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Review article

Effectiveness of complex regional pain syndrome treatment: A systematic review

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ABSTRACT

Complex regional pain syndrome (CRPS) is a descriptive term for a complex of symptoms and signs typically occurring following trauma of the extremity. Typical symptomatology includes severe pain, swelling, vasomotor instability and functional impairment of the affected limb. At present there is no one, effective method of treatment of the condition. A large number of treatments have been investigated but major multicentre randomized controlled trials are lacking. This study presents the results of a systematic review of the evidence on effectiveness of treatment methods in CRPS.

It is a follow-up to earlier reviews of randomized controlled trials on CRPS treatment published between 1966 and 2016. Results. The review of randomized controlled trials showed that only bisphosphonates were found to give uniformly positive effects, statistically significantly better than placebo. Improvement has been reported with topical dimethyl sulfoxide, systemic steroids, spinal cord stimulation and graded motor imagery/mirror therapy programmes. The available evidence does not support the use of other treatments in CRPS, however they are frequently used in clinical practice.

Conclusion: Available evidence, although numerous, does not necessarily reflect what is truly effective and what is sham in the management of CRPS.

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1. Introduction

Complex regional pain syndrome (CRPS) is a complex of symptoms typically occurring following trauma of the extremity. At present the ''Budapest criteria'' for diagnosis are commonly accepted and frequently used in scientific studies although subjective and open to exaggeration [1]. There is no definitive single test for confirming or excluding CRPS. The diagnosis relies on clinical assessment with the requirement for a sufficient number of symptoms and signs to be present. A lack of understanding of the underlying pathophysiology for CRPS contributes to the difficulty in developing definitive treatments. A large number of treatments have been investigated but major multicentre randomized controlled trials are lacking and the primary outcome parameters (pain, function)

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are subjective. There is consensus concerning the fundamental role of early therapeutic intervention as it may prevent the disease transition from acute to a chronic form, although it is not yet proven how this changes the course of CRPS [2].

2. Methods

This systematic review is a follow-up to earlier reviews of randomized controlled trials (RCTs) of CRPS treatment published between 1966 and 2014. Five studies were considered and used in this analysis:

- Review of 18 RCTs published from 1966 to 2000 [3].
- Review of 21 RCTs published from 1980 to 2000 [4].
- Review of 35 RCTs published from 1980 to 2005 [5].
- Review of 41 RCTs published from 1950 to 2009 [6].
- Review of 29 RCTs published from 2000 to 2012 [7].

Three other reviews of randomized, controlled trials that focused on specific CRPS treatments, published between 2012 and 2016 were analyzed:

- Review of 18 RCTs focused on physiotherapy, published from 1999 to 2014 [8].
- Review of 3 RCTs focused on ketamine infusions, published from 1999 to 2014 [9].
- Review of 12 RCT focused on the efficacy of local anaesthetic sympathetic blocks, published from 2005 to 2015 [10].

No other, relevant studies have been found up to the completion of this review in October 2017.

In this review CRPS is considered ''early'' when it had lasted less than 6 months or ''chronic'' (long-standing) when it had lasted more than 6 months. It is likely these criteria will change as diagnosis becomes swifter and more reliable not least as 6 months is quite late to initiate treatment.

3. Results

The following therapeutic interventions were assessed in these studies.

3.1. *Calcitonin*

It has been used in CRPS because of its analgesic properties through release of β-endorphin in the central nervous system and its inhibition of bone resorption. Four RCTs investigated the effect of calcitonin in a nasal spray (three) or subcutaneous (s.c.) injections (one) in the treatment of 163 patients with acute and chronic CRPS. Nasal calcitonin spray was administered in doses of 200–400 U/day for 3–4 weeks, whereas s.c. calcitonin 100 U/day was given for 8 weeks. In two studies, calcitonin was combined with an intensive physiotherapy regimen, which was the same in the treatment and placebo groups. All but one trial were small, including fewer than 30 patients in one study arm. At a mean follow-up of 2 (range 1–2) months, statistically significant differences were noted in pain scores (using a four-point pain scale) and in ranges of motion, favouring the treatment (nasal calcitonin, 300 U/day for 3 weeks) group in one study [11]. The other studies showed no intergroup differences in terms of pain relief, improvement of ranges of motion and grip strength, reduction of oedema, stiffness or vasomotor changes [6,7,12]. There is conflicting evidence with respect to the efficacy of calcitonin for the treatment of CRPS. This treatment is relatively simple, safe and therefore frequently used in clinical practice. Its efficacy is confined to early CRPS i.e. lasting less than 6 months. One disadvantage of use calcitonin is intolerance which occurs in about 30% of patients; in particular they may experience unpleasant adverse symptoms during first 1–2 days of calcitonin administration.

3.2. *Bisphosphonates*

They have been used in CRPS because of their potential to inhibit bone resorption. Four RCTs investigated the effect of bisphosphonates in a total of 118 patients with acute and chronic CRPS (duration 3 to 22 months) affecting the upper or lower limb. Three types of bisphosphonates: alendronate, pamidronate and clodronate were used in i.v. infusions (three) or orally (one). Alendronate 7.5 mg/day was administered intravenously (i.v.) for 3 days and after 14 days [13]; alendronate 40 mg/day was administered orally for 8 weeks followed by 4 weeks nontherapeutic period and 8 weeks open extension [14]; clodronate 300 mg/day was administered i.v. for 10 days [15]; pamidronate 60 mg was given in single i.v. infusion [16]. In all studies drug therapy was combined with formal physiotherapy. At a mean follow-up of 6 (range 1–13) months, all four studies showed statistically significant differences in pain relief, improvement of function and overall improvement favouring the treatment groups.

In one trial bisphosphonate (parecoxib) combined with clonidine and lidocaine was given in a regional intravenous regional block (Bier block). This therapy decreased pain more than either i.v. parecoxib with regional lidocaine and clonidine, or a control group, without bisphosphonate [17].

There is not strong evidence for the efficacy of bisphosphonates, with no high-quality trials although positive findings from one on i.v. pamidronate and one on oral alendronate. Oral alendronate administered in high dose is not licensed in some countries. The trials differed with regard to disease duration and included patients with early and chronic CRPS. In spite of positive but not very strong evidence for the effectiveness of this therapy, it is not frequently used in clinical practice. Two ongoing trials should be published in 2017/2018 providing further evidence.

3.3. *Free radical scavengers*

They have been used in CRPS because of their anti-inflammatory potential. This therapy is based on the assumption that CRPS is caused by an exaggerated inflammatory response to trauma, mediated by an overproduction of toxic oxygen and hydroxyl free radicals. Four RCTs investigated the effect of these drugs involving 210 patients with acute and chronic CRPS [18–21]. Three free radical scavengers were used: dimethyl sulfoxide (DMSO) (topical for 2 months), N-acetylcysteine (oral for 4 months) and mannitol (i.v. for 5 days). In

one study, the intervention (topical DMSO for 3 weeks) was compared to another intervention – intravenous regional blockade with guanethidine (twice per week for three weeks) [18] and in the other study, two interventions were compared, topical DMSO vs oral N-acetylcysteine, both for 4 months [19]. The others were compared against placebo. In all studies drug therapy was combined with formal physiotherapy. At a mean follow-up of 4 (range 2–12) months follow-up statistically significant differences were noted in a scoring system based on pain, disability, oedema, skin colour and ranges of motion, favouring treatment with DMSO vs guanethidine in one study. This study involved only patients with early CRPS, lasting <3 months [18]. The other studies showed no intergroup differences in terms of pain relief, improvement of ranges of motion and grip strength or reduction of other features of CRPS.

There is moderate evidence for the effectiveness of topical 50% DMSO cream in reducing the symptoms of early CRPS. Likewise, there is moderate evidence for the effectiveness of oral N-acetylcysteine in reducing the symptoms of chronic CRPS. Free radical scavengers have been used frequently in clinical practice, mostly in the Netherlands.

3.4. *Intravenous regional sympathectomy*

This therapy is based on the assumption that CRPS is associated with a dysfunction of the sympathetic nervous system. Thus, sympathetic interruption using intravenous regional blocks (Bier blocks) consisting of local anaesthetic and an anti-sympathetic drug might have a beneficial effect. Five RCTs have investigated the effect of this therapy, involving a total of 101 patients with acute and chronic CRPS [22–26]. Three drugs were tested: guanethidine (an inhibitor of the presynaptic release of norepinephrine; three trials); droperidol (an alpha adrenergic antagonist; one trial); and ketanserin (a serotonin type 2 receptor antagonist; one trial). In three studies the active drugs and placebo were diluted in normal saline and in one study the drug (guanethidine) and placebo were diluted in 0.5% prilocaine [24]. The treatment consisted of 2–4 blocks administered at weekly intervals. In all studies drug therapy was combined with formal physiotherapy. At a mean follow-up of 9 (range 1–24) weeks follow-up no benefits were found from adding intravenous regional anti-sympathetic comparing to intravenous regional saline or prilocaine (placebo).

There is relatively weak evidence for the effectiveness of i.v. regional sympathectomy for treatment of CRPS. At present this treatment is not popular and, if used, is confined to patients responding positively to a phentolamine test.

Two other RCTs compared different anti-sympathetic modalities: regional intravenous blocks with guanethidine vs regional intravenous blocks with reserpine (an agent inhibiting norepinephrine synthesis and depleting norepinephrine stores) vs plain 1% lidocaine; and regional intravenous blocks with guanethidine vs stellate ganglion blocks with lidocaine [27,28]. In the former study, every subject underwent treatment with all three solutions in a randomized fashion at weekly intervals. Both trials were small, including 12 and nine patients respectively.

At mean follow-ups of 24 and 2 months, respectively, no significant differences were noted between the treatment groups in terms of pain relief and functional improvement. Three of 12 patients receiving guanethidine or reserpine blocks obtained significant pain relief lasting 12 months [28].

3.5. *Sympathetic ganglion blocks*

The stellate and lumbar sympathetic ganglia are responsible for the sympathetic innervation of the upper and lower limbs, respectively. Blocking of these ganglia results in inhibition of sympathetic efferent action in the affected limb. Four RCTs involving 90 patients with early and chronic CRPS investigated the effect of sympathetic ganglion blocks. One low-quality RCT involving seven patients with chronic CRPS investigated the effect of sympathetic blocks performed with 1% lidocaine vs normal saline for stellate ganglion blockade and with 0.125% bupivacaine vs normal saline for lumbar sympathetic chain blockade. The two therapeutic or saline blocks were separated by an interval of 7–10 days. Immediately after the injections no differences were found between the analgesic effects of the two types of injection. The duration of pain relief was greater with lidocaine/bupivacaine than saline blocks (5 days vs 12 h) [29]. One high-quality RCT involving 15 patients with early CRPS who responded to a single stellate ganglion block (>50% pain relief) compared the effect of the addition of a series of five stellate ganglion blockades over 1 month to a combination of oral drug therapy and physiotherapy. At a follow-up of one month after the last injection no intergroup differences were observed [30]. One high-quality RCT involving 25 patients with early and chronic CRPS compared the effect of three interventions: stellate ganglion block with 1% lidocaine (9 patients) vs stellate ganglion ultrasound block (9 patients) and vs stellate ganglion saline block (7 patients). A total of ten therapeutic blocks with 1% lidocaine were performed. The ultrasound block consisted of 5 min of intermittent ultrasound application at 3 W/cm^2 over the stellate ganglion. A total of ten ''sham'' saline blocks were performed. All groups had further rehabilitation. At a follow-up all one month after the last blockade, no intergroup differences in pain relief or functional improvement were observed [31].

One high-quality RCT involving 43 patients with early and chronic upper limb CRPS compared the effect of three interventions: stellate ganglion block with 1% lidocaine (14 patients) vs stellate ganglion block with 1% lidocaine plus 30 μg clonidine (15 patients) and vs regional intravenous block with 1% lidocaine plus 30 μg clonidine (14 patients). A series of five stellate ganglion/regional intravenous blockades were preformed at weekly intervals. At a follow-up all one month after the last blockade, no intergroup differences in pain relief or functional improvement were observed [32].

Other two low-quality RCTs involving 24 patients with chronic lower limb CRPS investigated the effect of lumbar sympathetic chain lesions with 7% phenol or thermal radiofrequency application. At a mean follow-up of 3 (range 2–4) months, a reduction in pain scores compared with baseline was noted in both groups, but no intergroup differences were observed [33,34].

Likewise with intravenous regional sympathectomy, there is relatively weak evidence supporting the effectiveness of sympathetic ganglion blocks in CRPS. At present this treatment is rarely used, and, if so, mostly in patients with chronic lower limb CRPS.

3.6. Steroids

They have been used in CRPS because of their anti-inflammatory action. The underlying rationale was same as in use of free radicals scavengers. Four RCTs investigated the effect of steroids administered over a period form 4 to 12 weeks in 148 patients with chronic CRPS. In two of the studies the patients had specific post-stroke CRPS (so called shoulder-hand syndrome). Two of four trials were small, including 12 and 17 patients in one study arm [35,36]. Three types of steroids were used: prednisone (10 mg/day orally until clinical response or maximum of 12 weeks) [35] and methylprednisolone (8 mg/day orally, then taper dose for two weeks) [36]; and in one study involving 60 patients, prednisolone (40 mg/day orally for two weeks tapering to a dose of 10 mg/week) was compared with piroxicam 20 mg/day [37]. All these three trials were of relatively low quality. Immediately after treatment there were statistically significant differences in pain relief, reduction in signs of CRPS features and improvement favouring the treatment groups in three trails. The results of the most recent high-quality RCT, showed that the efficacy of 60–100 mg oral prednisone administered for 2–3 weeks was statistically significant but limited in treating CRPS of more than 3 months duration not responding to previous treatment [38].

One high-quality RCT investigated the effect of three regional intravenous blocks of 40 mg methylprednisolone in 10 ml of 2% lidocaine vs saline blocks, given as one block per week for 3 weeks. At follow-up at 4 weeks therapeutic blocks were no more effective than saline in treating early CRPS [39].

In spite of relatively weak evidence for the effectiveness of steroids for treatment of CRPS, they are frequently used in clinical practice, especially in early CRPS (a error type I is likely to be present) Steroids appear to be useful in chronic CRPS for patients after stroke, but less so in post-traumatic/injury CRPS.

3.7. Anticonvulsants

The use of anticonvulsants is based on the assumption that pain in CRPS may be (at least in part) neuropathic. Anticonvulsants (gabapentin, pregabalin) with proven analgesic effects in other neuropathic pain syndromes, might be beneficial in pain control. One high-quality RCT investigated the effect of gabapentin (1800 mg/daily given over 3 weeks) in a double-blind randomized crossover trial involving 46 patients with chronic CRPS. There were no differences in pain scores (the primary outcome measure in the trial) between the treatment and control groups. However, using global perceived pain relief, more patients receiving gabapentin reported an improvement in pain control [40]. It is noticeable that gabapentin dose that was used (1800 mg/daiy) is not the maximum (2400 mg/day) recommended for the treatment of neuropathic pain.

There is moderate evidence for the effectiveness of gabapentin reducing some of the pain symptoms (including hyperaesthesia and allodynia) in CRPS patients. Although frequently used, anticonvulsants appear not to be particularly useful in clinical practice.

3.8. Physiotherapy (various types)

Various methods of physiotherapy are recommended as part of the multimodal treatment of CRPS. It seems obvious that exercises are beneficial in restoration of ranges of motion, strength and in improving function of the affected hand. However, the underlying mechanisms of physical therapy in pain control remain obscure. There are several theories explaining this, including release of endorphins in the central nervous system, stimulation of sensory nerve endings of peripheral afferent nerves, spinal cord-mediated analgesia and anti-inflammatory effects. Graded motor imagery (GMI) and mirror therapy may reduce pain and increase mobility by ameliorating maladaptive somatosensory and motor cortex reorganization [41,42]. In general, physiotherapy is aimed at better adaptation to pain, improving posture, movement, activities of daily living and psychosocial functioning [43].

Eighteen RCTs have investigated the effect of various (dozens) kinds of physiotherapy involving a total of 739 patients with acute and chronic CRPS. They treated a mean of 41 (range 13–135) patients per study [8]. Two broadly similar types of rehabilitation, graded motor imagery (6 week programme) and mirror therapy (4 week programme) might be useful for reducing the pain and disability associated with post-traumatic and post-stroke CRPS. This beneficial effect has been maintained up to 6 months after therapy [41–45]. However only the patients following uncomplicated distal radial fractures with early CRPS had proven benefit. The two low-quality trials were conducted in the same centre setting [41,42]; the effectiveness of this therapy has not been reproduced by other studies. The two low-quality RCTs involving 72 patients with early post-stroke CRPS investigated the effect of mirror therapy vs placebo (covered mirror). At a mean follow-up of 6 months, a meaningful reduction of pain and functional improvement were seen in the treatment groups [44,45].

Oerlemans et al. employed multimodal physiotherapy in the treatment of 135 patients with CRPS lasting <12 months. After initial drug therapy with free radical scavengers (DMSO or N-acetylcysteine), vasodilators and trigger point lidocaine injections, the patients were randomized to physiotherapy, occupational therapy or minimal ''social work'' intervention (control therapy). After a mean follow-up of one year, no significant differences were observed in the reduction of pain or improvement of function between the three groups [43]. There is no convicting evidence supporting the effectiveness of other physiotherapy treatments [8].

There is moderate evidence of effectiveness of GMI and mirror therapy in CRPS, however, a type II error is likely to be present. Physiotherapy in general is likely to have a positive effect on the impairment level in patients with chronic CRPS but less effect on pain reduction. It is commonly accepted as a part of the standard treatment of CRPS.

3.9. Spinal cord stimulation

This therapy is based on the assumption that electrical stimulation of the spinal cord (SCS) engenders spinal cord-mediated analgesia and anti-inflammatory effects [46]. One low-quality RCT studied the use of spinal cord stimulation and

physiotherapy vs physiotherapy alone in 54 patients with chronic CRPS; these patients have been reported further at follow-ups of 2 and 5 years [47]. At follow-up of 2 years, statistically significant differences were noted in pain scores and seven-point global perceived effect scale, favouring the treatment group. No differences were found for the changes in functional status and quality of life [47]. At 5 years follow-up the difference between the intervention and control groups was lost [48].

There is moderate evidence for the effectiveness of the spinal cord stimulation in giving some reduction in pain symptoms in CRPS patients. SCS has no effect on function, it is an invasive procedure and its effect is unpredictable and appears only to be temporary. Regardless it enjoys increasing popularity, particularly for patients with chronic CRPS and has been recommended by the National Institute for Clinical Effectiveness (NICE) in the UK, which has a reasonably high bar to acceptance.

3.10. *Ketamine*

The use of ketamine for the treatment of CRPS is based the role of glutaminergic N-methyl-D-aspartate receptor (NMDA) in the process of ''sensitization'' in the central nervous system. There is some evidence that ketamine has strong NMDA-receptor blocking (antagonist) properties resulting in inhibition of the central sensitization mechanism. Three low-level RCTs have investigated the effect of intravenous (two studies; 60 and 19 patients) or topical (one trial; 20 patients) ketamine, involving patients with acute and chronic CRPS [9]. Two studies showed statistically significant differences in pain relief, favouring the treatment (i.v. ketamine) groups. This effect was, however, transient: the lowest pain scores were one week after the ketamine treatment. No positive effect on function was observed. In one study, the application of topical 10% ketamine did not lead to pain relief but it reduced allodynia. The level of evidence of these studies was 2B, suggesting only a weak recommendation and moderate-quality evidence for the use of ketamine in the treatment of CRPS [9].

Regardless of this conclusion, i.v. ketamine treatment enjoys increasing popularity, particularly for patients with chronic CRPS, resistant to any other therapy. It offers at least temporary relief from severe, debilitating pain, however it does not improve the function of the affected limb.

3.11. *Fentanyl*

Opioid drugs, including fentanyl, are commonly used to treat neuropathic pain and are considered effective. There is some evidence that pain in CRPS may have, at least in part, a neuropathic component [49]. One study has investigated the effect of fentanyl in patients suffering from various types of neuropathic pain, including postherpetic neuralgia, chronic postoperative pain and CRPS. Transdermal fentanyl (one-day fentanyl patch) was titrated over 10–29 days to establish the maximum tolerated and effective dose (12.5–50 μg/h). One hundred and sixty three patients who responded to this therapy were then entered into a randomized withdrawal phase. The number of participants completing the study was 47/84 (56%) with fentanyl and 28/79 (35%) with placebo. Nearly 60% of participants taking fentanyl were satisfied and very satisfied with their treatment at the end of the study, compared with about 40% with placebo [50]. There is insufficient evidence to support or refute the suggestion that fentanyl works for any neuropathic pain condition.

3.12. *Amputation*

Amputation of the limb is a definitive treatment that may be considered in so-called ''end-stage'' CRPS. Fortunately this is seen rarely. In this long-standing, therapy-resistant disease, apart from intractable, debilitating pain, several new problems may be encountered such as a totally dysfunctional limb, severe recurrent infections and chronic trophic ulcers. Therefore amputation of the limb may be appropriate for pain relief and improving patients' quality of life. Twenty-six studies, involving 111 amputations in 107 patients have investigated the effect of amputation on pain relief and patients' satisfaction. None of these 26 studies was an RCT. The primary reasons cited for amputation were pain (80%) or a dysfunctional limb (72%). Recurrence of CRPS in the stump was reported in twelve studies and occurred in 31 of 65 patients (48%); phantom pain occurred in fifteen patients (23%). Thirty-six patients were fitted with prostheses; 14 of these patients used the prosthesis. Patient satisfaction was reported in eight studies, but the nature of the satisfaction was not clearly explained. Changes in patient quality of life were reported in three studies (15 patients): quality of life improved in five patients and the joy of life improved in another six patients [51]. Available evidence does not clearly delineate the beneficial and adverse effects of an amputation for long-standing, therapy-resistant CRPS. Whether to amputate or not remains an unanswered question.

3.13. *Vitamin C for prevention CRPS*

Vitamin C has been suggested as a low-risk intervention that might limit excessive soft tissue injury and prevent CRPS. The mechanism of action of vitamin C is thought to be by inhibiting local inflammatory cascades via antioxidant mechanisms. Four high-quality RCTs have investigated the effect of vitamin C for preventing the development of CRPS. The studies compared vitamin C with placebo in a total of 1081 patients following distal radial fractures (the studies assessed 123, 195, 427 and 336 patients respectively) [52–55]. All four trials included predominantly older women and a mix of intra- and extra-articular fractures of the distal radius. In two trials, patients were treated with operative and nonoperative techniques, whereas the two other trials included only nonoperative management. In two trials patients were randomized to 500 mg of vitamin C daily for 50 days vs placebo (1:1), in one study a dose of 1000 mg of vitamin C was used in the same manner, whereas one randomized patients to 200, 500, or 1500 mg of vitamin C daily for 50 days vs placebo (3:1). All studies showed a statistically significant reduction in CRPS incidence in groups receiving vitamin C vs placebo at a follow-up of one year. Therefore, a general conclusion from these studies is that it is likely that oral administration of 500–1000 mg of vitamin C per day for 50 days from the date of the

injury reduces the incidence of CRPS in patients following distal radial fractures. Following this conclusion, it is frequently used in clinical practice and is also recommended by the American Association of Orthopedic Surgery for patients following distal radial fractures [56].

However, all of the studies have numerous limitations, including:

(a) use of non-Budapest criteria of diagnosis of CRPS, instead using the older criteria of Veldman et al. and Atkins et al. [57,58];
(b) two of the studies had statistically significant dichotomous primary outcomes and their fragility indices were each one event or fewer [52,53];
(c) all studies reported surprisingly high incidence of CRPS in the control groups of 10–12%, at a mean follow-up of one year, suggesting use of invalid diagnostic criteria; and
(d) there were 103 patients lost to follow-up across the four trials. The scenario in which all missing patients were assumed to have CRPS is improbable, but it is equally improbable that none of these patients developed CRPS, as was assumed in these studies. Bearing in mind above limitations, the most recent systematic review by Evaniew et al. suggests that the literature is conflicting and fails to demonstrate a statistically significant effect for vitamin C in preventing CRPS in patients with distal radius fractures [59].

4. Discussion

The review of RCTs showed that only bisphosphonates were found to give uniformly statistically significant effects over placebo but the studies were not high quality. Some improvement has been reported with topical DMSO, systemic steroids, spinal cord stimulation and graded motor imagery/mirror therapy programmes. The available evidence does not support the use of other treatments in CRPS. This conclusion is typical and common for many meta-analyses in this topic. This may prompt one to reflect that there is a lack of good evidence for or against any treatment of CRPS and lead to therapeutic nihilism.

As mentioned in the introduction, CRPS comprises a broad spectrum of clinical forms which may be driven by different pathophysiological mechanisms. The degree to which individual mechanisms contribute to CRPS may differ between patients and even within one patient over time [5,49,60]. These facts may explain the difficulty in achieving an evidence-based treatment of CRPS. These studies suggest that there is not and cannot be one, universal treatment for all forms of CRPS; rather treatment should be targeted to the particular clinical manifestation (i.e. different for early or for chronic CRPS).

Clinically appreciable CRPS is a rare disease, therefore, it is difficult to recruit large numbers of patients to conduct a randomized study. Likewise, it is difficult to select patients with uniform disease pattern in order to avoid a heterogeneous patient population, typical of many studies which further biases the results of the clinical trials [7,60].

In addition the studies use heterogeneous primary outcome measures, e.g. some are focused on pain, other on improvement of function. It is very uncommon to use ''recovery from CRPS'' as a primary outcome measure because full recovery is rare and there is also no commonly accepted definition of recovery.

The review of RCTs showed that only bisphosphonates were found to give uniformly positive effects, statistically significantly better than placebo. Improvement has been reported with topical DMSO, systemic steroids, spinal cord stimulation and graded motor imagery/mirror therapy programmes. The available evidence does not support the use of other treatments in CRPS, however they are frequently used in clinical practice. This discrepancy shows that available evidence does not necessarily reflect what is truly effective and what is sham in the management of CRPS.

Conflict of interest

None declared.

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