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Advances in the Treatment of Complex Regional Pain Syndrome: An Analysis of Current Evidence and Future Directions

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Abstract

Background: Complex regional pain syndrome (CRPS) is a rare, multi-symptom condition characterised by severe pain that is disproportionate to the severity of the injury. Due to the lack of a standardised and fully effective treatment pathway, innovative supportive methods are being implemented in its management.
Aim: The aim of this article is to summarise modern treatment methods and outline current research trends in the management of CRPS.
Material and methods: A narrative review was conducted using the PICOS framework. Adult patients with CRPS type I or II were included. To focus on modern approaches, interventions for which moderate- and high-quality evidence was published after 2010 were considered, with priority given to systematic reviews and meta-analyses.
Results: In neurorehabilitation, the efficacy of guided motor imagery (GMI), pain exposure therapy (PEPT) and virtual reality (VR) in reducing pain has been demonstrated. In early-phase pharmacotherapy, bisphosphonates (e.g. neridronate) demonstrate high efficacy. Ketamine infusions effectively interrupt the mechanisms of central sensitisation. In treatment-resistant patients, advanced interventional techniques are used successfully: dorsal root ganglion (DRG) stimulation, spinal cord stimulation (SCS), and repetitive transcranial magnetic stimulation (rTMS).
Conclusion: Modern treatment of CRPS is based on the integration of neurorehabilitation, pharmacotherapy and precision interventional techniques. New therapeutic approaches, including targeted biological therapies and advanced neuromodulation, offer promising prospects.

Keywords: complex regional pain syndrome, neuromodulation, neurorehabilitation, pain management, virtual Reality

1. Introduction

1.1 Definition

Complex regional pain syndrome (Sudeck's syndrome) is a rare, multi-symptomatic condition whose primary symptom is severe pain that is disproportionate to the severity of the injury. Although the first references to the condition can be found in 16th-century literature, it was not until 1994 that the IASP established the international name for the condition and introduced its diagnostic criteria. [i]

This condition manifests itself through a range of symptoms affecting the nervous, vascular and musculoskeletal systems. Treatment is usually challenging, mainly due to the lack of a single, standardised treatment pathway. Treatment requires close collaboration between specialists from various fields, including physiotherapists, doctors and psychologists. We distinguish CRPS type I and type II. Type I is characterised by symptoms typical of CRPS, but no direct nerve damage is found. In type II, the symptoms are usually similar to those of type I, but direct damage to a peripheral nerve can be identified. [ii]

1.2 Epidemiology

Epidemiological data on CRPS remain inconsistent due to diagnostic difficulties, reporting methods and data limitations, and geographic variability. The reported incidence of CRPS in the general population varies between 5.4 and 29 per 100,000 individuals. [iii, iv]
CRPS predominantly affects postmenopausal women aged between 60 and 70. CRPS is observed approximately 3.5 times more frequently (ratio: 3.4) in women than in men. The condition occurs more frequently in the upper limb than in the lower limb. [4]

However, it is worth noting how frequently CRPS occurs in at-risk individuals who have experienced a triggering event (e.g. trauma, surgery, nerve injury). Among this group, the pooled 24-month prevalence of CRPS from 103 studies (n = 261,433) was 6.46% (95% CI 5.46–7.53). Furthermore, this prevalence is highest among those who experienced both trauma and surgery, at 13.80% (95% CI 0.00–59.08); for participants who experienced only trauma, it is 12.99% (95% CI 1.18–28.26) and for those who underwent surgery only, it is 5.86% (95% CI 4.53–7.30). [v]

Among injuries, fractures were the most common cause, accounting for approximately 40% of this group. [De Mos] It is also important to note that there is a group of patients who presents with CRPS symptoms but in whose case no triggering factor has been identified. This group accounts for 10–26% of patients. [vi]

1.3 Pathophysiology

There is no single pathogenic mechanism underlying CRPS. Its pathophysiology is explained by various, likely co-occurring processes. However, the literature emphasises pathomechanisms based on inflammation and disorders of the nervous system. [vii]

Following the action of a triggering factor, tissue damage occurs. This results in typical inflammation characterised by increased temperature, swelling, redness, pain, and functional impairment. [viii] This is reflected in elevated inflammatory markers in both acute (interleukin 8, soluble tumour necrosis factor receptors I (sTNF-RI) and II (sTNF-RII)) and chronic phase of CRPS (including TNFα, bradykinin, sIL-1RI). Elevated levels of these markers are observed in blood, cerebrospinal fluid and in blister fluid. [ix] This indicates a systemic component of the disease.

The nervous system is affected by neuroinflammation, which is responsible for the initiation and persistence of CRPS. In patients, increased production of substance P by peripheral nerve fibres has been observed. [x] This process leads to sensitization of nerve endings. Neuroplasticity processes occur within the CNS. Regression of the somatosensory cortex responsible for innervating the damaged area has been observed. [xi] Autonomic dysregulation of the nervous system is another important mechanism. In the acute phase of CRPS, a local decrease in noradrenaline concentration stimulates a compensatory up-regulation (increase in density) of peripheral adrenergic receptors. [7]

It is noteworthy that associations have also been demonstrated between CRPS and genetic factors (associations were confirmed between CRPS and human leukocyte antigen-related alleles), oxidative stress and psychological factors (greater preoperative anxiety prospectively predicts acute CRPS symptoms following total knee arthroplasty). [xii, xiii, xiv]

1.4 Clinical Presentation

The primary symptoms of CRPS are pain, vasoconstrictive, autonomic, trophic and motor disorders. However, their prevalence varies and they rarely all occur together. Ott and

Maihöfner conducted a population-based study involving 1,043 patients. They examined the symptoms and described them quantitatively.

Pain was typically rated at 5.12 ± 2.26 on the NRS, mostly located in deep structures. This is the most typical and debilitating symptom of CRPS. It is described as burning, stabbing or 'electric' and is characterised by an intensity disproportionate to the triggering event. It is frequently, in 85% of cases, accompanied by sensory disorders. These include, for example, allodynia and hyperalgesia. This can cause even a gentle touch to provoke severe pain.

In terms of motor disorders, 61% showed some form of reduced active movement. 75% revealed a reduction in grip strength in the handgrip test or during tiptoe-standing.

Oedema, in its soft and congestive form, was observed in 70% of cases. Cyanosis occurred in 33% of patients, and hyperaemia in 38%. 40 % of patients reported increased sweating, and 39% had increased hair and nail growth. [xv, xvi, xvii]

The onset is usually triggered by a factor located in the distal parts of the limbs, including the hands and feet. As the disease progresses, symptoms usually spread proximally. [xviii, xix]

Symptoms fluctuate over time – both during the course of a single day and over the course of the illness – which can make diagnosis and monitoring of treatment more difficult.

CRPS is also associated with numerous comorbid conditions and symptoms. Due to the prolonged nature of the condition and the severity of the symptoms, patients often present with psychiatric disorders, including mood disorders, anxiety disorders, insomnia, substance use disorder, personality disorders, and somatic symptom disorder.xx Cognitive impairment may also occur. [xxi]

Patients may also present with cardiovascular disease (arrhythmia), metabolic disorders (hypercholesterolaemia), gastric disorders (reflux), and endocrine disorders (impaired hypothalamic-pituitary-adrenal axis). [xxii, xxiii, xxiv]

The gold standard for diagnosis is the IASP Budapest Criteria, which were validated in 2010 and have established themselves in both the scientific and clinical communities.

In order to diagnose CRPS, all four of the following criteria must be met:

1) Continuing pain, which is disproportionate to any inciting event
2) Must report at least one symptom in *three of the four* following categories:
    a) Sensory: reports of hyperesthesia and/or allodynia

b) Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
c) Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry
d) Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

3) Must display at least one sign at time of evaluation in *two or more* of the following categories:
    a) Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
    b) Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry
    c) Sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry
    d) Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4) There is no other diagnosis that better explains the signs and symptoms. [xxv]

In addition to the aforementioned classification into CRPS I and CRPS II, which is an aetiological classification, there is another important phenotypic classification. This takes skin symptoms into account, forming an important part of the clinical picture. We distinguish the warm and cold stages. The warm stage is associated with inflammation and is characterised by prominent oedema, warmth, and redness of the skin in the affected limb. The cold stage, associated with autonomic dysfunction and possible endothelial dysfunction, includes cold and blue skin in the affected area, with less prominent oedema. In the warm stage, pain usually lasts 4.7 months, whereas in the cold stage it lasts 20 months. Hence, the warm stage is generally considered to have a better prognosis than the cold stage. [xxvi]

1.5 Imaging diagnostic

As we can see, the diagnosis of CRPS relies on the analysis of clinical symptoms. However, imaging studies are performed during the diagnostic process, primarily to rule out other conditions and provide additional information.

On X-ray, severe patchy osteopenia (which is important to differentiate from disuse osteopenia) and subperiosteal bone resorption can be observed. However, these changes only appear after several weeks or months of the disease. [xxvii]On MRI, we can observe bone marrow edema signal (particularly subcortical), joint effusion, or muscle atrophy in later stages. [xxviii] One of the widely used imaging studies is the three-phase bone scan. This nuclear medicine method shows increased blood flow and blood pool due to hyperemia, as well as delayed periarticular uptake in the affected limbs. [xxix, xxx]

The results of a meta-analysis based on 24 RCTs analyzed the diagnostic efficacy of three-phase bone scintigraphy, magnetic resonance imaging, and X-ray in CRPS. Three-phase bone scintigraphy demonstrated significantly better sensitivity and negative predictive values. However, no statistical significance was found between the imaging techniques when evaluating specificity and positive predictive value. [xxxi]

1.6 Aim

The aim of this article is to summarise modern treatment methods and outline current research trends in the management of CRPS.

2. Materials and method

This narrative review utilized the PICOS framework to structure the inclusion criteria. Population: includes adult patients diagnosed with CRPS type I or II, in the acute or chronic stage, in accordance with the Budapest or Orleans criteria. Patients with neuropathic pain of a different etiology were excluded. Intervention: To focus on modern approaches, the review included interventions for which evidence of moderate to high quality had been published after 2010. Historically established techniques, which are already extensively described in the classical literature on the subject, were deliberately omitted in favour of innovative therapeutic methods. Comparison: involves evaluating recent advancements against the traditional ‘gold standard’ of care. Furthermore, where applicable, the efficacy of novel interventions is analysed in relation to placebo- or sham-controlled trials to determine their clinical superiority. Outcome: The outcomes assessed in this review focus on clinical efficacy and functional recovery. The primary endpoint is the reduction in pain intensity, measured by validated scales such as the Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS). Secondary outcomes include improvements in range of motion (ROM), quality of life indicators, and the stabilisation of autonomic symptoms. Study design: this review prioritises high-quality systematic reviews and meta-analyses published since 2010. Additionally, to capture 'Future Directions' prospective and cohort studies, pilot trials, case series and expert consensus guidelines were analyzed to provide a comprehensive overview of the current therapeutic landscape.

3. Result

3.1 Advances in Physiotherapy and Neurorehabilitation

3.1.1 Graded Motor Imagery

Graded Motor Imagery (GMI) is a motor imagery technique used to achieve cortical reorganisation. It utilises the principle of neuroplasticity and involves gradually stimulating activity at the level of the cerebral cortex and reducing its inhibition. It facilitates sensory and motor cortex reorganisation and gradually activates cortical networks without causing a protective pain reaction. These stages are implicit motor imagery (lateralisation), explicit motor imagery and mirror therapy.

Motor imagery is the learning of body awareness, in which the patient learns to distinguish one side of the body from the other and recognise them as separate. In patients with pain conditions, such as CRPS, this function may be impaired. It can be trained by reviewing images of the left and right limbs. Lateralisation training aims to establish an accurate cortical representation of a given body part. Explicit motor imagery involves imagining movement without actually performing it. In the process, we activate brain regions similar to those activated during the actual movement. Mirror therapy utilises the visual illusion of movement to In this part, we move the healthy limb, which we observe in a mirror. The observed reflection gives the patient the impression of moving the affected limb and leads to further neural pathway formation. [xxxii, xxxiii] A 2024 meta-analysis demonstrated a clinically significant reduction in pain intensity and related disability as immediate (up to 24 hours), short-term (from 24 hours to 3 months), and, most importantly, long-term (more than 3 months) effects (pain: SMD -1.18; 95% CI: -1.89 to -0.46; disability: SMD 1.18; 95% CI: 0.46 to 1.89). [xxxiv] One RCT (95% CI) showed a 23.4 mm (16.2 to 30.4 mm) reduction in pain between pre- and post-treatment (100 mm visual analogue scale). A similar effect size was also observed in terms of improved patient function, and the effects persisted at the follow-up conducted 6 months after treatment. [xxxv] Another RCT (randomised controlled trial) found a reduction of 20 points on the NPS scale (a

50-point scale used to quantitatively assess the quality of neuropathic pain). (Moseley, G. Lorimer. "Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial.") [xxxvi] Despite promising results, the quality of the available evidence is rated as moderate, mainly due to the small sample sizes, the variety of treatment protocols, and the heterogeneity of the patient populations. Nevertheless, given its safety, non-invasiveness and relatively high efficacy, GMI is currently one of the key methods in the modern approach to the treatment of CRPS.

3.1.2 Pain Exposure and Physical Therapy

Pain Exposure and Physical Therapy (PEPT) is a revolutionary therapeutic approach aimed at breaking the fear of pain. In this therapy, pain is treated as a ‘false alarm’ that is not associated with tissue damage. The patient is encouraged to perform physical exercises and carry out daily activities despite the accompanying discomfort. The therapy is conducted entirely without the use of medication or orthopaedic aids. The therapist acts as a motivator but ignores the symptoms reported, and the burden of the work and the inner determination rest solely with the patient. Although there is a limited number of studies, all the significant ones demonstrate the effectiveness of this therapy. [xxxvii, xxxviii]

One study observed a 57% improvement in pain levels from baseline to 12 months after the last treatment session ($A1 = 58.2$; $A2 = 25.2$, $p < 0.001$). However, it is worth noting the impact of this therapy on motor function. The active range of motion, defined as the difference between sides, decreased by 66% ($p < 0.001$). The difference between sides in grip strength decreased by 52% ($p < 0.001$). [xxxix] Due to its simplicity, it is also a low-cost treatment. Researchers have shown that it is 39% cheaper than conventional physiotherapy. [xl]

The authors of one study focused on potential adverse effects. Although the certainty of the evidence in this regard is very low, given the outcome measures used, the available data do not indicate any long-term worsening of symptoms or functional ability, nor any serious adverse effects associated with pain provocation during CRPS physiotherapy. [xli]

3.1.3 Virtual Reality

Virtual reality (VR) is an increasing popular tool in pain management. It involves attempting to replace real sensory experiences with an artificial, computer-generated environment. By influencing cognitive and sensory processing, VR supports the recalibration of body representation (BR), which may alter nociceptive processing and reduce pain intensity.[xlii, xliii]. A systematic review from 2025, based on 2 RCTs and 2 uncontrolled experimental studies, indicates that rehabilitation using VR can effectively reduce pain in patients with CRPS. Various approaches – such as modifying the appearance of the limb (e.g. visibly reducing swelling and restoring a natural colour to the skin), virtual body substitution or the integration of physiological signals (e.g. heart rate integration – a virtual, healthy hand visible in VR goggles gently pulses or changes colour in synchronisation with the patient's own, real heartbeat. This cardio-visual convergence causes the brain to recognise this limb as its own) – have shown an improvement in BR and a reduction in pain, although the effects depended on the method used. [xliv, xlv] Personalised VR interventions, tailored to the patient's individual needs and primary symptoms, are also promising. [43]

In an RCT involving 45 participants with treatment-resistant CRPS of the upper limbs and body perception disorders (BPD), participants were shown a digital image of their affected hand for 1 minute. The image was digitally modified in the experimental group to match the patient's description of the desired appearance of the hand, whilst it remained unchanged in the control group. The subgroup was observed 2 weeks after the session. The best results were observed in terms of improvement in liking of hand appearance, and changes in perceived lightness were found between groups. A significant reduction was demonstrated on the BATH scale (a 7-item, self-report questionnaire used to assess subjective changes in body perception, such as feelings of detachment, distorted size, or reduced awareness). The reduction in pain measured after 2 weeks (1.2 on the NRS scale), although not as dramatic as with other methods, also plays a significant role in the overall treatment. [45]

3.2 Advances in Pharmacotherapy

3.2.1 Bisphosphonates

Bisphosphonates are an important component of pharmacotherapy for CRPS pain management, particularly in cases accompanied by algodystrophy. Although these are drugs primarily used to reduce osteoclast activity and promote anti-resorption, in CRPS bisphosphonates likely modulate various inflammatory mediators whose expression is elevated. [xlvi] Given the relatively recent introduction of neridronate into CRPS therapy, the growing body of scientific evidence and its increasingly frequent recommendation for this condition, the authors decided to include this drug in the present review. It has the bestdocumented clinical efficacy. Randomised trials have shown that as early as one month after the start of treatment, approximately 66% of patients achieve at least a 50% reduction in pain intensity. [xlvii] Furthermore, a significant improvement in sensory symptoms is observed – after 12 months, hyperalgesia resolved in 84.3% of patients, and allodynia in 88.1%. Reduced range of motion improved in over half of patients (53.5%). [xlviii]

The latest analyses indicate that neridronate – like other bisphosphonates – has a beneficial effect in the early stages of treating severe pain. In the longer term, however, its efficacy may be limited, particularly beyond six months. The drug's effectiveness is further hampered by the risk of adverse effects. [xlix]

3.2.2 Ketamine

Ketamine is primarily known as an antagonist of the N-methyl-D-aspartate (NMDA) receptor. This receptor is responsible for amplifying the signal between neurons, leading to hyperalgesia and central sensitisation. Ketamine reverses this process. [l] Although the potential use of intravenous ketamine in the treatment of CRPS was first reported in the literature as early as the late 20th century, only in recent years has stronger evidence of the therapy's efficacy emerged. [li] A 2018 meta-analysis confirms the analgesic effect of the therapy ($p < 0.000001$). The authors of the publication also used the pain relief rate (which is defined as the percentage of participants who achieved 30% or higher pain relief. The immediate pain relief event rate was 69% (95% confidence interval (CI) 53%, 84%) . The pain relief event rate at the 1–3-month follow-ups was 58% (95% CI 41%, 75%).lii This evidence is also supported by a 2021 systematic review. [liii] However, it has been shown that larger total doses of ketamine are correlated with longer periods of pain relief. Nevertheless, very-high-dose infusions are often limited by financial cost and adverse effects such as nausea, vomiting, psychotomimetic effects, headache, fatigue, and sedation. [53, liv]

3.3 Advances in Interventional Techniques

3.3.1 Spinal cord stimulation

Spinal cord stimulation (SCS) is an advanced treatment method involving the implantation of a device that transmits electrical impulses to the spinal cord. The system comprises thin electrodes (leads) placed in the epidural space and a pacemaker-like generator implanted under the skin, often near the buttock or abdomen. [lv] The main aim of SCS is to modulate nociceptive signals (including via the so-called 'gate control' mechanism, whereby electrical stimulation activates large-diameter afferent fibres, thereby inhibiting the transmission of pain signals from smaller nociceptive fibres) before they reach the brain, effectively interrupting the sensation of pain. [lvi] Systematic reviews highlight the effectiveness of the therapy in pain reduction. [lvii, lviii] As reported by the study by Canós-Verdecho et al., 12 months after SCS application, there was a reduction of 5.6 points (Low Frequency SCS) or 4.8 points (High Frequency SCS) on the NRS scale, depending on the frequency used. [lix] This highlights the relatively long-term effect of the therapy, which is one of the limitations of other therapeutic methods. Due to its invasive nature, SCS should be used in patients in cases where conventional methods have not produced a sufficient effect. Adverse effects include relatively common hardware problems (affecting around 30% of patients) and less frequently, neurological complications (spinal cord injury) and perioperative complications (infections). [lx, lxi]

3.3.2 Dorsal Root Ganglion Stimulation

Dorsal Root Ganglion **(**DRG) stimulation is a similar method, also based on neuromodulation. The main difference, however, is that the electrode is placed in the dorsal root nerve root ganglion. This is the point where sensory fibres enter the central nervous system. This method therefore allows for more accurate and precise stimulation, capable of targeting a specific dermatome. Studies demonstrate the superior efficacy of this method compared to SCS. After 12 months, 74.2% of patients in the DRG group achieved therapeutic success (>50% reduction in VAS score), which was a higher proportion than in the SCS group (53%). DRG stimulation also resulted in a significantly greater improvement in general mood, physical fitness, overall health and social functioning.lxii In a study assessing one of the complications, which is paresthesia, DRG stimulation produces paresthesias that are less frequent, less intense, with a smaller area of the body affected and less dependent on changes in position compared to SCS. [lxiii]

In 2017, the socio-economic effects of neurostimulation therapies were also assessed. The benefit, measured in terms of quality-adjusted life years (QALYs), was greater for DRG than for SCS (4.96 ± 1.54 and 4.58 ± 1.35 QALYs, respectively). Although the cost of DRG therapy was higher (higher conversion rate from trial to permanent implant and shorter battery life), future technological developments are likely to reduce the cost per QALY in favour of DRG. [lxiv]

3.3.3 Repetitive Transcranial Magnetic Stimulation

Neuroplasticity can be induced non-invasively using a form of brain stimulation known as repetitive transcranial magnetic stimulation (rTMS). An electromagnetic coil is placed on the scalp to generate a magnetic field. Magnetic stimulation alters cortical excitability in the stimulated area and in areas distant transynaptically. High-frequency stimulation (≥5 Hz) increases cortical excitability, promoting the formation of new neural pathways. Low-frequency stimulation (≤3 Hz) inhibits pathological hyperexcitability.

As indicated by a 2020 meta-analysis, although no improvement in pain was observed immediately after treatment, such an improvement emerged one week after the treatment protocol: (SMD = −1.173, 95% CI = −1.709 to −0.637, P < 0.001).lxv Individual studies indicate a 20–50% reduction in pain. [lxvi]

Patients also experienced improved sleep quality following treatment, due to a reduction in sleep-related anxiety.lxvii However, the long-term outcomes and safety profile of the therapy need to be assessed, as the use of TMS for other indications has been associated with headaches, scalp discomfort, nausea and dizziness, and, most seriously, although rarely, epileptic seizures (7 per 100,000 sessions). [lxviii]

3.4 Future Directions

3.4.1 Physiotheraphy

In physiotherapy, sensory training and prism adaptation are new methods that may soon be incorporated into treatment.

Sensory training is aimed at restoring normal processing of sensory stimuli and reducing allodynia and hyperalgesia. The therapy involves gradual exposure to tactile stimuli of varying texture and intensity (e.g. Braille-like haptic tasks) and sensory discrimination exercises. Individual protocols demonstrate the therapy’s effectiveness, but the results should be evaluated in pooled analyses. [lxix, lxx, lxxi]

Prism adaptation is a sensorimotor training technique. It is used to reduce lateralised biases in attention, spatial representations, and (ocular) motor performance in hemispatial neglect. One possibility is that it increases the focus of attention on the side affected by CRPS compared to the unaffected side. The protocol involves patients performing a series of repetitive, rapid movements to point at visual targets whilst wearing goggles fitted with prismatic lenses that shift the field of view by 10 degrees. This forces sensorimotor recalibration to compensate for the visual error and improve the impaired spatial representation of the limb. Although it is based on theoretical assumptions regarding the correction of spatial representation disorders in patients with CRPS, its clinical efficacy remains to be confirmed. [lxxii, lxxiii]

3.4.2 Pharmacotheraphy

Antibody-based therapies initially raised great hopes for the treatment of CRPS; however, recent large-scale randomised controlled trials (RCTs) have failed to confirm their significant clinical benefit. [lxxiv] This applies to a wide range of treatments, including intravenous immunoglobulin (IVIG), biologics such as TNF-α inhibitors (e.g. infliximab) and immunomodulators such as lenalidomide. Despite these setbacks, the unprecedented pace of development in biological medicine and the annual launch of new monoclonal antibodies allow researchers to look to the future with justified optimism. Currently, researchers' attention is focused both on advanced animal models (e.g. neuronal Reg3β/macrophage TNF-α–mediated positive feedback signalling) and on ongoing clinical trials (e.g. fremanezumab). [lxxv, lxxvi] Furthermore, given the specific profile of inflammatory cells appearing in patients' serum, innovative strategies directly aimed at the targeted reduction of pathological antibody titres appear to be a highly promising direction. [lxxvii]

Hopes are also linked to low-dose naltrexone, alpha-adrenergic agonists/antagonists, glial activation inhibitors, topical medications (e.g. prazosin), medical cannabis and memantine. [lxxviii lxxix, lxxx, lxxxi, lxxxii]

3.4.3 Interventional Techniques

Invasive therapies awaiting validation include peripheral nerve stimulation and botulinum toxin.

The field of peripheral nerve stimulation includes TENS (transcutaneous electrical nerve stimulation), subcutaneous electrical stimulation (SQS) and electroacupuncture (EA). Although individual studies offer hope for TENS therapy, a systematic review from 2025 concluded that there was insufficient evidence of its efficacy. [lxxxiii] Other methods, such as SQS and EA, have not been studied in pain typical of CRPS, or only isolated case series have been published. [lxxxiv] As higher-quality evidence emerges, these procedures may be incorporated into treatment in the future.

Botulinum toxin is a neurotoxic protein used to temporarily block the release of acetylcholine at the neuromuscular junction, leading to reversible muscle relaxation. It is widely used in medicine, primarily in dermatology and neurology. The exact mechanism of action in CRPS has not been described, however, a meta-analysis revealed a significant reduction in pain between 3 weeks and 1 month after intervention (WMD, −1.036, 95% CI, −1.673 to −0.400) but not at the second follow-up between 2 and 3 months after treatment (WMD, −0.895, 95% CI, −2.249 to 0.458). It is a promising method, but due to the short duration of pain relief observed so far, limited sample sizes, the invasiveness of the method, and potential side effects that have not yet been identified, no definitive conclusions regarding this method have been drawn. [lxxxv]

3.4.5 Biomarkers

Biomarkers can play a role not only in diagnosis but also in supporting the treatment process. They can identify specific groups of patients who are likely to benefit from a particular therapy (e.g. anti-inflammatory treatment) and can be used to monitor the effects of treatment. [lxxxvi] Preliminary studies in animal models attribute such a role to microRNA. [lxxxvii] Research is also ongoing into markers of increased bone metabolism associated with CRPS, such as osteoprotegerin. [lxxxviii]

3.4.6 Neuropsychiatric aspects

The role of neuropsychiatric factors is usually secondary. These disorders rarely trigger the disease; rather, they are a direct consequence of its debilitating course. They include disorders such as depressive episodes, generalised anxiety, and chronic stress. These conditions exacerbate somatic symptoms by stimulating adrenergic pathways and pro-inflammatory processes. Although the literature still lacks a comprehensive body of rigorous randomised trials dedicated exclusively to patients with CRPS, clinical data extrapolated from other chronic pain syndromes unequivocally confirm the effectiveness and necessity of professional psychological support. [15, lxxxix]

For this reason, providing patients with CRPS – particularly those who have suffered extensive trauma and are struggling with chronic pain – with ongoing psychological and psychiatric care is an indispensable element of modern treatment.

4. Discussion

Owing to the enormous heterogeneity of CRPS symptoms, the key to therapeutic success lies in a personalized, multimodal approach combining rehabilitation in the broadest sense, pharmacotherapy and invasive techniques. New therapies aim to achieve better therapeutic outcomes. Despite good results, one must bear in mind the durability of treatment effects, adverse effects, patient compliance and costs. It is therefore important that new therapies are incorporated into the treatment process in accordance with an optimal risk-benefit ratio. They should be integrated into existing, well-established and researched methods. In accordance with the Malibu and Minneapolis guidelines, the core of recovery is gradual, strictly controlled motor reactivation. [xc] This progresses smoothly from non-invasive imagery techniques (such as GMI or mirror therapy), through mechanical desensitisation, to full loading of tissues during daily activities. In parallel, as required by symptoms or treatment failure, pharmacotherapy and interventional therapies are added. The process of selecting medications must be based on flexible algorithms, such as the one proposed by Chang et al. – where therapy begins with a steroid pulse, and subsequent medications (including antidepressants or opioids) are tested in short, two-day cycles to facilitate rapid verification of their efficacy. In cases of resistance to standard treatment, intravenous infusions of ketamine or lidocaine are used. [xci] Interventional therapies should also be introduced gradually, starting with the least invasive. One should begin with local and regional nerve blocks, progressing through intrathecal drug administration and neurostimulation, and eventually moving on to sympathectomy and motor cortex stimulation. Guiding the patient through this complex process requires close coordination among the entire team of experts: physiotherapists, occupational therapists, rehabilitation specialists, pain management specialists, neurologists, orthopaedic surgeons and neurosurgeons. [xv]

Future research initiatives stand before a double challenge: they must rigorously evaluate existing treatments while paving the way for new therapeutic strategies. Interventions in widespread use – particularly those not yet backed by robust empirical evidence – require urgent methodological evaluation. Multicentre, double-blind, randomised controlled trials (RCTs) should become the gold standard here, with their results contributing to high-quality systematic reviews and meta-analyses. Given the current shortage of objective clinical data, reliably filling this knowledge gap will almost certainly lead to a redefinition of current standards of care. In turn, research trends should simultaneously explore rehabilitation protocols, targeted biological therapies, minimally invasive interventions and the role of neuropsychiatry in the treatment of CRPS.

5. Conclusion

Modern treatment of complex regional pain syndrome (CRPS) is based on the integration of neurorehabilitation, including graded motor imagery, exposure therapy and virtual reality. In terms of pharmacotherapy, bisphosphonates play a key role in the early phase, as do ketamine infusions, which effectively disrupt the mechanisms of central sensitisation. For patients resistant to standard invasive procedures, new precision interventional techniques may be applied. These include spinal cord stimulation, dorsal root ganglion stimulation, and non-invasive repetitive transcranial magnetic stimulation. They demonstrate significantly higher efficacy than traditional neuromodulation methods. Further progress in the clinical management of CRPS absolutely requires rigorous validation of emerging therapies through multicentre randomised trials and meta-analyses

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