NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

Journal of Education, Health and Sport. eISSN 2391-8306.

Journal Home Page
https://apcz.umk.pl/JEHS/index

WÓJTOWICZ, Jan, UJAZDA, Damian, GŁĄB, Weronika, DOMINIAK, Oliwia, KOMOŃ, Aleksandra, and GROBELNY, Artur. Complex Regional Pain Syndrome: Contemporary Diagnostic and Therapeutic Methods. Journal of Education, Health and Sport. 2026;90:70220. eISSN 2391-8306. https://doi.org/10.12775/JEHS.2026.90.70220

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 24.03.2026. Revised: 03.04.2026. Accepted: 16.04.2026. Published: 19.04.2026.

Complex Regional Pain Syndrome: Contemporary Diagnostic and Therapeutic Methods

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ABSTRACT

Introduction and aim of the study. Complex Regional Pain Syndrome (CRPS) is a chronic condition, most commonly affecting the limbs, characterized by pain disproportionate to the initial injury and various autonomic, sensory, vasomotor, and motor symptoms. CRPS significantly reduces patients' quality of life, and its complex pathophysiology—which involves inflammatory, neurogenic, and autoimmune processes—poses significant diagnostic and therapeutic challenges. This study aims to present and analyze contemporary diagnostic and therapeutic methods used in the management of CRPS, focusing on current scientific knowledge and future perspectives.

Current knowledge. The diagnosis of CRPS is primarily based on the Budapest criteria, which are characterized by high sensitivity but moderate specificity. Contemporary imaging techniques, such as three-phase scintigraphy, SPECT/CT, and thermography, play an increasingly significant role by enabling the identification of changes in tissue perfusion and bone metabolism. The treatment of CRPS requires an integrated approach combining pharmacotherapy, rehabilitation, interventional methods, and psychological support. Pharmacotherapy, including corticosteroids, bisphosphonates, and vitamin C, has proven effective in alleviating pain and reducing inflammation. Studies have shown that vitamin C, administered at 500–1000 mg daily, significantly decreases the risk of CRPS following injuries and limb surgeries. Rehabilitation, including mirror therapy and graded motor imagery, is crucial for restoring limb function. Advanced methods such as spinal cord stimulation (SCS) and dorsal root ganglion stimulation (DRG) have demonstrated efficacy for cases resistant to conventional treatment. Experimental approaches, including the use of metformin and medical marijuana, show promising results but require further investigation.

Conclusion. Early diagnosis and the implementation of individualized treatment are crucial for improving therapeutic outcomes and quality of life in patients with CRPS. Combining clinical criteria with advanced imaging techniques can enhance diagnostic accuracy. Vitamin C, as an affordable and safe preventive measure, should be routinely used in at-risk groups. A comprehensive therapeutic approach incorporating pharmacotherapy, rehabilitation, and neuromodulation forms the foundation of CRPS treatment. Future research should focus on developing innovative therapeutic methods and better understanding the disease's pathophysiological mechanisms, which will enable the formulation of more effective treatment strategies.

Keywords: complex regional pain syndrome, Sudeck's disease, diagnosis, treatment

INTRODUCTION

Complex Regional Pain Syndrome (CRPS) is a chronic pain condition that primarily affects the limbs and is characterized by pain disproportionate to the initial injury or triggering factor. The clinical presentation involves autonomic, sensory, and vasomotor disturbances [1]. Symptoms include spontaneous pain, hyperalgesia (increased sensitivity to pain), allodynia (pain from normally non-painful stimuli), swelling, vasomotor abnormalities, motor dysfunction, and trophic changes in the skin, hair, and nails. CRPS is classified into two main types: type 1, formerly known as reflex sympathetic dystrophy, which occurs without nerve damage, and type 2, or causalgia, where nerve damage is evident [2]. The pathophysiology of CRPS is multifactorial, often arising as a consequence of bone injury. The disease can develop even after minor injuries, particularly when prolonged limb immobilization occurs [3]. The mechanisms underlying CRPS remain controversial, though peripheral and central processes are thought to play key roles. Potential pathogenic factors include chronic and neurogenic inflammation and autoimmune mechanisms, as indicated by elevated levels of proinflammatory cytokines in CRPS patients. In the acute phase, a heightened proinflammatory response involving cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) leads to localized redness, swelling, and elevated skin temperature.

Additionally, the literature highlights microcirculatory damage, genetic factors, and cortical reorganization resembling mechanisms observed in phantom limb pain. Nevertheless, distinguishing CRPS subtypes often proves challenging [4]. The genetic basis of CRPS has been investigated extensively, though no definitive associations have been established. However, a link between CRPS and the expression of HLA genes, such as HLA-DQB1, suggests a possible role of adaptive immune responses in its pathogenesis. Preliminary research in epigenetics also indicates that DNA methylation modifications, particularly in regions associated with immune function, may contribute to CRPS development [5].

METHODS

This analysis focuses on scientific publications related to Complex Regional Pain Syndrome (CRPS), including the latest findings on diagnosing and treating this condition. The data sources comprise publications available in peer-reviewed scientific journals and official databases: PubMed/MEDLINE, Web of Science, and Scopus. The language of the publications was limited to English and Polish. The following keywords were used: "complex regional pain syndrome," "Sudeck's disease," "Budapest criteria," "complications of bone fractures," and "algodystrophic syndrome." Bibliographies of the retrieved articles and additional sources were manually reviewed to ensure comprehensive data collection.

DIAGNOSIS

The diagnosis of CRPS primarily relies on clinical criteria, as no definitive objective test exists to confirm the condition. The most commonly used diagnostic tool is the Budapest Criteria, developed

by the International Association for the Study of Pain. These criteria demonstrate high sensitivity (99%) but moderate specificity (68%). They require the presence of pain disproportionate to the initial injury and symptoms in at least three of four categories (sensory, vasomotor, sudomotor/oedema, and motor/trophic), along with clinical signs in at least two of these categories during the examination. Auxiliary tests such as ultrasonography, thermography, and bone scintigraphy differentiate CRPS from other potential causes of the observed symptoms [6].

Clinical Diagnostic Criteria for CRPS To diagnose CRPS, all the following criteria (A–D) must be met. If fewer subjective or objective symptoms are present (criteria B and/or C are not fulfilled), the condition can be classified as unspecified CRPS (Complex Regional Pain Syndrome – Not Otherwise Specified, CRPS-NOS).				
A		The patient has continuing pain which is disproportionate to any inciting event		
B		The patient reports at least one symptom in 3 or more of the categories		
C		The patient displays at least one sign in 2 or more of the categories		
D		No other diagnosis can better explain the signs and symptoms		
Category			**Symptom (the patient reports a problem)**	**Sign (you can see or feel a problem on examination)**
I	Sensory	Allodynia (to light touch/brush stoke and/or temperature sensation and/or deep somatic pressure and/or joint movement), and/or	Reported hyperesthesia also qualifies as a symptom	

		hyperalgesia (to pinprick)		
II	Vasomotor	Temperature asymmetry and/or skin colour changes and/or skin colour asymmetry		
III	Sudomotor/oedema	Oedema and/or sweating changes and/or sweating asymmetry		
IV	Motor/trophic	Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair/nail/skin)		

Rycina 1. The Budapest criteria

In modern diagnostics, nuclear medicine techniques, such as three-phase bone scintigraphy, are increasingly utilized to confirm uncertain cases, particularly during the first year of the disease [6.5]. This imaging modality allows for detecting changes in tissue perfusion and bone metabolism characteristic of different stages of CRPS. In the early stages, scintigraphy shows increased blood flow and radiotracer uptake during vascular and tissue phases, indicative of active inflammatory processes. Enhanced uptake in bones and around joints can be observed in the delayed phase. In advanced stages, changes may include normalization of blood flow with persistent delayed-phase uptake. Hybrid imaging

modalities like SPECT/CT combine functional scintigraphic imaging with precise anatomical visualization, enhancing diagnostic accuracy. This approach is particularly useful in complex cases [7]. Other technologies, such as thermography, support the assessment of skin temperature asymmetry, a hallmark symptom of CRPS.

Nevertheless, diagnosis remains primarily clinical, with technical studies aiding mainly in the differentiation of CRPS from other conditions with similar symptoms, such as neuropathies or rheumatic diseases. Current guidelines emphasize the need for an integrated diagnostic approach that considers somatic and psychosocial aspects [7.5]. Evaluating the impact of CRPS on the patient's daily activities and addressing psychological factors, such as fear of movement or emotional disturbances, is crucial as these can influence disease progression. The introduction of novel diagnostic tools, including scaled neuropsychological tests and biomarkers, represents a significant step toward more precise CRPS identification and improved therapy personalization [8].

TREATMENT

Treating Complex Regional Pain Syndrome (CRPS) requires an integrated and interdisciplinary approach that includes pharmacological, physiotherapeutic, and psychological interventions. The primary therapeutic goals are pain reduction, improved limb function, and psychological support for the patient. Early diagnosis and prompt initiation of therapy are crucial, as they significantly increase the chances of functional recovery and reduce symptom severity [9]. One of the most essential treatment components is rehabilitation, which involves gradually increasing activity, desensitization techniques, strengthening exercises, and methods such as mirror therapy and motor imagery. Key elements include oedema management, regular aerobic exercises, and weight-bearing techniques, such as "scrubbing and carrying." Studies indicate that these techniques are particularly effective in alleviating allodynia and hyperalgesia, characteristic features of CRPS [10]. Pharmacotherapy in CRPS focuses on managing inflammation, sensitization, vasomotor disturbances, and motor dysfunction. Corticosteroids and bisphosphonates effectively reduce pain and control inflammation, particularly during the early stages of the disease. Antioxidants, such as vitamin C, support microcirculation and mitigate oxidative damage caused by free radicals [11]. A systematic review and meta-analysis by Seth et al. (2022) demonstrated that vitamin C significantly reduces the risk of developing CRPS type I after surgical procedures on the upper and lower limbs. Daily supplementation of vitamin C at doses of 500–1000 mg for 42–50 days was associated with a 67% reduction in the risk of CRPS compared to placebo. These findings were consistent regardless of the fracture site or vitamin C dosage, confirming the efficacy of this approach in various orthopaedic contexts [12]. Hernigou et al. (2021) conducted a prospective study on 329 patients following foot and ankle surgeries, demonstrating that a daily intake of 1 g of vitamin C for 40 days reduced the risk of CRPS by 81% compared to the control group. These findings suggest that vitamin C is a simple, cost-effective, and efficient method of preventing CRPS in orthopaedic patients, particularly those at high risk of developing the condition [13]. A literature review by Giustra et al.

(2021) also highlighted the benefits of vitamin C supplementation at doses of 500–1000 mg daily for 45–50 days in preventing CRPS type I after limb injuries and orthopaedic surgeries. Of the six studies analyzed, five confirmed the efficacy of vitamin C in reducing the risk of CRPS. The authors emphasize that the mechanism of vitamin C's action may involve its antioxidant properties and its ability to stabilize reactive oxygen species, which can damage microcirculation and exacerbate inflammatory processes [14]. In treating central and peripheral sensitization, gabapentin and pregabalin are commonly used to reduce excessive neuronal excitability. Vasomotor disturbances can be alleviated with vasodilators, such as nifedipine or tadalafil, while dystonia and other motor issues can be managed with baclofen or botulinum toxin. Experimental applications of botulinum toxin and ketamine have shown promising results, although further studies are needed to confirm their efficacy [15]. Additionally, studies have suggested that both natural and synthetic marijuana may reduce pain levels in CRPS patients. However, the current evidence for the effectiveness of medical or synthetic marijuana in treating CRPS is limited. Most data come from small case series and individual studies of low methodological quality, making it difficult to draw definitive conclusions [16]. Studies on the use of metformin in an animal model of Complex Regional Pain Syndrome (CRPS) indicate that early, short-term treatment with this drug can effectively reduce pain and swelling symptoms. Metformin, an AMP-activated protein kinase (AMPK) activator, significantly decreased mechanical allodynia and restored impaired functional behaviours in mice with CRPS. Furthermore, it reduced limb swelling, suggesting an anti-inflammatory effect at the injury site. The findings also revealed that metformin influences molecular pathways involved in the pathogenesis of CRPS, particularly AMPK expression in dorsal root ganglion neurons. Reduced AMPK activity and increased expression of the mechanistic target of rapamycin (mTOR)-associated proteins may play a crucial role in the development of pain and hypersensitivity symptoms [17]. Psychological methods also play an important role in therapy. Research on the psychological characteristics of patients with chronic CRPS shows that their personality profile differs from that of healthy individuals and patients with other chronic pain conditions or depression. CRPS patients exhibit higher levels of somatic sensitivity, depression, and anxiety compared to healthy individuals, although their psychopathological symptoms are less severe than those observed in patients with severe depression [17.5]. A notable finding is the tendency of CRPS patients to minimize and underestimate psychological symptoms, which can contribute to diagnostic difficulties and delays in appropriate treatment. Additionally, the intensity of pain is significantly correlated with the severity of depressive symptoms, underscoring the need for assessing and treating emotional disturbances in CRPS patients, even when they appear to be moderate [18]. These findings highlight the importance of psychological support, including cognitive-behavioral therapy, in managing chronic pain, anxiety, and depression associated with CRPS. Exposure-based movement techniques help patients overcome their fear of activity, which is essential for returning to functioning [19]. In more advanced cases, invasive methods such as sympathetic nerve blocks, spinal cord stimulation (SCS), or dorsal root ganglion stimulation (DRG) are employed, offering precise pain relief in specific areas [20]. Spinal cord stimulation (SCS) is an effective therapeutic method for treating

Complex Regional Pain Syndrome (CRPS), particularly in cases resistant to conservative treatment. The effectiveness of SCS is most pronounced in the short term (6 months to 2 years), though its long-term efficacy may decline, as highlighted in a review by Mattie et al. Advanced technologies, such as dorsal root ganglion stimulation (DRG), have shown even greater precision in pain relief and improved physical and psychosocial functioning compared to traditional SCS. DRG stimulation is also associated with fewer position-dependent paresthesia changes, making it more comfortable for patients. Studies emphasize the importance of therapy individualization, considering patient preferences and responses to various stimulation parameters, such as frequency and wave type. A personalized approach can enhance therapy efficacy and patient satisfaction [21]. Sympathetic nerve blocks, such as stellate ganglion blocks for the upper limbs and lumbar sympathetic blocks for the lower limbs, are valuable interventional procedures in treating CRPS. Their effectiveness depends on precise execution, which can be enhanced by fluoroscopic and ultrasound-guided techniques, improving safety and accuracy [22].

DISCUSSION

A comparison of findings on currently available diagnostic and treatment methods for Complex Regional Pain Syndrome (CRPS) provides valuable insights but must be considered within certain limitations. One of the primary challenges is the lack of definitive, objective diagnostic tests, which leads to reliance on clinical criteria, such as the Budapest Criteria. Although these criteria exhibit high sensitivity, their specificity is moderate, which can result in diagnostic errors. Cegła et al. demonstrated that imaging techniques, such as scintigraphy and SPECT/CT, serve as significant diagnostic support, yet further research is needed to optimize their role in clinical practice [7]. Melf-Marzi et al. highlighted the increasing use of innovative diagnostic methods, such as scaled neuropsychological tests and biomarkers, with promising outcomes, suggesting they may shape the future of CRPS diagnostics [8]. Rehabilitation plays a key role in CRPS treatment, forming one of the pillars of an interdisciplinary therapeutic approach. The primary objectives of rehabilitation are pain reduction, improved range of motion, and restoration of limb function, enabling patients to regain independence in daily life [10].

Regarding pharmacotherapy, the review revealed the efficacy of several treatments, but most of the underlying studies were methodologically limited. Pharmacological interventions, including corticosteroids, bisphosphonates, and gabapentin, show beneficial effects; however, additional research is needed to determine their long-term efficacy and safety [10]. This discussion underscores the need for a more integrated approach combining advanced diagnostic methods and personalized treatment strategies to enhance CRPS management. Further research is essential to address existing gaps and optimize diagnostics and therapeutic outcomes. Studies by Seth et al., Hernigou et al., and Giustra et al. highlight the significant role of vitamin C in preventing CRPS due to its antioxidant properties. These studies emphasize that this approach is cost-effective, safe, and easy to implement in clinical practice. While its role in prevention is well-documented, less attention has been given to the potential application of vitamin C in treating CRPS [12,13,14]. Research by Martin CW. on the effects of marijuana on pain

relief suggests a possible positive response in reducing CRPS symptoms; however, the limited number of studies prevents drawing definitive conclusions [16]. Similarly, Das et al. underscore the potential of AMPK activators, such as metformin, as promising therapies for CRPS-related pain. With its safety profile and widespread use in treating type 2 diabetes, metformin offers a low-risk therapeutic option, particularly in reducing opioid use for chronic pain management [17]. Psychological therapies should also be prioritized, as emotional disorders such as depression and anxiety significantly influence disease progression and treatment outcomes [18,19]. Interventional methods, including spinal cord stimulation (SCS) and sympathetic nerve blocks, are effective therapeutic options for CRPS, particularly in cases resistant to conservative treatment. Systematic reviews indicate significant reductions in pain intensity and improved quality of life for patients undergoing these therapies [20,21,22].

CONCLUSIONS

- **Diagnosis of CRPS**: The Budapest Criteria remain the foundation for CRPS diagnosis, offering high sensitivity but moderate specificity. Modern imaging techniques, such as three-phase scintigraphy, SPECT/CT, and thermography, provide valuable support, particularly in differentiating CRPS from other conditions. These methods enable the early detection of functional and metabolic changes in bones, though further research is needed to optimize their diagnostic utility.
- **Rehabilitation as a cornerstone of treatment**: Rehabilitation plays a pivotal role in CRPS therapy, encompassing gradual activity increases, desensitization techniques, mirror therapy, and weight-bearing exercises. Combining physiotherapy with pharmacological interventions and psychological support enhances treatment efficacy.
- **Pharmacotherapy**: Corticosteroids, bisphosphonates, and gabapentin have demonstrated efficacy in reducing pain and inflammation, particularly during the early stages of the disease. Additionally, daily supplementation of 500–1000 mg of vitamin C significantly reduces the risk of CRPS after surgical procedures, underscoring its role in prevention.
- **Emotional disturbances in CRPS**: CRPS patients often exhibit symptoms of depression and anxiety, which are correlated with pain severity. Cognitive-behavioural therapy and other psychological support methods are crucial for improving therapeutic outcomes.
- **New therapeutic directions**: Experimental approaches, such as the use of metformin and medical marijuana, show promising results but require further clinical research to confirm their efficacy and safety.

- **Interventional methods**: Spinal cord stimulation (SCS) and dorsal root ganglion stimulation (DRG) have effectively reduced pain in patients resistant to conservative treatment. DRG offers greater precision and less discomfort compared to traditional SCS.
- **The importance of individualized therapy**: CRPS treatment must be tailored to the disease's pathophysiological mechanisms, patient preferences, and treatment response. Early diagnosis and an interdisciplinary approach are key to improving patients' quality of life and reducing chronic complications.

In summary, this study highlights the need for further research into innovative diagnostic and therapeutic methods and the integration of personalized approaches in CRPS management.

Disclosure

Authors contribution: Jan Wójtowicz, Damian Ujazda, Weronika Głąb, Oliwia Dominiak

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Visualisation: Jan Wójtowicz, Damian Ujazda, Weronika Głąb, Oliwia Dominiak

All authors have read and agreed with the published version of the manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

Funding Statement: No external funding was received to perform this review.

Board Statement: Not applicable – this review included an analysis of the available literature.

Statement of Informed Consent: Not applicable.

During the preparation of this work, the authors used Open AI to improve language and readability, text formatting, verification of bibliographic styles, and basic data analysis. After

using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the substantive content of the publication.

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