

CLINICAL NEUROSCIENCES

Efficient Treatment for Complex Regional Pain Syndrome: A Critical Review.

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ABSTRACT

INTRODUCTION: Complex Regional Pain Syndrome (CRPS) is a neurological disorder, where one or more limbs are affected by pain disproportionate to the stimulus. Its exact pathology remains widely debated and there are currently several treatments available for the disease. No single treatment regimen has been proven to be superior, and there are no standardised guidelines or treatment algorithms.

This review aims to provide an update on the current evidence for the treatments available for CRPS management. It further seeks to explore the possible aetiology of the disease, and whether the proposed pathophysiology is associated with the efficacy of treatment(s).

METHODS: The literature was searched across AMED, BNI, CINAHL, EMBASE, HBE, HMIC, Medline, PsycINFO, and PubMed databases. Only human-based studies published within the last 15 years, with more than 10 participants were included. Common intervention themes were pharmacotherapy, psychotherapy, physiotherapy, and neurosurgery.

RESULTS: There is a lack of strong evidence favouring any given method of CRPS treatment. Physiotherapy proved most efficient where it was patient-oriented and featured a long-term treatment with gradual pain exposure and concurrent psychiatric support. Pain-oriented pharmacotherapy was largely inefficient, with no evidence to support the use of ketamine, opioids, NSAIDs or local anaesthesia. The efficacy of bisphosphonate use and neurosurgical interventions, especially in the field of spinal stimulation proved particularly efficacious.

CONCLUSION: Despite a huge number of studies in the literature, there is currently no definitive evidence to support any given aetiology or treatment regime. However, a number of specific interventions have been shown to work, lending some support the case for a central reorganisation or peripheral change origin of the disease.

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INTRODUCTION

Complex Regional Pain Syndrome (CRPS) is a debilitating disease characterised by stimulated or spontaneous pain that is generally disproportionate to the inciting event and accompanied by a wide range of autonomic, sensory, dystrophic and motor disturbances (Schwartzman *et al.*, 2009).

The symptoms were initially attributed to approximately 80 different diseases in English literature alone, and there was a call for a unified definition of this disorder (Todorova *et al.*, 2013). The International Association for the Study of Pain (IASP, 1993) provided a set of diagnostic criteria for CRPS. However, the IASP guidelines were not widely accepted, and the Budapest Consensus which followed, based largely on Harden/Bruehl Criteria, received wider recognition in the clinic (Smith, 2006).

The aetiology of CRPS remains debated. Several theories have been proposed based on the observed pathophysiological changes. Speculations have arisen that the CRPS is most likely caused by a trauma-related peripheral nociceptive overstimulation that in turn causes sustained central sensitisation (Harden *et al.*, 2013). The researchers argued that if this were the case, nutrition and blood flow to the affected limb could potentially reverse the symptoms. Whilst promising results in rats were reported (Sabovich *et al.*, 2008), no conclusive evidence is available.

There is evidence for the cortical reorganisation of the somatosensory cortex (Juottonen *et al.*, 2002, Maihöfner *et al.*, 2005, Pleger *et al.*, 2003). Using functional magnetic resonance imaging (fMRI), the researchers reported a strong correlation between increased signalling in both S1 and S2 regions, as a reaction to painful stimuli.



Additionally, compared to controls, patients with CRPS have significant grey matter differences in pain-related areas, with further alterations after therapy (Erpelding *et al.*, 2016).

In contrast, the peripheral origin hypothesis suggests the involvement of sympathetic ganglia (SG). Pseudorabies virus injection was used to identify the role of the SG blockade in the treatment of neuropathic pain and hot flashes, which are typical for the CRPS (Lipov *et al.*, 2009). Signalling was detected in regions responsible for modulation of heat, pain and emotion, thus, the impairment of signalling via SG could explain the CRPS symptoms. This statement was confirmed by the fMRI studies on CRPS patients (Bogduk, 2001). Furthermore, noradrenaline overdose can cause hot flashes and irregularities in body temperature, which are observed in CRPS. Indeed, large levels of noradrenaline are often reported in CRPS patients (Xanthos *et al.*, 2008).

METHODS

The review was conducted on the basis of the database searches and exclusion protocols summarised in Figure 1. Search strategy is available online (DOI: 2017/12/etfc501pc/)

RESULTS

PHARMACOLOGICAL INTERVENTIONS

An ideal pharmacological CRPS treatment would provide full recovery of the affected region, both in terms of function and analgesia. However, in the guidance issued by the Royal College of Physicians (RCP London, 2012), the authors expressed a great concern about the lack of evidence of an effective pharmacological treatment. Different methods of pharmacological interventions currently used in clinic are summarised in Figure 2.

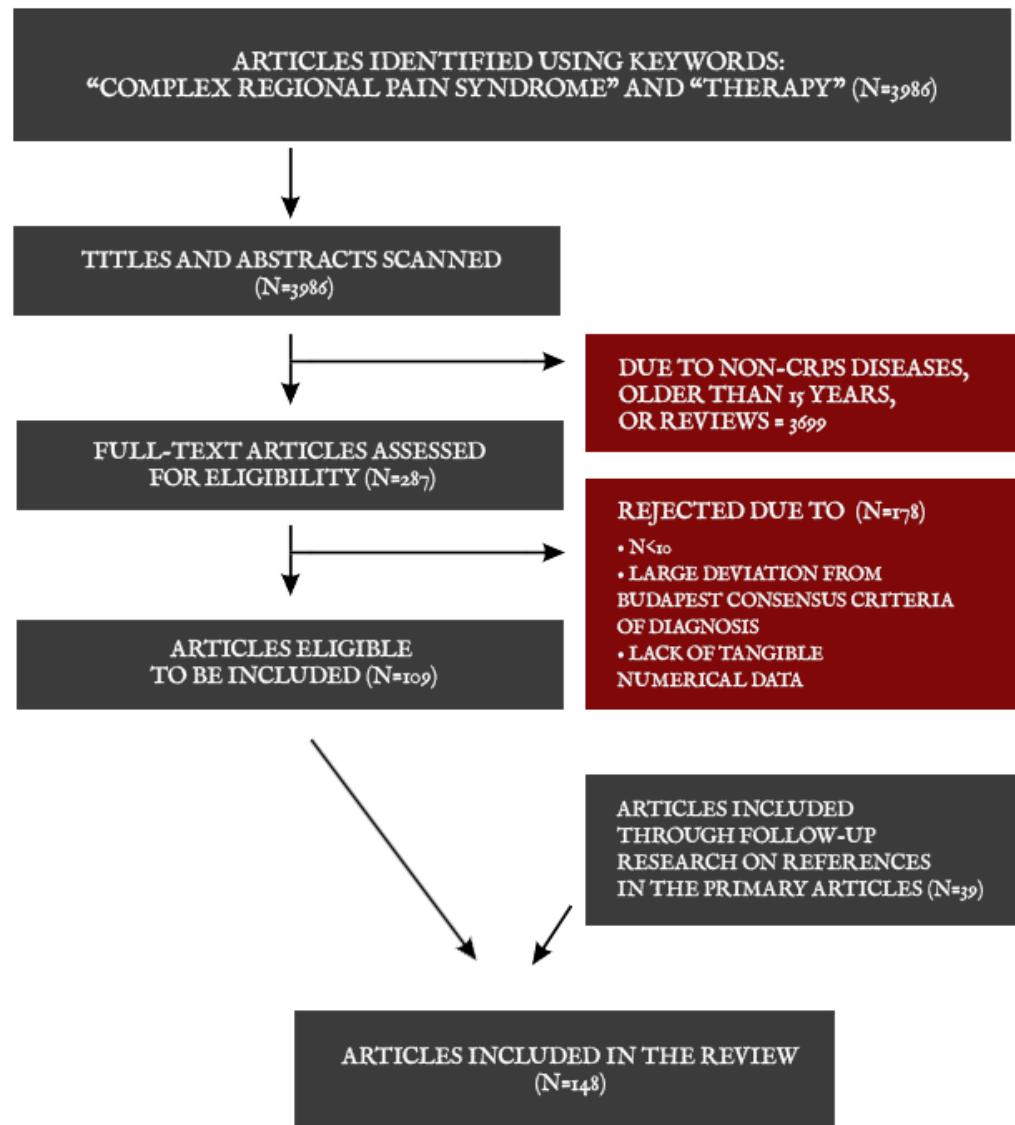


FIGURE 1. Flow chart of studies included in the analysis and methods used to include or reject papers in the review. The search was conducted using the terms summarised in the search strategy. Studies examining diseases that were inconsistent with the common consensus of the Budapest criteria or lacked tangible numerical data were excluded.



Diagnosis of CRPS (Harden et al., 2013)

- Chronic pain that is disproportionate to the inciting event
- At least 1 symptom in at least 2 categories: sensory / vasomotor / oedema / motor
- No other diagnosis or explanation is found

The non-steroidal anti-inflammatory drugs (NSAIDs) are the first choice of therapy for neuropathic pain. However, they are associated with significant side effects, due to the cardiovascular, gastrointestinal and renal involvement (BNF, 2017). The use of NSAIDs is based on the hypothesis that they may reduce inflammatory symptoms associated with CRPS pain through the inhibition of the COX enzyme.

Perez and colleagues argued that an NSAIDs-only approach could be harmful to patients due to lack of further treatment and frequent exacerbations of the pain, caused by little or no psychological support (Perez et al., 2010). The use of NSAIDs in the treatment of CRPS is not supported by current evidence (Breuer et al., 2014, Bianchi et al., 2006). Despite that, many guidelines still recommend the administration of NSAIDs in cases of neuropathic pain (Stanton-Hicks et al., 1998, Raja and Grabow, 2002, Kirkpatrick, 2003). Due to the lack of consensus on the diagnostic criteria, treatment often relies on the assumption that the patient must undergo NSAIDs-only treatment first, in order to be offered further options. This procedure may delay appropriate treatment for CRPS patients and could have devastating effects on their wellbeing, as constant pain and lack of clinical appreciation are strongly linked to the development of depression (Nicholl et al., 2014, Schroeter et al., 2015).

Corticosteroids and antioxidant-based immunomodulation

Corticosteroids and free radical scavengers have shown promise in alleviating CRPS pain (Kingery, 1997) and improved the clinical status of some patients, when administered orally (Christensen et al., 1982, Kalita et al., 2016). However, the anti-inflammatory efficiency of corticosteroids has been debated (Wesseldijk et al., 2008, Forouzanfar et al., 2002). A small-scale trial showed improvement on the CRPS severity scale including VAS at 6 and 12 months follow up with prednisone (Bianchi et al., 2006).

As an inflammatory response involves generating excessive amounts of the free radicals, it would be logical to justify the use of free radical scavengers. Indeed, a study of 148 patients showed a significant improvement in terms of recovery of function in a treatment involving a combination of paracetamol and free radical scavengers (dimethylsulfoxide 50% (DMSO) or N-acetylcysteine (NAC)), (Perez et al., 2003). However was no significant effect on pain with either of the agents used. A randomised double-blind trial with topical application of DMSO also showed significant improvement of symptoms over the placebo group (Zuurmond et al., 1996).

Ketamine and NMDA antagonists

Ketamine may be considered a controversial drug due to the poor pharmacokinetics, and substantial side effects, including psychotomimetic profile, nausea, vomiting and decline in cognitive function (Strayer and Nelson, 2008, Kim et al., 2016). The risk of misuse and addictive features resulted in the drug being discouraged for the pain treatment in the UK (NICE, 2014).

However, there is some evidence for the benefits of ketamine in CRPS. Two studies concluded that a prolonged course of ketamine infusion resulted in significant pain relief (Sigtermans et al., 2009, Correll et al., 2004). Although pain relief reported for up to 3 years post-treatment with repeat treatment, Ketamine infusion studies carry the downside of needing an inpatient setting for the administration and observation of the patient. In one study, 6 patients reported hallucinations whilst another 4 patients showed an alteration in hepatic enzyme profiles requiring the treatment to be terminated (Correll et al., 2004). The improvements would, however, not qualify for the NICE QALY threshold (Paulden et al., 2014), as the cost of the treatment was too high to warrant a small improvement of the quality of life.

Current investigations have turned to weaker NMDA antagonists such as memantine (Ahmad-Sabry and Shareghi, 2015). Out of 56 CRPS patients studied retrospectively, 13 showed complete remission from CRPS with memantine treatment for at least 9 months and 18 showed improvement of VAS whilst some allodynia remained (Sinis et al., 2007). Furthermore, promising results were shown in a randomised double-blind placebo-controlled study in which memantine or placebo was co-administered with morphine and standard physiotherapy. Significant improvement of pain in the affected limb was found with memantine over placebo. The authors also reported a significant change in cortical nociceptive processing observed by functional magnetic resonance imaging (Gustin et al., 2010).

Bisphosphonates

Bisphosphonates are classically used for the treatment of osteoporosis as they prevent the loss of bone density. There is some evidence that bisphosphonates may be effective in neuropathic pain including CRPS.

A randomised controlled study of i.v. neridronate (100mg), with a one year's follow-up, reported recovery in all 82 patients (Varenna et al., 2013). The adverse effects of polyarthralgia and/or fever were less severe, compared to other pharmacological treatment with clinical improvement reported. Several previous other studies have reported a significant reduction in pain with the use of various bisphosphonates (Adami et al., 1997, Varenna et al., 2000, Manicourt et al., 2004, Kubalek et al., 2001). Furthermore, a human RCT study, on an open CRPS cohort (27 participants) reported long-term improvement of all patients in both functional recovery and pain alleviation (Robinson et al., 2004), later confirmed in post-stroke CRPS patients (Eun Young et al., 2016).

The bisphosphonate-based studies in the literature were performed on the patients most likely to have suffered pain generated from osteoclastic overactivity (Varenna et al., 2013). It was thus argued that this treatment is only efficient in the cases of osteopathic aetiology. Indeed, the underlying molecular mechanism of bisphosphonate action involves inhibition of osteoclasts. However, there is some evidence that bisphosphonates proved

PHARMACOLOGICAL INTERVENTIONS				
NSAIDS AND OVER-THE-COUNTER ANALGESIA	KETAMINE AND NMDA ANTAGONISTS	CORTICOSTEROIDS AND ANTIOXIDANTS	BISPHOSPHONATES	OTHER AGENTS
<ul style="list-style-type: none"> Not recommended as a stand-alone treatment Still widely used in GP surgeries No or little effect reported in CRPS patients Paracetamol is effective in conjunction with free radical scavengers 	<ul style="list-style-type: none"> Poor pharmacokinetics and substantial side effects Unlicensed for treatment in the UK Highly discouraged in clinical practice due to cost-benefit ratio Weaker NMDA-antagonist like memantine can work in some patients, resulting in complete remission and pain score improvements 	<ul style="list-style-type: none"> Proved to alleviate pain in a limited number patients Drugs act on the free radicals released during CRPS-related inflammatory response Allowed in many countries, not recommended by NICE Dimethylsulfoxide (DMSO) and N-acetylcysteine (NAC) were the most effective agents 	<ul style="list-style-type: none"> The only pharmacological treatment recommended by Royal College of Physicians Most useful in bone-related pain, as its mode of action relies on inhibiting osteoclasts Strong evidence of RCTs to support the efficiency of treatment Little or no side effects 	<ul style="list-style-type: none"> Gabapentin showed mild effects on pain in CRPS Limited evidence for moderate improvement in pre-gabalin or ziconotide There is no evidence for opioids or cannabinoids efficiency in CRPS pain

FIGURE 2. Visual summary of the pharmacological interventions used for the treatment of CRPS

efficient in several animal models of CRPS in general (Yanow *et al.*, 2008).

Substantial clinical data is still lacking to confirm the efficacy of bisphosphonates. The exact molecular mechanism of bisphosphonate function in pain unrelated to bone-resorption remains unknown.

Cation-channel blockers

Gabapentin, although originally marketed as an anti-epileptic compound, have proven valuable for pain relief in neuropathic pain conditions, including CRPS (Mellick and Mellick, 1995). However, later trials showed only mild effects on pain in CRPS, suggesting a subpopulation of CRPS patients may benefit from Gabapentin (van de Vusse *et al.*, 2004). A single case-report has been published on the use of pregabalin in a 15-year-old girl suffering treatment-resistant CRPS. The authors suggested that pregabalin may facilitate rehabilitation in some patients, although the evidence present is limited (Saltik *et al.*, 2016).

Ziconotide is an atypical analgesic thought to exert its action via the N-type voltage-gated Calcium channel. Administered intrathecally, showed moderate improvement of VAS scores, as well as effects on oedema, skin abnormalities and mobility (Kapur *et al.*, 2009). However, significant side effects included mood difficulties, hallucinations, and urinary retention.

Opioids

Despite the wide use of opioids for pain management, there is currently not enough clinical evidence to support their use in CRPS. Indeed, we found no studies evaluating opioids on their own. Morphine + NDMA receptor antagonist study revealed the superiority of the combination therapy over morphine alone (Gustin *et al.*, 2010) but there was no non-opioid group in the trial. When used in conjunction with carbamazepine, morphine trends were insignificant (Harke *et al.*, 2001)

Cannabinoids

Despite the recent interest in the use of cannabinoids for non-cancer pain, we found no studies investigating the efficacy of cannabinoid treatment in CRPS. A single study, however, reported elevated plasma levels of endogenous anandamide in a small scale prospective study of CRPS following traumatic injury (Kaufmann *et al.*, 2009).

NON-PHARMACOLOGICAL INTERVENTIONS

Pain exposure methods

Pain exposure physiotherapy (PEPT) is a therapy regimen involving the patient moving the affected extremity despite the pain, avoiding responses to pain-induced behaviour, and encouraging the normal use of the limb. It has been offered as a safe and efficient alternative for pain reduction and functional improvement (van de Meent *et al.*, 2011). A study in 106 CRPS patients reported that whilst analgesic treatment was not effective in chronic pain, pain exposure treatment showed positive results in 90% of patients, with full recovery in 46% cases (Ek *et al.*, 2009). A similar outcome was reached in a 56 patients' PEPT study (Barnhoorn *et al.*, 2015).

Another study conducted on children confirms the efficiency of PEPT on a group of 103 patients. The initial rate of full recovery (92%) declined to 88% due to later recurrence (Sherry *et al.*, 1999). The treatment outcome review suggests that children are more committed to PEPT and thus respond better to the treatment and recover faster after recurrence episodes. It may be thus stipulated that in order to replicate similar results in adults, there must be a strong psychological support from the healthcare professionals, good understanding and education about the disease (Wilder, 2006).

It is highly favourable that the adults be presented with a tangible source of improvement tracking, for example, a pain chart or graph indicating the improvement of the VAS or functional recovery, or a virtual reality engagement tool (Won *et al.*, 2015).

One of the hypotheses of the pathological origin of the CRPS suggests that the syndrome is caused by the cortical reorganisation. The Graded Motor Imaginary (GMI) method is a sequential set of visuomotor exercises and has been developed to act as a PT-like treatment, claiming to be targeting cortical regions affected by the disease. The programme involves laterality training, imagined limb movements and mirror feedback therapy (Gay *et al.*, 2007). A review of fourteen randomised studies featuring GMI concluded that the method is efficient irrespective of the measurement parameters (e.g. disability, movement, pain scores, etc.) (Daly and Bialocerkowski, 2009), and was proved to act more efficiently than the standard PEPT, with significantly greater improvement in motor recovery and functional status in stroke patients with CRPS, compared to standard PT alone (Lagueux *et al.*, 2017, Pervane Vural *et al.*, 2016, Topcuoglu *et al.*, 2015). Another study suggested the beneficial effects of hypnotherapy, especially in the return to work, with 80% of participants resuming employment after therapy (Lebon *et al.*, 2017).

However, the high efficacy was not reflected in the public hospital clinical settings. Out of 32 patients enrolled in a recent trial, there was a reduction in VAS measurement pain of 0.6 [95% CI -0.3 – 1.5] and 0.2 [95% CI -0.9 – 1.2], depending on the centre. However, the functional improvement was still reported to be significant in the tested group (Kim *et al.*, 2002).

The authors can suggest a number of reasons why the enthusiastic effects of the previous investigations were not replicated in the study. The common denominator of all there is a lack of a comprehensive attention and follow up, with a reduced number of hours of care received, as compared to the other studies. It is unfeasible to provide constant outpatients care and supervision in the NHS hospital, where physiotherapy services are limited. However, whether the “real life” protocol of the GMI affects its efficiency is yet to be investigated.

SURGERY

There is major concern associated with surgeries in CRPS patients. Recurrence of symptoms and aggravation of pain are often observed in post-operatively (Ackerman and Ahmad, 2008).

However, surgical decompression (Bignion *et al.*, 2014) and neurolysis (Straube *et al.*, 2013) showed promising results. In their review, Borchers and colleagues described nine post-operative reports, where significant or complete pain relief and functional restoration were observed (Borchers and Gershwin, 2014). Another study achieved a 71% overall success rate with surgical T2 sympathetic ganglionectomy (Herz *et al.*, 1993). Less invasive thoracoscopic sympathectomy resulted in improvement of half (6) of cases, although another half (6) of patients suffered from a variable degree of recurrence (Rizzo *et al.*, 2004). It should be noted that surgical treatments are not recommended as first-line treatment for CRPS, and therefore the surgical interventions are trialled in the drug-resistance cases of CRPS only.

The emergence of the Radio Frequency (RF) techniques in sympathectomies offers another avenue to improve the outcome of surgical interventions (Albayrak *et al.*, 2016). A relatively comprehensive case series review of 148 cases of unilateral or bilateral sympathectomies reported a 91% improvement rate over 3 year follow-up period (Wilkinson, 1996).

Another retrospective review reported that the outcome of peripheral nerve surgery was “excellent” in 40% of upper extremity cases and 47% lower extremity cases; “good” result was achieved in 40% and 33%, respectively (Dellon *et al.*, 2010). The factors taken into account in the assessment was: measures of pain, ability to perform work, opiate use and functional recovery.

Stellate ganglion ablations

The stellate ganglion has been of a particular interest in the study of many neuropathic pain diseases. It has been shown to act as a first or second order neuron in connections to the insular cortex, amygdala, and hypothalamus. These nuclei play an important role in the regulation of temperature and neuropathic pain, which is thought to be causing CRPS. Ablation of this region results in a decrease in the nerve growth factor, which in turn decreases the levels of noradrenaline. The decline in the availability of both factors leads to alleviation of the CRPS symptoms, which explains why the surgical interventions worked in CRPS patients. However, the exact mechanism of this pathway is still to be fully investigated (Lipov *et al.*, 2009).

Nerve stimulations

Spinal Cord Stimulation has been proposed as a treatment for CRPS, but due to current safety concerns and the unpleasantness of the patient’s experience, it was long discouraged and is only offered as a treatment of last resort. Recent evidence suggests that it should be considered earlier and is financially sustainable for the NHS (Poree *et al.*, 2013, Sears *et al.*, 2011, Kriek *et al.*, 2017). Spinal stimulation has been proved to be an effective alternative for analgesic medication and to offer effective pain management on its own (Gopal *et al.*, 2016, Reddy *et al.*, 2016, Sanders *et al.*, 2016). To that end, high frequency repetitive spinal stimulation also improves sensory loss in CRPS patients (David *et al.*, 2015).

Levy and colleagues suggested that neuromodulation could be a potentially effective treatment of CRPS, involving Deep Brain Stimulation (DBS) and Peripheral Nerve Stimulation (PNS) (Levy *et al.*, 2012). There are currently no randomised controlled trials available to support these treatments. However, DBS has been reported to achieve pain relief in chronic pain syndromes in 79% of patients after up to 15 years follow-up (68 patients) (Kumar *et al.*, 1997). Transcutaneous electrical nerve stimulation (TENS) has been used in a small randomised controlled trial of 30 patients, with improvement noted in both sham and actual TENS therapy. The significantly greater decrease in oedema and pain intensity was noted with TENS, with a minor difference in mobility.

However, the study featured no long-term follow-up (Bilgili *et al.*, 2016).

Furthermore, dorsal root ganglion (DRG) stimulation was a preferred method to dorsal column stimulation (van Bussel *et al.*, 2017) by most patients in the studies, with DRG stimulation being better than dorsal column stimulation across a multitude of modalities (Deer *et al.*, 2017).

Amputation

Amputation has also been suggested as a possible surgical solution. However, a multitude of post-op cases of phantom limb syndrome and pain recurrence result in amputation being discouraged as a pain relief remedy *per se*. Current guidelines restrict its usage in CRPS treatment (Bodde *et al.*, 2011), despite some evidence that it may significantly lower the pain (Midbari *et al.*, 2016).

Controversy in surgical interventions

Good classification and appropriate choice of surgical intervention are of a paramount importance in the effective treatment of CRPS. Whilst it is often difficult to precisely diagnose the type of neuropathic pain in the clinical setting, a series of recent cases provide evidence that overall surgical treatment is, in most cases beneficial, in terms of analgesia and functional recovery (Borchers and Gershwin, 2014).

However, a substantive number of patients do not report a significant decrease in pain or functional improvement after the surgical procedure. It has been claimed that some of the persistent pain, reported in neurosurgical studies is not CRPS-related, and may be attributed to nerve distortions, caused by e.g. fibrosis, foreign bodies, arteriovenous fistulae or false aneurysms (Birch, 2009), which could explain why the interventions did not result in significant pain reduction.

PSYCHOLOGICAL INTERVENTIONS

There is no good-quality evidence to support a direct correlation between psychological trauma and CRPS development (Beerthuizen *et al.*, 2009). However, a number of case reports suggest that addressing psychological trauma results in pain relief and functional restoration (Hughes, 2014). Interestingly, the case studies presented by (Hughes, 2014) are not psychology-only interventions, and most of them feature failed attempts of pharmaceutical and/or surgical therapy. It is not clear whether the previous treatments aided the effects of psychotherapy in these cases.

In physiotherapy, the responsiveness of a patient is largely improved, when psychological management is in place (Kapural *et al.*, 2009). The psychological intervention also helps alleviate the symptoms of depression and anxiety, which in turn improves recovery and relieves symptoms that are secondary to CRPS.

Clinical Summary

Albeit the lack of strong evidence favouring a given method of CRPS treatment, there are a few groups of treatment that proved particularly effective.

Pharmaceutical analgesic interventions have emerged, some of which offered reasonable benefit for the patients. Weak NMDA-antagonists have shown promising results in the treatment of CRPS, although further evidence is needed.

Physiotherapy treatments have reported very promising results, whilst being considered safe and non-invasive. Successful physiotherapy tends to be patient-oriented and features long-term treatment with pain exposure being gradually applied over the course of several months.

Neurosurgical treatments provide encouraging results over a three-year follow-up period and prove beneficial for patients in the majority of cases reviewed. Furthermore, there is a number of promising case studies featuring neuro-stimulation

Pathophysiology notes

The origin and mechanism of CRPS are not known. There is a multitude of hypotheses in the literature that could be grouped into three main topics.

THE CENTRAL HYPOTHESIS suggests that the changes in S1 and S2 result in the top-down reorganisation of the pain sensation pathway.

This is supported by the neuroanatomical fMRI studies, and some treatments targeting cortical reorganisation result in efficient pain relief and functional recovery of the CRPS patients. However, the mechanism of reorganisation is not fully understood and seems to involve two separate pathways. Some pharmacological interventions, as well as physiotherapy, appear to target this mechanism with reasonable success.

PERIPHERAL HYPOTHESIS claims that the change in SG can cause the NGF overproduction and increased noradrenaline levels, which stimulates the central nuclei responsible for pain and thermoregulation.

This hypothesis explains heat flashes and neuropathic pain in CRPS. It is supported by the animal model studies, whereas the treatment targeting SG blocks are efficient in CRPS symptoms alleviation. However, the links between SG and the central nuclei are not confirmed by the good quality evidence in the literature.

CONCLUSIONS

It is not entirely unlikely that the CRPS is a common term for the much distinct neuropathological disorders of different aetiology, but a common clinical presentation.

However, whilst classification of the disease is important from the theoretical point of view, patients cannot wait till the disease is fully understood and catalogued. In order to assess which treatment is the most efficient in alleviating the pain and inducing functional recovery, common pain assessment criteria must be agreed.

The analysis and comparison of different treatments, or indeed novel developments in the field should be subject to the common diagnostic and assessment criteria, for a standardised way to compare the outcomes and provide a more coherent advice for the patients. At present, the most successful treatment appears to be a combination of pharmacological and non-pharmacological management. This review calls for further investigation into the true efficacy of the commonly prescribed treatments for CRPS.

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