group ($P = 0.01$). Subsequently, these authors proceeded to follow their patients over time. At two years, they observed that the SCS/ physiotherapy group continued to display better results (both for pain and GPE).[44] Nevertheless, at five years, there were no intergroup differences in any of the measured parameters.[45] Furthermore, over the five-year study period, 42% of patients with SCS experienced at least one complication (e.g., pulse generator failure, lead displacement, need to revise the pulse generator pocket).[42,44,45] Thus, in the absence of long-term benefits and in light of the frequent side effects in patients with CRPS, we concluded that additional RCTs were required to support the use of SCS.

In 2017, Kriek *et al.*[43,46] proceeded to tackle the absence of long-term benefits seen with SCS in CRPS patients. They hypothesized that analgesic loss over time[45] could be explained by neural adaptation and therapeutic benefits could be regained by using higher frequencies or alternate modes of SCS. These authors implanted 40 patients suffering from refractory CRPS with a spinal cord stimulator and standard stimulation therapy (40 Hz) was carried out during three months. Subsequently, all responders ($n = 33$) underwent (in random order) two-week periods of sham (placebo) stimulation, standard stimulation, burst stimulation, and stimulation using 500 Hz or 1000 Hz. The five treatments were separated by two-day washout cycles. Twenty-nine patients completed the crossover trial. Kriek *et al.*[46] observed significantly lower VAS pain scores (measured three times a day and averaged over a four-day period), decreased numerical rating scale scores for "average pain" and "minimal pain" (MPQ), as well as improved GPE satisfaction scores with all treatments compared to placebo. Nevertheless, no intergroup differences in pain scores were detected among the different modes of stimulation. At the end of the crossover period, 48% of subjects selected standard stimulation as their preferred mode whereas 21%, 14%, and 14% opted for 500 Hz, 1200 Hz, and burst stimulation, respectively. In contrast, only 3% of patients chose placebo stimulation.[46]

In the largest RCT to date (multicenter design with 22 investigative sites), Deer *et al.*[47] set out to compare SCS and dorsal ganglion root stimulation (DRGS) in refractory lower limb CRPS. One hundred forty-six subjects were randomized to SCS versus DRGS and underwent trial stimulation of the allocated modality. Responders ($n = 115$) then received the allocated treatment for the duration of the study period (one year). Deer *et al.*[47] observed that, at all measurement intervals (three, six, nine, and 12 months), DRGS resulted in greater success (defined as $\geq$ 50% reduction in VAS pain score compared with baseline coupled with the absence of neurostimulation-induced adverse events) than SCS. In the 105 patients who completed the year-long study, success rates remained higher in the DRGS group (74% *vs* 53%; $P < 0.001$). Furthermore, throughout the trial, improvements from baseline in the interference, activity, and affective scales (BPI) were consistently greater with DRGS than SCS. At 12 months, DRGS patients were less likely to report paresthesias in non-painful areas (5.5% *vs* 39%; $P < 0.001$). Moreover, they also experienced greater improvements in mood (i.e., total mood, tension, depression, confusion) compared to their SCS counterparts. Similarly, they displayed statistically significant improvements in the physical component score and general health and social functioning scales of the Short Form-36. Nevertheless, no intergroup differences were detected in terms of patient satisfaction and incidence of serious adverse events.

In 2017, using a crossover protocol, van Bussel *et al.*[48] compared DRGS with dorsal column stimulation in 12 patients afflicted with refractory CRPS of the knee. One-week treatment periods were separated by a two-day washout period. These authors reported that a significantly higher proportion of patients preferred DRGS to dorsal column stimulation (83% *vs* 17%; $P = 0.04$). The main reason stemmed from the fact that, with DRGS, no stimulatory vibrations were felt.[48]

Interpretation

In the last eight years, only three trials have investigated the benefits of SCS or DRGS. Higher frequencies and alternate modes of stimulation seem to provide minimal benefits for SCS. Dorsal root ganglion stimulation constitutes a promising new therapy for refractory CRPS, as it results in significantly improved analgesia, function, and mood at one year compared with SCS. Further confirmatory trials and long-term follow-up are required to validate the benefits of DRGS.

Intravenous regional and peripheral sympathetic blocks

Intravenous regional blockade (IVRB)

Intravenous regional blockade involves the injection of therapeutic agents directly into the venous circulation of a CRPS-affected limb after the application of a tourniquet. Our previous review identified 11 RCTs examining this modality and found no evidentiary support for the use of guanethidine, reserpine, droperidol, ketanserin, atropine, or lidocaine-methylprednisolone.[2] In contrast, one study reported that the addition of bretylium to a local anesthetic increased the analgesic duration of IVRB.[49]

Since 2009, only two trials have investigated the use of IVRB for CRPS. In a pilot study with a crossover design involving ten patients with lower limb CRPS, Eckmann *et al.*[50] examined the effect of IVRB using a solution of 0.5% lidocaine (50 mL) containing various doses of ketorolac (0, 30, 60, and 120 mg). No significant benefits in terms of analgesia and edema were found for any of the ketorolac doses, leading the authors to abandon plans for a larger trial. In 2010, Nascimento *et al.*[51] compared IVRB (using 70 mg of lidocaine and 30 µg of clonidine) with stellate ganglion blocks (70 mg of lidocaine with and without 30 µg of clonidine) in 43 patients afflicted with upper limb CRPS. These authors found no intergroup differences in terms of pain scores and duration of analgesia.

Peripheral sympathetic blocks

Sympathetic pathways (e.g., stellate ganglion, thoracic and lumbar sympathetic chains) have been targeted by several authors for the treatment of upper and lower limb CRPS. Investigated strategies have included local anesthetic blockade, chemical neurolysis, and radiofrequency ablation. Our previous review article found five trials comparing the therapeutic benefits of different block techniques and injectates.[2] In the only placebo-controlled RCT, Price *et al.*[52] reported that local anesthetic agents, when compared to normal saline, prolonged the duration of action but did not alter the peak effect of stellate ganglion and lumbar sympathetic blocks (LSBs). Carroll *et al.*[53] found that the addition of botulinum toxin to local anesthetic increased the analgesic duration of LSB. Although no analgesic differences could be detected between thermal radiofrequency and phenol neurolysis, the latter may provide longer lasting sympatholysis for LSB.[54]

Since 2009, three additional RCTs have investigated the benefits of thoracic/lumbar sympathetic blocks for CRPS. Meier *et al.*[55] recruited 23 pediatric patients afflicted with lower limb CRPS and, using a crossover design, compared the effects of lidocaine 1% administered either intravenously or through a paravertebral catheter positioned adjacent to the lumbar sympathetic chain. These authors found that only paravertebral lidocaine produced significant reductions in mean pain intensity of allodynia to brush (mean -1.4; 95% confidence interval [CI] -2.5 to -0.3) and to pinprick temporal summation (mean -1.3; 95% CI -2.5 to -0.2) on a zero- to ten-point colour analogue scale.[55] Nevertheless, no residual effect was seen at 12 hr. In another trial involving 29 adults with upper extremity CRPS, de Oliveira Rocha *et al.*[56] compared thoracic sympathetic blocks using 10 mL of ropivacaine 0.375% and 100 mg of triamcinolone injected paravertebrally at T2 with the same solution injected subcutaneously. No intergroup differences were found in the primary outcome (average pain score derived from the BPI) at one month. Nevertheless, the mean (SD) of the BPI average pain intensity item was significantly lower at 12 months in the thoracic paravertebral group [3.5 (3.5) *vs* 5.9 (2.9); $P = 0.046$]. In 2014, Freitas *et al.*[57] investigated the potential benefits of pulsed radiofrequency (PRF) of the lumbar sympathetic chain in patients afflicted with lower limb CRPS. These authors randomized 39 subjects to PRF (three cycles of 120 sec at 42°C per level) or conventional block (using 10 mL of lidocaine 2% and 100 µg of clonidine per level) of the lumbar sympathetic chain at the L2-3 and L3-4 levels. Freitas *et al.*[57] found no intergroup differences in pain scores and pain quality at 24 hr, seven days, as well as two, four, and six months.

Since 2009, three RCTs have investigated the benefits of stellate ganglion blocks for CRPS. In 2012, Yoo *et al.*[58] compared landmark- and ultrasound-guided stellate ganglion blocks in 42 patients with upper extremity post-stroke CRPS. Although larger volumes of local anesthetic were injected with the landmark technique (10 *vs* 5 mL of lidocaine 0.5%), VAS pain scores were significantly lower at two and four weeks with ultrasound guidance. Nevertheless, no intergroup difference was noted in terms of hand volume. In the same year, Toshniwal *et al.*[59] compared seven-day continuous stellate ganglion block and infraclavicular brachial plexus block in 30 patients with upper extremity CRPS. Compared to baseline, both groups improved significantly in all measured outcomes and displayed similar range of motion and edema scores during the four-week follow-up period. Finally, in the most recent trial ($n = 40$), Askin *et al.*[60] sought to determine the potential therapeutic benefit associated with low-dose, high-frequency ultrasound beams applied to the cervical sympathetic chain. Three dose groups (0, 0.5, and 3 watts·cm^{-2}) were compared in the setting of 20 daily five-minute sessions applied to the C7 level. Askin *et al.*[60] detected no alteration in sympathetic skin responses between treatment and control groups. Furthermore, no intergroup differences were found in any of the outcome measures (pain scores, range of motion, grip strength).

Interpretation

The cumulative evidence does not support for the use of guanethidine, reserpine, droperidol, ketanserin, atropine, lidocaine-methylprednisolone, or ketorolac for IVRB. To date, only bretylium has demonstrated benefits when added to a local anesthetic agent for IVRB. Trials published since 2009 seem to suggest an expanding role for peripheral sympathetic blocks. For instance, placebo-controlled RCTs report a beneficial effect of sympathetic blockade, which was found to be of short duration (< 12 hr) in children with lower limb CRPS undergoing lumbar sympathetic block and of longer duration (12 months) in adults with upper limb CRPS undergoing thoracic sympathetic block. Continuous infraclavicular brachial plexus blocks may offer an interesting alternative to stellate ganglion blocks. Compared to the conventional landmark-based technique, ultrasound guidance can increase the analgesic duration of stellate ganglion blocks. The current evidence does not support the use of PRF of the lumbar sympathetic chain (compared with conventional local anesthetic blockade) or low-dose/high-frequency ultrasound beams applied to the cervical sympathetic chain. Additional trials are required to compare stellate ganglion blocks and IVRB (using lidocaine and clonidine).

Adjuvant therapy

Physical therapy (PT)

In the previous review article, only modest benefits for CRPS could be found with PT.[2] For instance, Oerlemans *et al.*[61] reported some improvement in MPQ scores and active range of motion of the thumb in patients undergoing PT for a year compared to those receiving occupational or control therapy. However, subsequent follow-up studies detected no intergroup differences in overall impairment.[62,63] The optimal frequency of PT also remained unknown, as Lee *et al.*[64] found no difference in outcomes for children who were allocated to one or three sessions of PT per week (total of six weeks).

In the last eight years, only one RCT ($n = 30$) has investigated the benefits of PT for CRPS. Barnhoorn *et al.*[65] compared conventional and pain exposure physical therapy (PEPT) in individuals with upper limb CRPS. In PEPT, patients were told that the pain experienced constituted a false signal; thus, standard medical therapies were stopped and additional aids such as crutches were discouraged. Patients were then advised that the pain would decrease as they started to regain function. Allodynia was reduced through self-massage and use of the affected limb. Subjects received a maximum of five sessions of PEPT (40 min per session). Treatment outcomes were assessed using the impairment level sum score-restricted version (ISS-RV), which included active range of motion, VAS, MPQ, and skin temperature at three, six, and nine months. Using an intent-to-treat analysis, Barnhoorn *et al.*[65] found no difference between the study groups at any time point. In fact, patients improved over time regardless of treatment allocation.

Aerobic exercise

To date, only one RCT has investigated the role of aerobic exercise in the treatment of CRPS. In 2015, Topcuoglu *et al.*[66] enrolled 40 subjects who had experienced a cerebrovascular accident with hemiplegia one to six months prior to the trial and who were also diagnosed with CRPS of the upper limb. During the study period, all patients underwent routine physical and medical therapy (e.g., transcutaneous electrical nerve stimulation, cold packs, retrograde massage, contrast bath, and analgesics). Subjects were randomized to conventional treatment alone or combined with aerobic exercise. The latter entailed aerobic crank ergometry (i.e., "arm cycling") and was carried out during 30 min each day at a frequency of five days per week. Topcuoglu *et al.*[66] observed that patients in the combined treatment group reported significantly less hyperalgesia, metacarpal joint tenderness, wrist pain with

dorsiflexion, and sweating. Furthermore, except for night shoulder pain, VAS scores were also significantly decreased for both the shoulder and hand at rest and during movement. Aerobic exercise also resulted in improved functional independence measure (FIM) scores for both cognitive and motor function, Nottingham Health Profile scores for pain and fatigue, as well as improved mood, as measured by the Beck Depression Scale.[66]

Transcutaneous electrical nerve stimulation (TENS)

The benefits of TENS in CRPS are purportedly derived from endogenous opioid release and improved vasodilation.[67] In 2016, Bilgili *et al.*[67] recruited 30 patients with upper limb CRPS and randomized them to receive active or sham TENS. In addition, all subjects underwent exercise therapy as well as contrast and whirlpool bath. Resting pain was assessed using a VAS while neuropathic pain was assessed with the Leeds Assessment of Neuropathic Signs and Symptoms (LANSS) and Douleur Neuropathique en 4 Questions scales.[67] These measures improved significantly for both groups over time; however, the treatment arm showed significantly more improvement in VAS scores and LANSS than its sham counterpart. Volumetric measurements were used to estimate edema of the affected arm. Again, both groups improved during treatment but the TENS group displayed significantly more reduction in edema compared with control. Active range of motion of the wrist and functional capacity (i.e., grip strength and the Duruoz Hand Index) were also assessed.[67] Although significant improvements were found compared with baseline, Bilgili *et al.*[67] detected no differences between the TENS and control groups.

Mirror therapy (MT)

In our previous review article,[2] we reported that two RCTs had investigated the benefits of motor imagery programs (MIPs), which encompassed recognition of hand laterality, the imagined hand, 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).[68,69] These trials found MIP-related improvements in terms of pain and function.[68,69] However, at the time, no RCT had assessed isolated MT in the setting of CRPS.

In the last eight years, two RCTs have investigated the rehabilitative benefits of MT for stroke patients with CRPS. In 2009, Cacchio *et al.*[70] randomized 48 patients to undergo conventional rehabilitation with or without daily MT for four weeks. These authors reported significant decreases in self-reported pain at rest, pain with active movement, as well as allodynia one week after treatment with MT. These improvements were still present at six months. Furthermore, functional improvement (measured using the functional ability and performance time in the Wolf Motor Function Test[70] and quality of movement item in the motor activity log) was also significantly improved with MT compared with conventional therapy at one week and six months.[70] In 2016, Pervane Vural *et al.*[71]randomized 30 patients afflicted with CRPS following a stroke to a four-week period of standard therapy with or without MT (30 min·day^{-1}). Compared with standard therapy without MT, combined treatment resulted in greater improvements in VAS, FIM-motor, Fugl-Meyer Assessment (MA)-wrist, and FMA-hand scores as well as shorter median [IQR] hospital stays (30 [21-60] *vs* 41 [30-60]; $P = 0.01$).[71] Nevertheless, no intergroup differences were detected in terms of spasticity (assessed by the Modified Ashworth Scale scores).[71]

Despite its benefits, MT carries inherent limitations, as it requires the presence of an intact limb. In 2014, Jeon *et al.*[72] proposed virtual body swapping as a possible alternative. This method aims to induce an illusionary body perception so a patient can identify a virtual body as his/her own. Jeon *et al.*[72] showed a short video clip (filmed from the first person perspective) that consisted of four body movements (opening/closing fist, flexion/extension of elbow, plantar/dorsiflexion, flexion/extension of leg). Subjects randomized to the treatment group were instructed to mimic as well as mentally rehearse these movements whereas control subjects only watched the video clip. Jeon *et al.*[72] observed that the treatment group displayed less body disturbance perception (as evaluated by the modified Body Perception Disturbance Questionnaire). However, pain scores were similar between the two groups.

Interpretation

Physical therapy remains a common adjuvant treatment for CRPS. Nevertheless, additional RCTs are needed to investigate its long-term benefits and optimal frequency. The available evidence does not support the use of PEPT. Aerobic exercise constitutes a promising adjuvant therapy for upper limb CRPS; however, further confirmatory trials are warranted. Although TENS results in decreased pain and edema, it seems to provide minimal functional benefits when combined with PT. Mirror therapy constitutes an interesting adjuvant treatment for post-stroke upper limb CRPS: in addition to improving pain control and function, it may also result in a shorter hospital stay. Further investigation is required to evaluate virtual reality headsets and body swapping.

Limitations

Our methodology contains several limitations. First, the current review serves only as an update to our previous review article.[2] Thus, no attempt was made to produce a meta-analysis. We reasoned that the wide spectrum of therapeutic modalities used for CRPS, limited number of trials published for each treatment, and variable study methodology would not have supported such quantitative pooling of data. Second, similar to the previous review article,[2] we made no distinction between CRPS type 1 and type 2: except for the documented presence of neural injury, both entities appear to be clinically similar.[2] Third, the latest "Budapest criteria"[3] were used for diagnosis by only 56% of trials included for analysis. A complex pathologic entity such as CRPS requires strict and homogeneous diagnostic criteria to ensure clinical reproducibility/duplication of findings derived from different research institutions around the world. Finally, although most trials published since 2009 have employed blinded assessment, sample size justification was absent in approximately 43% of RCTs (Tables 1, 2, 3, 4, 5). This represents a potential methodologic limitation, as it may emphasize evidence derived from smaller RCTs. Furthermore, it raises the possibility that trials that failed to detect significant differences between control and treatment groups could have been insufficiently powered to do so.

Conclusions

A critical survey of the available RCTs can provide an effective tool to establish recommendations pertaining to the clinical treatment of CRPS. Since the publication of our first review article (which analyzed 41 RCTs published between 1950 and 2009),[2] a significant amount of new research has taken place: in the last eight years alone, our search criteria yielded 35 RCTs suitable for analysis. Despite current (and increasing) best evidence, many issues regarding therapeutic modalities for CRPS remain unresolved and thus require investigation through well-designed and meticulously conducted RCTs. Future trials should use the most recent and accepted diagnostic criteria for CRPS (e.g., the "Budapest criteria").[3] 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 not only pain relief but also reversal of trophic changes, improvement of functionality, mood, and, whenever possible, important outcomes such as length of hospital stay.[71] All published RCTs have thus far focused on single or dual therapeutic modalities: the role of multimodal therapy has been conspicuously absent from the literature and thus merits further investigation.

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APPENDIX Summary of randomized-controlled trials not included in the review

Study	Therapeutic modality investigated	Reason for non-inclusion
Lagueux *et al.*[73]	Transcranial direct current stimulation	Treatment not commonly used
Picarelli *et al.*[74]	Repetitive transcranial magnetic stimulation	Treatment not commonly used
Li *et al.*[75]	Acupuncture	Treatment not commonly used
Collins *et al.*[76]	Intravenous magnesium	Data for control group not analyzed
Duman *et al.*[77]	Manual lymphatic drainage	Treatment not commonly used
Dimitrijevic *et al.*[78]	Low-level laser therapy	Treatment not commonly used

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