Guidelines

Diagnostic Guidance for Chronic Complex Regional Pain Syndrome Type I and Type II from The American Society of Interventional Physicians (ASIPP)

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Background: Complex Regional Pain Syndrome (CRPS) is a challenging and often disabling condition marked by persistent pain, most commonly in a limb following injury or surgery. It presents with a wide array of symptoms, including intense pain, swelling, alterations in skin color and temperature, motor dysfunction, and trophic changes such as skin and tissue atrophy. While the precise cause of CRPS is not fully understood, it is thought to stem from abnormal nervous system activity, leading to heightened pain sensitivity and inflammatory responses. A thorough understanding of CRPS is essential for accurate diagnosis, effective treatment, and enhancing patients' quality of life.

Although attempts have been made to distinguish between acute and chronic CRPS, there are currently no established diagnostic criteria specific to chronic CRPS in medical literature.

Objective: This ASIPP guidance document offers updated, evidence-based recommendations for the diagnosis and management of Chronic Complex Regional Pain Syndrome (CRPS), with a primary focus on introducing novel, time-based diagnostic criteria specific to the chronic phase. These proposed criteria address significant gaps in the current literature, where existing standards, such as the Budapest Criteria, do not sufficiently differentiate between the acute and chronic stages of the condition.

Methods: An expert panel convened by the American Society of Interventional Pain Physicians (ASIPP) conducted a comprehensive literature review and employed a structured consensus process to develop recommendations. Acknowledging that the clinical and pathological characteristics of CRPS change significantly beyond 12 months, the panel proposed chronic-specific diagnostic criteria based on disease duration, clinical history, physical examination findings, and optional diagnostic tests. These draft criteria were refined through multidisciplinary input and expert consensus.

Results: The diagnostic framework for chronic CRPS consists of four key components:

1. General Criteria – Require fulfillment of the Budapest Criteria for at least 12 months, continued recognition of CRPS as a diagnosis of exclusion, and differentiation from generalized nociplastic pain syndromes.
2. History-Based Criteria – Mandate the presence of at least three out of five specific historical features.
3. Physical Examination Criteria – Include asymmetric limb findings, sensory disturbances, and musculoskeletal changes.
4. Optional Diagnostic Testing – May involve assessments such as intraepidermal nerve fiber density (IENFD) and imaging evidence of regional bone demineralization.

This framework builds upon the Budapest Criteria by incorporating time-dependent features of chronic CRPS, including musculoskeletal dystrophy, neurogenic inflammation, and sympathetic dysfunction. Emerging objective tools—such as quantitative sensory testing (QST), skin biopsy for IENFD, functional MRI, and serum biomarkers of neuroinflammation—may further support diagnosis in complex or uncertain cases.

Treatment recommendations highlight a multimodal strategy that integrates physical rehabilitation, pharmacologic management of neuropathic pain, sympathetic nerve blocks, and advanced neuromodulation. Emphasis is placed on individualized care pathways tailored to disease stage and patient-specific characteristics.

Conclusions: This article presents the first structured, time-sensitive diagnostic criteria for chronic CRPS, aimed at improving diagnostic accuracy and informing treatment strategies. Adoption of these criteria may enhance clinical outcomes and promote further research into the natural history and pathophysiology of CRPS progression.

Key Words: CRPS I and II, reflex sympathetic dystrophy, causalgia, Budapest Diagnostic Criteria, sympathetically mediated pain, sympathetic blocks

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1.0 Introduction

Complex Regional Pain Syndrome (CRPS) is a multifaceted and often debilitating condition marked by chronic pain, typically affecting an extremity after injury or surgery. It is characterized by a constellation of symptoms, including severe pain, swelling, alterations in skin color and temperature, motor dysfunction, and trophic changes. While the precise etiology remains unknown, CRPS is believed to stem from abnormal nervous system responses, resulting in heightened pain sensitivity and localized inflammatory activity (1). A thorough understanding of CRPS is essential for accurate diagnosis, effective treatment, and improved quality of life for affected individuals.

The history of CRPS dates back to the 19th century. In 1864, French physician Paul Marie Boucher first described cases involving painful, swollen extremities following trauma (2). Initially termed causalgia, the condition was linked to nerve injury and defined by severe, burning pain.

Throughout the early 20th century, clinical understanding evolved as more cases were associated with trauma and surgical interventions. This led to the introduction of the term reflex sympathetic dystrophy (RSD), which emphasized the suspected involvement of the sympathetic nervous system (3). This terminology remained in use until the late 20th century when deeper insights into pain mechanisms prompted a shift in classification.

In 1993, the International Association for the Study of Pain (IASP) adopted the term Complex Regional Pain Syndrome, better reflecting the heterogeneous nature and multifactorial pathophysiology of the condition (4). Subsequent research has focused on mechanisms such as neuroinflammation, autonomic dysfunction, and central sensitization—contributing to both diagnostic criteria and therapeutic strategies.

CRPS is currently categorized into two subtypes based on nerve involvement (5):

- CRPS Type I (formerly RSD) occurs without confirmed nerve injury and typically follows minor trauma. It presents with disproportionate pain, edema, and autonomic changes.
- CRPS Type II (formerly causalgia) follows a documented nerve injury, presenting with similar symptoms but with identifiable nerve damage as the underlying cause.

The distinction between these two types is clinically important, as it may influence both the understanding of disease mechanisms and the selection of appropriate interventions.

2.0 Methods

2.1 Rationale and Objectives

The diagnosis of CRPS is clinical in nature and is primarily based on a thorough patient history, detailed physical examination, and recognition of musculoskeletal degeneration along with secondary pain that emerges due to the ongoing nature of the disease.

CRPS remains a diagnosis of exclusion and should not be made when alternative medical conditions exist that could account for the presenting symptoms (5). Although attempts have been made to differentiate between acute and chronic forms of CRPS, there is currently no established diagnostic framework specifically for chronic CRPS. Chronic CRPS should demonstrate clinical signs and symptoms that reflect the long-term effects of the disease—such as atrophy, dystrophy, joint contractures, and secondary pain—which evolve over time.

While early intervention in acute and early chronic CRPS may lead to resolution, patients with advanced chronic CRPS, particularly those who have developed nociplastic pain features and profound musculoskeletal atrophy and dystrophy, may reach an irreversible stage and may not respond to curative therapies.

A defining characteristic of chronic CRPS is the progressive accumulation of musculoskeletal and neuropathic complications, driven by abnormal biomechanics of the affected limb and tissue degeneration in both superficial and deep structures. Patients frequently develop secondary pain in the contralateral limb or in other parts of the body as compensatory mechanisms emerge. Despite being critical indicators of disease progression, these chronic physical consequences of CRPS are poorly addressed in current literature—underscoring the need for and foundation of the ASIPP Chronic CRPS Guidance.

The literature identifies several key unmet diagnostic needs for CRPS:

1. Standardized Diagnostic Criteria: The absence of universally accepted diagnostic criteria often results in misdiagnosis, delays, or incorrect clinical judgment. Clearer, evidence-informed criteria are necessary to enhance diagnostic precision.
2. Biomarkers: The ongoing search for reliable biological or imaging markers to confirm CRPS remains a priority. Current diagnosis is heavily reliant on clinical judgment, which can vary significantly between providers.
3. Differential Diagnosis: Improved tools and strategies are needed to distinguish CRPS from other nociplastic and neuropathic pain syndromes, ensuring patients receive the appropriate diagnosis and care.
4. Early Diagnosis: Prompt identification is critical. Research should focus on recognizing early risk factors and signs, as early treatment improves outcomes.
5. Understanding Pathophysiology: Advancing the understanding of underlying processes such as neuroinflammation and central sensitization could inform more accurate and biologically grounded diagnostic criteria.
6. Patient-Reported Outcomes: Validated tools to systematically assess patient-reported symptoms and functional limitations are necessary to support both diagnosis and treatment monitoring.

2.2 Application

While these guidelines may be utilized by various specialties, they are specifically intended for physicians involved in the management of chronic Complex Regional Pain Syndrome (CRPS), including interventional pain physicians, pain medicine specialists, neurosurgeons, orthopedic surgeons, physiatrists, neurologists, and rheumatologists. These guidelines are not prescriptive or inflexible recommendations for diagnosis or treatment. Rather, it is expected that clinicians will tailor care plans to the individual patient's clinical presentation, medical condition, preferences, and needs, in conjunction with their own clinical judgment and expertise.

Accordingly, these guidelines do not constitute a "standard of care." While not all guidance is supported by high-grade evidence, clinical consensus and experience may justify the use of certain interventions—even in the absence of formal grading.

The purpose of these guidelines is to equip clinicians, patients, payors, and regulators with a framework to assess whether available evidence supports the concept of a "standard" approach to chronic CRPS therapy. In this context, standard refers to interventions that are appropriate for the majority of patients, favoring practicality, feasibility, and ease of use, without sacrificing therapeutic efficacy or increasing the risk of harm (6–11).

It is essential to distinguish between the use of the term "standard" in these guidelines and the legal term "standard of care," which is commonly invoked in medico-legal settings. This distinction ensures that the guidelines support clinical flexibility and individualization rather than impose rigid mandates.

Ultimately, addressing these considerations may lead to enhanced diagnostic accuracy, earlier intervention, and more effective long-term management of CRPS.

2.3 Origins of the Paper and Composition of Guideline Development Group

Following the panel titled "CRPS: Current & Emerging Concepts"—held during the ASIPP Annual Meeting in Dallas, TX, on April 4–6, 2024—the need for new diagnostic criteria for improved understanding of CRPS, particularly chronic CRPS, was strongly emphasized. This session generated significant discussion and identified the diagnosis of chronic CRPS as a key area of unmet clinical need. In response, ASIPP convened a multidisciplinary panel of experts to review the current evidence, consider diverse clinical perspectives, and formulate guidance on the diagnosis of chronic CRPS.

The panel—comprising the article's authors and committee members—was tasked with evaluating the evidence related to both acute and chronic CRPS diagnosis, and with drafting distinct sections of the article.

This group represented a wide spectrum of academic and community-based clinicians and scientists, spanning various specialties, disciplines, clinical settings, and geographic regions, all of whom brought expertise in CRPS diagnosis and treatment. In total, 24 members participated. The panel incorporated both clinical experience and patient perspectives to develop comprehensive recommendations for the diagnosis of chronic CRPS Types I and II. Meetings were conducted through in-person sessions, virtual platforms, and telephone conferences.

The multidisciplinary composition included individuals with backgrounds in methodology, epidemiology, and health services research, as well as direct clinical care. Specifically, the panel consisted of:

- 2 research scientists
- 19 anesthesiologists with subspecialty training in interventional pain management
- 2 physiatrists specializing in pain medicine
- 1 neurologist
- 1 psychiatrist
- 1 epidemiologist
- 1 psychologist

The panel included both academic faculty and private practice clinicians, all of whom are actively involved in the management of chronic pain.

2.4 Disclosures of Guideline Funding Source

The guidelines for the diagnosis of chronic CRPS Types I and II were commissioned, developed, reviewed, and endorsed by ASIPP without the involvement of any external funding sources. The entire process—including guideline preparation and authorship—was fully funded by ASIPP, with no financial support or influence from industry.

2.5 Disclosure and Management of Financial Conflicts and Confluence of Interests

Potential conflicts and confluence of interest for all panel members over the past five years were disclosed and documented during the initial panel meeting. The scope of disclosure extended beyond financial relationships to include factors such as personal experiences, clinical practice patterns, academic interests, and professional advancement.

This approach aligns with the broader definition of "confluence of interest" outlined by the Institute of Medicine (IOM), which defines it as "a set of circumstances that creates a risk that professional judgment or actions regarding the primary interest will be unduly influenced by a secondary interest" (12–15). While financial conflicts of interest are commonly recognized, the IOM emphasizes that secondary interests—including aspirations for academic recognition, future funding, professional promotion, or favoring colleagues—can also exert undue influence on decision-making.

The Institute of Translational Medicine and Therapeutics (15) further elaborates on this concept, advocating for the use of "confluence of interest" over "conflict of interest," noting that the latter can carry a pejorative connotation. Their analysis underscores that academic bias can be driven more by the pursuit of prestige than financial gain, and they argue for a uniform approach to minimize such bias in clinical research across academic settings. The panel acknowledged that diversity of specialty among primary authors also represents a source of potential bias.

Following thorough review and discussion of these disclosures, the panel determined that members with potential conflicts could continue to participate. However, individuals with relevant conflicts were recused from specific discussions or drafting portions of the guidelines related to their declared interests. These members also agreed not to engage in any communication with industry representatives regarding the guidelines prior to their publication.

All panel communication was conducted via

email and virtual platforms, with reviews and revisions completed electronically. Discussions occurred in conjunction with ASIPP-related meetings, but no travel arrangements were provided, and no financial compensation was offered to participants.

Full disclosures and competing interests are listed at the end of this article.

2.6 Key Questions

These guidelines address the following key clinical questions identified by the panel:

1. Is there a clinical distinction between acute and chronic CRPS?
2. Can diagnostic criteria for the acute phase be appropriately applied to chronic CRPS?
3. Do the history and physical examination findings used to determine the presence or absence of CRPS differ between the acute stage and later stages of the condition?
4. Do patients with chronic CRPS develop time-dependent features, such as atrophy, contractions, or contractures?
5. Does the current literature adequately characterize the clinical presentation of acute versus chronic CRPS?
6. Does the existing literature sufficiently define diagnostic criteria specific to chronic CRPS?

Additionally, the guidelines explore the following supplemental topics and questions:

1. Why is distinguishing between acute and chronic CRPS clinically important?
2. Since CRPS often follows distal extremity trauma, at what point should the diagnosis transition from acute to chronic?
3. What are the defining characteristics that distinguish acute from chronic CRPS?
4. What specific chronic-phase features apply to CRPS Types I and II?
5. Should CRPS be reclassified into acute and chronic phases for diagnostic and therapeutic purposes?
6. What does the current literature reveal about biomarkers and clinical indicators in the acute phase of CRPS Types I and II?
7. What is known about biomarkers and clinical indicators for the chronic phase of CRPS Types I and II?
8. What limitations exist within the current CRPS diagnostic criteria?
9. How do historical and physical exam findings differ between early and advanced stages of CRPS?
10. At what point in disease progression should chronic CRPS features be expected to appear?
11. How should clinicians approach cases of long-standing CRPS where objective, time-dependent features are absent?
12. What are the potential consequences of documenting a CRPS diagnosis in patients who do not meet diagnostic criteria for chronic CRPS?
13. Does the absence of chronic CRPS markers negate the presence of chronic pain?
14. What alternative diagnoses should be considered when a patient does not meet criteria for chronic CRPS?

2.7 Evidence Review

These guidelines were developed through a comprehensive evidence review and by integrating recommendations from other professional organizations and agencies. The development process was grounded in consensus-based decision-making among panel members.

As part of this effort, the panel reviewed a broad range of literature, including randomized controlled trials (RCTs) not previously included in systematic reviews, meta-analyses, narrative reviews, or existing clinical practice guidelines—particularly those focused on the diagnosis, safety, and use of treatment modalities in patients with chronic CRPS.

Following initial preparation, the full text and key questions were circulated for review among all authors. Feedback was collected, revisions were incorporated, and final recommendations were refined and unanimously approved by the panel.

2.8 Adherence to Trustworthy Standards

The development of these guidelines adhered to the Institute of Medicine (IOM) standards (16) and the National Guideline Clearinghouse's Extent Adherence to Trustworthy Standards (NEATS) instrument (16,17). The NEATS instrument was specifically designed and validated for use by trained staff at the AHRQ National Guideline Clearinghouse to evaluate the extent to which clinical practice guidelines conform to recognized standards of trustworthiness.

2.9 Grading or Rating the Quality or Strength of Evidence

Given that these guidelines are focused on diagnostic criteria, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework was deemed not applicable.

2.10 Assessment and Recommendations of Benefits and Harms

These guidelines aim to clearly outline the potential benefits, burdens, risks, and harms associated with the interventions discussed, and to explicitly link this information to each specific recommendation.

2.11 Evidence Summary of Recommendations

The documents accompanying these guidelines provide summaries of the relevant supporting evidence and clearly link that information to the corresponding recommendations.

2.12 Specificity of Recommendations

To the greatest extent possible, the guideline recommendations are clear, specific, and unambiguous, and are designed to assist in the diagnosis of chronic CRPS.

2.13 External Review

These guidelines underwent external peer review in accordance with the editorial policies of the publishing journal, Pain Physician. Additionally, they were published on the ASIPP website and featured in the ASIPP newsletter, with active solicitation of feedback from stakeholders, scientific and clinical experts, professional organizations, patients, and the general public.

2.14 Updating Chronic CRPS Guidance Guidelines

ASIPP will update these guidelines as needed in response to significant changes in evidence, public policy, or relevant developments.

3.0 Evidence Review and Synthesis

Complex Regional Pain Syndrome (CRPS) Types I and II, formerly referred to as reflex sympathetic dystrophy and causalgia, is a multifactorial and often debilitating condition (5,18). As noted earlier, its recognition dates back to the 19th century, with evolving concepts over time. Subsequent evaluations introduced classifications such as sympathetically mediated pain and sympathetically independent pain, reflecting attempts to better characterize the syndrome's clinical presentation. In 1993, the International Association for the Study of Pain (IASP) officially adopted the term "complex regional pain syndrome", acknowledging the condition's inherent complexity and symptom variability (19).

The development of these guidelines involved a structured process that included a comprehensive literature review, detailed search strategies, data collection, and evidence synthesis.

3.1 Diagnostic Criteria Development and Clinical Presentations of Complex Regional Pain Syndrome (CRPS)

3.1.1 History of CRPS Criteria Development

The diagnosis of CRPS begins with the use of appropriate symptom terminology, which was not formally standardized until the past three decades. The most current and widely accepted diagnostic framework is the Budapest Criteria, established by the International Association for the Study of Pain (IASP) in 2003 (19). Prior to this consensus, a variety of terms were used to describe what is now recognized as CRPS, including "reflex sympathetic dystrophy syndrome" (20), "causalgia", "algodystrophy" (21), "shoulder-hand syndrome" (22), "Sudeck's atrophy" (21,23), and "peripheral trophoneurosis" (20,23). These names were coined based on observed clinical symptoms and empirical reports by physicians and surgeons, who noted the involvement of sympathetic, parasympathetic, sudomotor, and somatic nervous systems (24).

In addition to the Budapest Criteria, other lesser-known diagnostic tools include the Veldman criteria (20), the original Orlando (1994 IASP) criteria, and the Harden-Bruehl criteria (25). The challenge in establishing a unified diagnostic term historically stemmed from limited understanding of CRPS pathophysiology, substantial symptom overlaps with non-CRPS pain syndromes, and limitations of the Orlando criteria—particularly their high sensitivity but poor specificity.

To address these issues, the IASP convened in Budapest, Hungary in 2003 to develop a consensus-based update, resulting in what are now known as the Budapest Criteria. Initially created as a refinement of the original IASP criteria for research purposes, the Budapest Criteria have since undergone further validation and refinement. Their sensitivity, specificity, and diagnostic accuracy have been examined across various patient populations globally, reinforcing their role as the prevailing diagnostic standard for CRPS.

3.1.2 The "Budapest Criteria"

The Budapest Criteria, developed by the IASP, has become the most widely cited and utilized standard for the diagnosis of Complex Regional Pain Syndrome (CRPS). These criteria require the presence of ongoing pain that is disproportionate to any inciting event, along with both reported symptoms and observable signs in multiple domains. Specifically, symptoms must be present in at least three of four categories—sensory, vasomotor, sudomotor/edema, and motor/trophic—with clinical signs required in at least two of these categories during examination (5,26,27).

According to the Budapest Criteria (28), a clinical diagnosis of CRPS requires all of the following:

1. Continuing pain, disproportionate to any inciting event.
2. At least one reported symptom in each of the following four categories:
    - Sensory – reports of hyperesthesia and/or allodynia
    - Vasomotor – reports of temperature asymmetry and/or skin color changes
    - Sudomotor/Edema – reports of swelling or sweating asymmetry
    - Motor/Trophic – reports of decreased range of motion, motor dysfunction, and/or trophic changes affecting hair, nails, or skin
3. At least one observable sign in two or more of the categories during evaluation:
    - Sensory – evidence of hyperalgesia (e.g., to pinprick) and/or allodynia (e.g., to light touch, temperature, deep pressure, or joint movement)
    - Vasomotor – temperature asymmetry (>1°C), skin color changes, or asymmetry
    - Sudomotor/Edema – presence of edema, sweating changes, or sweating asymmetry
    - Motor/Trophic – reduced range of motion, motor dysfunction (e.g., weakness, tremor,

dystonia), and/or trophic changes (e.g., hair, nail, or skin abnormalities)

4. No other diagnosis better explains the observed signs and reported symptoms.

Despite improvements in diagnostic consistency brought by the Budapest Criteria, diagnosing CRPS remains challenging due to its variable clinical presentation and the absence of definitive diagnostic tests. Strict adherence to the criteria may lead to misdiagnosis or underdiagnosis, particularly in patients with atypical, long-standing, or fluctuating symptoms (29,30). Moreover, the overlap of CRPS features with other chronic pain syndromes, such as neuropathic pain and fibromyalgia, can further complicate diagnostic efforts.

To address these limitations, the Valencia consensus adaptations of the Budapest Criteria have been proposed. These adaptations seek to account for symptom fluctuation and the development of CRPS in multiple limbs (31). The goal is to increase diagnostic flexibility, ensuring patients who exhibit characteristic signs of CRPS—but may not meet the strict Budapest Criteria—are still recognized and appropriately managed.

3.1.3 Subtype Taxonomies of CRPS

CRPS is recognized for its heterogeneous and dynamic presentation, with symptoms that vary significantly between patients and often evolve over time. The condition's fluctuating nature, combined with a lack of recognition for chronic determinants and absence of a defined timeframe for symptom progression, is not fully addressed by the current diagnostic criteria. This complexity presents significant challenges in both diagnosis and management (29,30).

The identification of distinct CRPS subtypes has helped to better characterize this variability. For example, symptoms such as severe edema or vasomotor changes may diminish over time, while persistent pain, motor dysfunction, and trophic changes may become more dominant as the disease progresses. However, the Budapest Criteria incorporate both acute and chronic signs into a seemingly monophasic framework, without accounting for the temporal evolution of the disorder.

Several classification systems have been proposed to further differentiate CRPS subtypes. The most widely accepted is the traditional division into:

- CRPS Type I (formerly Reflex Sympathetic Dystrophy), which occurs without a confirmed nerve injury, and
- CRPS Type II (formerly causalgia), which is associated with a documented nerve lesion (32–34).

Patients with Type II CRPS tend to experience more severe pain, greater sensory disturbances, and increased motor dysfunction compared to those with Type I (35). This classification, introduced by the International Association for the Study of Pain (IASP) in 1994, has served as a foundational framework in CRPS diagnosis.

Another proposed model divides CRPS into two clinical phases: warm and cold.

- The warm phase is typically associated with acute CRPS and is characterized by inflammatory signs, including increased warmth, swelling, edema, and vasomotor changes (28,36).
- The cold phase, more common in chronic CRPS, involves a cool, bluish, and sweaty limb, often accompanied by muscle atrophy, joint contractures, trophic skin changes, and osseous abnormalities (28,36).

This warm–cold distinction also correlates with temporal progression, where warm CRPS presents with a shorter median pain duration (approximately 4.7 months) and is most often seen in acute cases, while cold CRPS is associated with longer durations (around 20 months) and is prevalent in chronic presentations (36,38). These differences can aid in distinguishing acute versus chronic CRPS on physical examination. However, it is important to note that features of both warm and cold CRPS may coexist in the same limb, adding further complexity to clinical assessment (39).

3.1.3.1 Other Classification Schemes

Another common classification approach distinguishes chronic CRPS as pain and associated symptoms that persist for longer than three months, while acute CRPS refers to cases lasting less than three months. However, some studies propose that CRPS should be classified as chronic only when symptoms continue beyond six months and are accompanied by secondary complications, such as atrophy and joint contractures (40).

Due to the variable progression of CRPS among individuals, it is unlikely that a definitive timepoint for the transition from acute to chronic can be established in human studies. Nevertheless, translational animal models—particularly in mice and rats—have been used to investigate the underlying molecular changes associated with disease progression. In these models, timepoints of 3 to 4 weeks have been used to define

the acute phase, and 7 to 16 weeks to represent the chronic phase (41,42).

These timeframes correspond with distinct patterns of molecular signaling activity:

- In the acute phase, pathways such as chemokine signaling, glycogen degradation, and cAMP-mediated signaling are predominant.
- In the chronic phase, there is greater involvement of the coagulation system, granzyme A signaling, and aryl hydrocarbon receptor signaling (42).

These findings suggest that molecular profiling may offer valuable insights into the pathophysiological distinction between acute and chronic CRPS, complementing clinical observations.

3.1.3.2 2023 Subtype Taxonomy Schemes

Researchers have proposed more refined subtype classification systems for CRPS to better reflect its clinical and pathophysiological diversity (34). These schemes categorize CRPS into subtypes based on different dimensions:

- Sign and Symptom Domains
  - Predominantly vasomotor subtype
  - Predominantly neuropathic pain/sensory abnormalities subtype
  - "Florid CRPS" – characterized by widespread features, including motor and trophic changes
- Objective Clinical Signs
  - Peripheral inflammation subtype
  - Central/CNS pathophysiology subtype
  - Mixed subtype – exhibiting features of both peripheral and central involvement
- Inflammatory Biomarkers
  - Noninflammatory subtype
  - Subtype with elevated plasma cytokines

Understanding and identifying CRPS subtypes is critical for individualizing treatment approaches, as underlying mechanisms and therapeutic responses may vary significantly across subtypes. For instance, warm CRPS—associated with inflammatory features—may be more responsive to anti-inflammatory therapies, whereas cold CRPS may benefit from treatments targeting circulatory improvement and management of trophic changes.

3.2 Clinical Presentations of Complex Regional Pain Syndrome (CRPS)

3.2.1 Pain Characteristics

Pain is the hallmark and most defining feature of (CRPS). It is typically severe and disproportionate to the initial injury. Patients often describe the pain as burning, throbbing, or aching, with onset that may be immediate or may develop within days of the inciting event (32,34,43). This pain is not only intense but also persistent, and it frequently does not respond to standard pain management therapies.

The pain experienced in CRPS is multifactorial, incorporating nociceptive, neuropathic, and nociplastic components:

- Nociceptive pain is driven by ongoing tissue injury or inflammation.
- Neuropathic pain results from nerve damage or dysfunction.
- Nociplastic pain is believed to arise from central nervous system alterations in pain processing, occurring in the absence of identifiable tissue or nerve injury (34,43).

The simultaneous presence of these different pain mechanisms in a single patient highlights the complexity of CRPS and reinforces the need for a comprehensive, multimodal treatment strategy.

3.2.2 Sensory Abnormalities

Sensory abnormalities are a hallmark feature of CRPS and are essential for its diagnosis. The most frequently reported disturbances include:

- Allodynia – pain resulting from stimuli that do not normally provoke pain
- Hyperalgesia – an exaggerated response to normally painful stimuli (29,30,34,37)

In addition, hyperesthesia, or heightened sensitivity to sensory input, is commonly observed and contributes significantly to the intense discomfort experienced by patients (30,37).

The presence of these sensory abnormalities is a key component of the Budapest Criteria used to diagnose CRPS (26). Beyond their diagnostic value, these sensory changes also provide insight into the underlying pathophysiology of the condition, which is thought to involve both peripheral and central sensitization, as well as dysregulated sensory processing across multiple levels of the nervous system.

3.2.3 Autonomic Dysfunction

Autonomic dysfunction is a significant and frequently observed feature of CRPS, typically presenting as vasomotor and sudomotor abnormalities.

- Vasomotor changes include asymmetrical skin temperature and color between the affected and unaffected limbs. A temperature difference greater than 1°C is commonly reported and is suggestive of autonomic dysregulation (31,34,44).
- Sudomotor abnormalities, such as abnormal sweating patterns—including hyperhidrosis (excessive sweating) or anhidrosis (lack of sweating)—along with edema, further highlight the role of autonomic involvement (30,31).

These autonomic symptoms are not only distressing for patients but also provide valuable diagnostic insight. The presence of both vasomotor and sudomotor dysfunction often represents one of the earliest clinical signs of CRPS and can be instrumental in distinguishing CRPS from other pain syndromes.

3.2.4 Motor and Trophic Symptoms

Motor dysfunction represents a key component of CRPS and plays a major role in the resulting disability. Frequently reported motor abnormalities include weakness, tremor, and dystonia, which may worsen over time and lead to considerable impairment in limb function (26,27,37). A decreased range of motion is also commonly observed, often intensified by pain and sensory disturbances that restrict voluntary movement (30,37).

In addition to motor deficits, CRPS is often accompanied by trophic changes—visible alterations in the skin, hair, and nails that signal the chronic nature of the disorder. These changes may include shiny or atrophic skin, abnormal hair growth patterns, and brittle or ridged nails (27,32,33,37). In more advanced stages, bone demineralization or osteoporosis may develop, further complicating the clinical presentation and elevating the risk of fractures.

3.3 Sympathetic Nervous System Involvement

CRPS involves a complex interaction between the peripheral and central nervous systems, with the sympathetic nervous system playing a prominent role in its pathophysiology. One key mechanism is neurogenic inflammation, driven by neuropeptides such as Substance P and calcitonin gene-related peptide (CGRP), which are believed to contribute to the characteristic pain and swelling seen in CRPS (26). These neuropeptides facilitate nociceptor sensitization, resulting in the heightened pain response typical of the syndrome.

Another critical component is sympathetically maintained pain (SMP)—a condition in which pain is intensified by sympathetic activity. This phenomenon is thought to arise from abnormal interactions between the sympathetic and somatosensory systems, leading to an amplification of pain signaling (43).

Emerging evidence also points to a potential autoimmune component in CRPS. Studies suggest that autoantibodies targeting adrenergic and muscarinic receptors may contribute to the autonomic dysregulation observed in affected individuals (43).

3.4 Approach to Patients with Longstanding CRPS

A subset of CRPS patients may first present well into the chronic phase of the disease. The onset and progression of chronic features in CRPS can vary significantly among individuals, influenced by factors such as the severity of the initial injury, the timeliness and effectiveness of early intervention, and individual characteristics including age, comorbidities, and genetic predispositions (1).

Evidence indicates that chronic manifestations—such as muscle atrophy, joint contractures, and dystonia—are more likely to develop when the acute phase is inadequately treated. This underscores the critical importance of early, aggressive management in reducing the risk of progression to chronic CRPS (45).

3.5 Differential Diagnoses for Chronic CRPS

Patients with longstanding CRPS who no longer exhibit clear objective signs of the disease present a significant diagnostic and therapeutic challenge. In such cases, it is crucial to reassess the diagnosis, considering what would typically be expected in chronic CRPS and applying the most up-to-date diagnostic criteria.

For individuals who do not meet the criteria for chronic CRPS, it becomes important to explore alternative diagnoses, such as peripheral neuropathy, fibromyalgia, or other chronic pain syndromes (46). A comprehensive evaluation, including relevant imaging studies and laboratory testing, is essential to rule out these conditions. This ensures the patient receives an accurate diagnosis, appropriate treatment, and clear education about their condition moving forward.

3.6 Delayed Diagnosis and Impact

Delayed diagnosis is a well-documented challenge in the management of CRPS, with some studies reporting an average diagnostic delay of 3.9 years (5). This

delay is often attributed to limited awareness among healthcare providers, the subtle nature of early symptoms, and the frequent misattribution of symptoms to other conditions. Additionally, inadequate documentation, particularly regarding the progression from acute to chronic CRPS, can further hinder timely diagnosis and management. The consequences of such delays are significant, leading to prolonged pain, functional disability, and psychological distress for patients (5,34,47).

The psychological burden of CRPS is substantial. Many patients experience anxiety, depression, and post-traumatic stress disorder (PTSD) as a result of chronic pain and disability. These psychological effects underscore the importance of a comprehensive, multidisciplinary approach to CRPS care that addresses both physical and emotional health.

In summary, CRPS is a complex and multifactorial disorder that poses considerable challenges in both diagnosis and treatment. While the Budapest Criteria have provided a standardized framework for diagnosis, the heterogeneity of symptoms and clinical overlap with other pain syndromes often complicate the process. Despite advances in pharmacologic and interventional therapies, early recognition and a holistic, multidisciplinary treatment strategy remain essential to improving outcomes in CRPS management.

4.0 Clinical Differences Between Acute And Chronic CRPS and Applicability of Acute Phase Criteria to Chronic CRPS Diagnosis

The current diagnostic criteria for CRPS, while helpful in many cases, present several limitations—particularly when applied to chronic presentations. A key concern is the risk of overdiagnosis or misdiagnosis, as the criteria may inadvertently include patients with other chronic pain conditions that closely mimic CRPS (48). Notably, the Budapest criteria were developed with a focus on the acute phase of CRPS. The requirement to assess for disproportionate pain following an inciting event introduces an anchoring bias to that event, which may make these criteria appropriate for acute and subacute CRPS, but less effective for chronic forms of the condition. In contrast, the ASIPP criteria were developed to provide a more suitable framework for diagnosing chronic CRPS.

Existing diagnostic criteria emphasize symptoms such as allodynia, hyperalgesia, temperature asymmetry, and edema—features that are typically more prominent during the acute phase (49). However, these criteria are less applicable to chronic CRPS, which often involves additional signs like muscle wasting, joint contractures, and other indicators of long-standing pathology (50). These chronic features reflect irreversible structural changes and are not well captured in the current diagnostic framework.

One of the key challenges in CRPS management is determining when a patient transitions from acute to chronic CRPS. This transition is not clearly defined and varies by individual, depending on factors such as the severity of the initial trauma, timing of intervention, and presence of comorbidities. The Budapest criteria do not address this transition or its timeline, which limits their utility in chronic cases. Furthermore, once a diagnosis of CRPS is established, it often becomes a permanent label in the medical record, even if objective evidence of the condition is no longer present. This has led to increased advocacy for the development of diagnostic criteria that better reflect the evolving nature of chronic CRPS (51).

Despite the clinical significance of distinguishing between acute and chronic CRPS, the existing literature is largely focused on the acute phase. Few studies have examined the long-term progression of CRPS or characterized the distinct features of chronic disease (52). Additionally, there is no consensus on standardized diagnostic criteria for chronic CRPS, making diagnosis and management more difficult for patients with long-standing symptoms. This gap in knowledge highlights the need for further research to explore the natural history of CRPS and to identify reliable diagnostic markers for its chronic form (53).

Recognizing CRPS as a chronic phenotype, rather than merely a continuation of acute symptoms, has important prognostic implications. Chronic CRPS is often more resistant to treatment and may require different therapeutic strategies than those used for acute presentations.

5.0 Evaluation Of The Budapest Criteria And Applicable Objective Markers For Acute Versus Chronic CRPS Differentiation

The Budapest criteria, particularly their association with an inciting event, have been validated in multiple studies and are widely recognized for their sensitivity and specificity, especially in the acute phase of CRPS. However, the complexity and variability of CRPS can complicate the rigid application of these criteria—particularly in chronic cases where symptoms have evolved or fluctuated over time. In such contexts, the original inciting event may no longer be clinically relevant, and the concept of pain disproportionality loses its diagnostic value.

In this section, we examine the clinical utility and limitations of the Budapest Criteria, especially as they pertain to acute versus chronic CRPS, and explore the nuances of applying these criteria across different stages of the disease.

5.1 Sensitivity and Specificity of the Budapest Criteria

The assessment of the external validity, sensitivity, and specificity of the Budapest criteria is inherently limited by the absence of a definitive diagnostic gold standard, which would require a clearly established pathophysiologic or pathognomonic marker. As a result, the validation of the Budapest criteria is typically based on comparisons to earlier diagnostic frameworks. While the Budapest criteria have demonstrated improved sensitivity over prior iterations, their specificity remains moderate to poor.

For example, the 1993 Veldman criteria demonstrated a sensitivity of 0.67 and specificity of 0.78 in one study (54). In contrast, the original 1993 IASP criteria, which have faced widespread critique, exhibited sensitivity between 0.85 and 1.00 but much lower specificity, ranging from 0.36 to 0.60 (55). Evaluations of the initial Budapest research criteria in over a dozen studies have reported sensitivity ranging from 0.2 to 0.78 and specificity between 0.79 and 0.95 (55). When the modern Budapest clinical criteria were validated in 2010, they showed sensitivity of 0.99 and specificity of 0.68 (19). Later studies have found sensitivity ranging from 0.45 to 0.99 and specificity between 0.68 and 0.85 across various populations (55). While these findings generally confirm high sensitivity, they also underscore a limited specificity, which increases the risk of false-positive diagnoses.

In response, some have proposed physical examination maneuvers as supplementary or alternative diagnostic tools. One such test is the tourniquet ischemia test, in which a blood pressure cuff is used to exsanguinate the affected extremity, followed by evaluation of pain intensity and character changes (56). This test has shown a specificity of 0.88 and positive predictive value of 0.85, both of which exceed those of the Budapest criteria, suggesting a potential role for confirmatory clinical testing within the diagnostic algorithm.

The distinction between acute and chronic CRPS further complicates the evaluation of the Budapest criteria's diagnostic performance. Despite recognition of the clinical heterogeneity of CRPS, few studies have examined the sensitivity and specificity of the Budapest criteria specifically within proposed subtypes, such as acute versus chronic CRPS. Preliminary findings suggest that while the Budapest criteria may still be applicable in diagnosing chronic CRPS, their sensitivity may decline, increasing the risk of underdiagnosis or misdiagnosis in chronic presentations (57). This underscores the need for subtype-specific validation studies to ensure accurate identification and treatment of patients across the spectrum of CRPS.

5.2 Current Tools for Quantitative Scoring of Budapest Criteria

A critical limitation of the Budapest criteria is the absence of standardized grading scales or scoring systems. The criteria rely heavily on subjective symptoms, such as pain and sensory disturbances, with insufficient emphasis on objective clinical signs. This subjectivity introduces variability in diagnosis and may contribute to inconsistent treatment outcomes.

Although numerous scoring systems have been proposed to address this diagnostic gap since the consensus-based 2003 Budapest criteria, most of these alternatives have not undergone rigorous reliability or validity testing, limiting their clinical applicability and adoption.

5.2.1 Pain Presence and Quality of Life

The first criterion of the Budapest criteria is dichotomous, assessing only whether pain is present, without considering pain severity or the associated decline in quality of life—both of which are relevant for diagnostic decision-making. Pain is typically more intense during the acute phase of CRPS compared to the chronic phase. Additionally, central and peripheral sensitization, well-established mechanisms in

CRPS pathophysiology, can contribute to elevated pain intensity scores. Notably, some studies have identified a subset of patients who, despite lacking pain, exhibit all other clinical features of CRPS and are still considered to meet the diagnostic threshold (58). This presents a challenge, as pain has traditionally been viewed as the hallmark symptom of CRPS.

Relying solely on a binary pain assessment may reduce the sensitivity of the criteria and limits their usefulness in differentiating CRPS subgroups, such as acute vs. chronic presentations. To address this, clinically practical tools such as the Numerical Rating Scale (NRS), the Defense and Veterans Pain Rating Scale, the American Chronic Pain Association Quality of Life Scale, and the Short-Form McGill Pain Questionnaire can aid in categorizing subjective pain experiences (Table 1) (59–68).

Moreover, quantitative pain scoring plays a broader role in shaping how CRPS is perceived and managed. It influences healthcare utilization, diagnostic recognition, and clinician familiarity with the disorder. For example, pain specialists may be more likely to encounter patients with high NRS scores due to referrals from primary care providers, potentially skewing diagnostic patterns.

The experience of pain is also deeply interconnected with quality of life, functional disability, and employment status—factors that are not addressed by the Budapest Criteria. Tools such as the Impairment Level Sum Score (ISS), which quantifies impairment in a single limb, and the Pain Disability Index (PDI), which measures disability on a 0–10 scale, provide additional insight. The PROMIS-29 questionnaire further enhances assessment by evaluating psychological and functional domains, including anxiety, depression, fatigue, and sleep disturbance.

5.2.2 Physical Exam Markers

The second criterion of the Budapest Criteria relies heavily on a comprehensive review of systems and clinician evaluation of both subjective and objective "signs", often based on patient-reported symptoms. However, this approach introduces variability, as it lacks standardized grading scales for subjective findings such as hyperesthesia or nail changes. One potential refinement could be to assign a positive value only when a

Table 1. *Outcome measurement tools for patient-reported pain and quality of life.*

Patient Reported Outcome Measures	Outcome measure	Construct
Numeric pain rating scale (59)	Pain intensity	Numeric equivalent of visual analog scale of integers 0-10 of pain intensity
Defense and Veterans Pain Rating Scale (60)	Biopsychosocial impact of pain	Numeric scoring of integers 0-10 on pain interference with activity, sleep, mood, and stress
American Chronic Pain Association Quality of Life Scale (61)	Quality of life as measured by activity level	Scale of 0-10 based on descriptors of activity level such as "Stay in bed all day. Feel hopeless and helpless about life" to "Go to work/volunteer each day. Normal daily activities each day. Have a social life outside of work. Take an active part in family life."
Short-Form McGill Pain Questionnaire (62)	Qualitative pain	Pain sensory description, including "throbbing", "shooting", "stabbing", etc., paired with intensity from "none", "mild", "moderate", to "severe"
Pain Catastrophizing Scale (63)	Thoughts and feelings	A 13-item self-report questionnaire used to assess thoughts and feelings such as "I feel I can't go on" and "I anxiously want the pain to go away" paired with 0-4 degree scoring
EQ-5D-5L (64)	Health state	Descriptive system of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; each description has five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems
Pain Self-efficacy Questionnaire (65)	Confidence in performing activities while in pain	Measures self-described level of efficacy regarding daily functions such as doing household chores and socializing with others
Impairment Level SumScore (66)	Level of functional impairment	Measurement scoring from 5-50 on pain, active range of motion, temperature, and volume
Pain Disability Index (67)	Pain's impact on life	7 categories of life activity: family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care, life-supported activities (eating, sleeping, breathing)
PROMIS-29 (68)	Physical, mental, social wellbeing	0-5 scoring of health domains (physical function, anxiety, depression, fatigue, sleep disturbance, social roles/activities, pain interference)

patient's subjective report is corroborated by objective clinical signs as identified by the examiner.

The inclusion of clear, measurable physical exam findings, particularly those consistent with chronic disease progression, would enhance diagnostic precision and better inform treatment strategies. Furthermore, the Budapest criteria currently do not account for disease duration. This omission presents an opportunity: following the expected course of acute CRPS, objective markers and quantitative thresholds for physical signs could be incorporated into revised criteria for chronic CRPS (Table 2), improving both diagnostic accuracy and subtype classification.

5.2.3 Sensory and Vasomotor Markers

Sensory examination in CRPS can be enhanced through the use of quantitative sensory testing (QST), which measures thresholds for thermal and mechanical pain detection and assesses the integrity of A-delta and C-fiber nerve pathways. In a study by Maihöfner et al, hyperalgesia was noted as a hallmark in acute CRPS, while hypoesthesia was more common in chronic CRPS, likely due to progressive nerve injury (69). Additionally, sensitivity to cold and sharp stimuli may be more pronounced in chronic CRPS compared to acute cases.

Huge et al defined acute CRPS as < 12 months and chronic CRPS as > 12 months and used thermal QST to compare the affected and contralateral limbs. In acute CRPS, patients exhibited both warm and cold hyperalgesia, as well as warm and cold hypoesthesia, in the affected limb relative to the unaffected side (70). In chronic CRPS, thermal hyperalgesia was less severe, while hypoesthesia was more pronounced, suggesting progressive sensory dysfunction. Interestingly, paradoxical heat sensation—the perception of heat in response to cold stimuli—was observed only in acute CRPS. Notably, all QST abnormalities were also detected in the contralateral limb, indicating possible central sensitization.

Though not yet widely adopted in clinical pain practice, diffuse reflectance spectroscopy—a dermatologic technique used to objectively assess skin color—can aid in detecting microvascular perfusion and metabolic abnormalities, which may be more prominent in acute CRPS than in chronic stages (71).

Autonomic testing methods, such as the thermoregulatory sweat test (TST) (72) and the quantitative sudomotor axon reflex test (QSART) (73), provide objective assessments of sudomotor function. The TST involves the application of a sweat-sensitive indicator powder while the subject is placed in a humid chamber; the powder changes color in response to sweating (72). In contrast, QSART assesses postganglionic sympathetic cholinergic activity by applying electrical stimulation with acetylcholine and measuring the sweat response (73). In one study, both tests showed greater asymme-

Table 2. *Summary of physical exam findings.*

	Acute CRPS	Chronic CRPS	Useful Diagnostic Tests
Range of Motion		20% loss vs. contralateral limb (76)	
Limb girth		Decreased (muscle atrophy, contractures) (81)	
Grip Strength		25-50% vs. contralateral limb (76)	Force transducer measurement
Sweating	Increased sweat production during TST (74) Increased sweat production after QSART	Attenuated but still increased sweat production during TST No difference after QSART	Thermoregulatory sweat test Quantitative sudomotor axon reflex test
Hyper/ hypoalgesic changes	+warm and cold hyperalgesia +warm and cold hypoesthesia (when compared to contralateral limb) +paradoxical heat sensation	Less warm and cold hyperalgesia ++warm and cold hypoesthesia more severe (when compared to c/l limb)	
Skin Temperature	$\Delta T \geq +0.60°$ - 1.0°C (CRPS limb vs c/l limb) Warmer (74)	$\Delta T \geq$ - 0.60° - 1.0° C (CRPS limb vs c/l limb) Cooler	Infrared thermography Diffuse reflectance spectroscopy
Sensitivity to thermal stimuli		More sensitive bilaterally in chronic CRPS	

Thermal QST: thermal quantitative sensory testing
Findings are comparing affected limb to unaffected limb

try between affected and unaffected limbs during the acute phase, but at two-year follow-up, QSART differences diminished, while TST changes persisted, suggesting differing patterns of autonomic involvement over time (74).

de Boer et al observed that sensory signs such as hyperalgesia and allodynia, along with most motor symptoms (except range of motion limitations), were more frequently present in chronic CRPS, defined as lasting longer than six months (75). Conversely, vasomotor and sudomotor signs appeared less frequently in chronic cases, highlighting a shift in clinical features as the disease progresses.

5.2.4 Motor and Trophic Changes

Motor changes in CRPS can be objectively assessed by experienced clinicians through comparison of the affected limb with either the patient's baseline function or the contralateral limb. Key motor parameters include muscle bulk, tone, and strength. Strength is often evaluated using the Medical Research Council (MRC) Manual Muscle Testing scale, which grades muscle strength from 0 (no contraction) to 5 (full strength against resistance). In cases of mild or subtle weakness, force transducers can provide quantitative measurement of muscle activity. For instance, grip and pinch strength are commonly used metrics. In a study by Laulan et al, patients with chronic CRPS (12–13 months duration) demonstrated a 25–50% reduction in grip strength in the affected limb compared to the contralateral side, as measured by dynamometry (76).

Range of motion (ROM) should also be quantified objectively, as ROM limitations may help differentiate acute from chronic CRPS (77). One study found that patients with chronic CRPS lost on average, approximately 20% of joint movement in either the ankle or wrist of the affected limb compared to the unaffected side (78). However, ROM limitations in acute CRPS have not been well-characterized in the literature, though such metrics may offer high specificity if studied further.

Temperature testing in CRPS is influenced not only by ambient environmental conditions but also by internal thermoregulatory cycles and sympathetic nervous system activity (79). In one study, patients in the early stages of disease (2–21 weeks, predominantly acute CRPS) had warmer skin temperatures on the affected limb relative to the unaffected limb. At follow-up (22+ weeks), the affected limb became cooler, indicating a reversal in temperature asymmetry over time (74). Another study involving Type I CRPS patients across both acute and chronic phases observed minimal skin temperature differences at rest, but the temperature asymmetry became more pronounced during conditions of increased sympathetic activity (80).

While limb girth asymmetry is a commonly observed feature in CRPS (81), there is a lack of high-quality, quantitative studies evaluating its correlation with disease duration. Given the objectivity and diagnostic potential of such measurements, this represents an important future research direction that could enhance the specificity of CRPS diagnosis.

6.0 Etiopathology and Acute Versus Chronic Biomarkers Of CRPS

It is hypothesized that an autoinflammatory response to initial peripheral limb trauma plays a major role in the development of the acute phase of CRPS. Cross-sectional studies have shown that patients with CRPS display an exaggerated inflammatory response in the affected limb, leading to marked changes in sensory perception, temperature regulation, edema, and perfusion (5). Clinically, the limb may appear erythematous and swollen.

Key biomolecules contributing to vasodilation, plasma extravasation, edema, and trophic changes include neuropeptides, tumor necrosis factor (TNF), interleukin-6 (IL-6)-induced cytokines, growth factors, and low levels of norepinephrine—accompanied by heightened sensitivity of peripheral adrenergic receptors to catecholamines (82). This inflammatory cascade activates fibroblasts, osteocytes, and keratinocytes, further amplifying the local inflammatory response. Elevated levels of TNF and IL-6 have been identified in the skin, cerebrospinal fluid (CSF), and serum of CRPS patients.

The persistence of pain beyond the acute phase is thought to result from abnormal sympathetic nervous system regulation. Continued cytokine release increases norepinephrine levels and enhances adrenergic receptor expression on nociceptive fibers. As a result, the clinical presentation shifts: whereas acute CRPS is marked by inflammation, chronic CRPS is characterized by vasoconstriction, hyperhidrosis, and a pale or cyanotic limb, often with signs of fibrosis.

6.1 Potential Biomarkers of CRPS in the Clinical Setting

The treatment of Complex Regional Pain Syndrome (CRPS) should be multimodal and initiated promptly, as untreated or delayed management of acute CRPS can lead to chronic CRPS—often associated with persistent, treatment-resistant pain and long-term functional impairment. While the Budapest criteria remain the clinical standard for diagnosis, they do not account for the underlying etiopathology of CRPS, which may involve inflammatory, immune, psychosocial, central and peripheral nervous system alterations, sensitization processes, and genetic predispositions.

Several of these mechanisms can now be quantified through laboratory and imaging studies, offering diagnostic insights that extend beyond the scope of the Budapest criteria. This section emphasizes the clinical relevance of current research by identifying objective, etiopathology-based biomarkers that differentiate between early and late stages of CRPS (82-114). The goal is to facilitate timely and targeted intervention by integrating diagnostic tools that are:

1. Measurable
2. Accessible in a primary clinical setting
3. Supported by current literature

These biomarkers are summarized in Table 3.

6.2 Laboratory Biomarkers of Inflammation: Immune System Dysregulation

As previously discussed, inflammation is a key pathophysiological mechanism underlying CRPS and can be categorized into immune system dysregulation, neurogenic inflammation, and neuroinflammation. Although immune dysregulation was not initially accepted as a contributing mechanism—largely due to normal leukocyte counts and C-reactive protein (CRP) levels, which are traditional markers of systemic inflammation—emerging evidence supports its role, particularly during the early stages of CRPS (Table 4).

Notably, two major studies demonstrated elevated levels of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) in the blister fluid of CRPS-affected limbs compared to the contralateral limb (83,84). Alexander et al further found that systemic TNF-α levels were higher in CRPS patients than in healthy controls and correlated with disease severity, duration, and limb temperature asymmetry.

Among the most promising biomarkers of immune dysregulation in CRPS are mast cells and their soluble mediator, tryptase. Elevated tryptase levels have been detected in the blister fluid of affected limbs and correlate with pain scores (85). Interestingly, mast cells appear to be upregulated predominantly in the acute phase of CRPS (83,86), and their concentration is significantly higher in the affected limb compared to the contralateral side (83). This makes mast cells one of the few biomarkers capable of distinguishing between acute and chronic CRPS.

Systemic immune abnormalities have also been identified. CRPS patients exhibit increased levels of $CD14^+$ $CD16^+$ monocytes (87) and heightened T-lymphocyte activity, particularly involving CD25—a protein released by activated T-cells, which shows high specificity and sensitivity in distinguishing CRPS patients from healthy controls (88).

Finally, systemic microRNAs (miRNAs)—small noncoding RNA molecules involved in regulating adaptive

Table 3. *Summary of potential biomarkers of CRPS in the clinical setting.*

Biomarker	Local vs. Systemic	Source	Finding	Additional Comments
CRP/ Leukocytes (immune dysregulation)	Systemic	Venous Blood	Normal	If abnormal, consider concurrent infection or other pathology
TNF-alpha (82-8491,112) (immune dysregulation)	Local	Blister fluid	Elevated levels in acute CRPS (<3 mo.) contralateral limb	-Correlation with disease duration and severity -Correlation with limb temperature asymmetry
	Systemic	Venous Blood	Elevated levels in acute CRPS vs. healthy control	
IL-684 (112) (immune dysregulation)	Local	Blister fluid	Elevated levels in acute CRPS (<3 mo.) vs. healthy control	correlation w/ duration
Tryptase (85) (immune dysregulation)	Local	Blister fluid	High levels found in CRPS limb vs. Contralateral limb	-Positive correlation with pain scores -mast cell product
Mast Cell Number (86,112) (immune dysregulation)	Local	Skin biopsy	-Higher levels found in CRPS limb vs. Contralateral limb (83,87) -Elevated only in acute CRPS2 (86)	-Particularly promising
CD8+ T-lymphocytes (immune dysregulation)	Systemic	Venous Blood	Elevated in CRPS vs. Healthy control	
CD14+/CD16+ (87,113,114) (immune dysregulation)	Systemic	Venous Blood	Elevated in CRPS vs. Healthy control	Positive correlation w/cold allodynia (87)
CD25 (87) (immune dysregulation)	Systemic	Venous Blood	Elevated in CRPS	Sensitivity 90%; Spec: 89.5%
MiRNA (immune dysregulation)	Systemic	Venous Blood	18 miRNAs expressed in CRPS	-Able to further differentiate subtypes (89) -Potential to provide targeted therapy
SP (neurogenic inflammation)	Systemic	Venous Blood	Conflicting evidence	-Higher levels in chronic CRPS vs. acute CRPS (93,95) -No difference in CRPS vs healthy control (96)
CGRP (neurogenic inflammation)	Systemic	Venous Blood	Conflicting evidence	
MMP-2 (94) (neurogenic inflammation)	Local	Skin biopsy	-Higher in CRPS limb vs. contralateral limb -Higher in CRPS limb and contralateral limb vs. healthy control limbs -Low level in CRPS limb associated with trophic changes -Levels in contralateral limb inversely correlated to CRPS severity	Serum studies found no statistically significant differences
MMP-9 (94) (neurogenic inflammation)	Local	Skin biopsy	Positive correlation with CRPS severity	Serum studies found no statistically significant differences
α1-ARimmunoreactivity (99)	Local	Nerve bundle	-Greater in acute CRPS (<12 mo.) vs. intermediate (11-36 mo.) and chronic CRPS (>36 mo.) -Greater in CRPS limb vs. contralateral limb	
	Local	Blood vessel	-Greater in acute CRPS vs. Intermed and chronic CRPS	
	Local	Skin	-CRPS Type I: Greater in chronic b/l limbs (>36 mo.) vs. acute (<12 mo.) and intermediate (11-36 mo.) b/l limbs -CRPS Type II: Greater in acute (<12 mo.) and intermediate (11-36 mo.) in b/l limbs vs. chronic (>36 mo.) b/l limbs	

Table 3 cont. *Summary of potential biomarkers of CRPS in the clinical setting.*

Biomarker	Local vs. Systemic	Source	Finding	Additional Comments
Epidermal thickness and keratinocyte expression (83)	Local	Skin	-Greater in acute CRPS (<3 mo.) limb vs. contralateral limb -Greater in acute CRPS (< 3mo) vs. chronic CRPS (> 3 mo.)	
Biomarker			Finding	Additional Comments
Brain MRI			Atrophy of corresponding cortical representation of affected limb in chronic phase	
Extremity MRI			Gadolinium enhancement in acute but not chronic phase	small case study

CRP: C-reactive protein; miRNA:microRNA; IL: interleukin; sIL-2R: CD25 SP: substance P; CGRP: calcitonin gene-related peptide; MMP: Matrix metalloproteinase

Table 4. *Potential immune system dysregulation biomarkers of CRPS (90).*

Biomarker	Local vs. Systemic	Source	Finding	Additional Comments
CRP Leukocytes	Systemic	Venous Blood	Normal	If abnormal, consider concurrent infection or other diagnosis
TNF-alpha (84,90,91,)	Local	Blister fluid	Elevated levels in acute CRPS (<3 mo.) contralateral limb	-Correlation with disease duration and severity -Correlation with limb temperature asymmetry
	Systemic	Venous Blood	Elevated levels in acute CRPS vs. healthy control	
IL-6 (83,84)	Local	Blister fluid	Elevated levels in acute CRPS (<3 mo.) vs. healthy control	Correlation w/duration
Tryptase (85)	Local	Blister fluid	Higher levels found in CRPS limb vs. contralateral limb	-positive correlation with pain scores -mast cell product
Mast Cell Number (83,86)	Local	Skin biopsy	Higher levels found in CRPS limb vs. contralateral limb (83) Elevated only in acute CRPS (<3 mo.) (83,86)	particularly promising
CD8+ T-lymphocytes	Systemic	Venous Blood	Elevated in CRPS vs. healthy control	
CD14+/CD16+	Systemic	Venous Blood	Elevated in CRPS vs. healthy control	positive correlation w/cold allodynia (87)
CD25 (88)	Systemic	Venous Blood	Elevated in CRPS	Sensitivity 90%; Spec: 89.5%
MiRNA (89)	Systemic	Venous Blood	18 miRNAs expressed in CRPS	-able to further differentiate subtypes -potential to provide targeted therapy

CRP: C-reactive protein; miRNA:microRNA; IL: interleukin; sIL-2R: CD25

and innate immune responses—have shown distinct patterns in CRPS. Orlova et al identified 18 differentially expressed miRNAs in CRPS patients, which also varied by CRPS subtype (89). These findings suggest that miRNAs may serve as both diagnostic markers and potential targets for future therapy.

6.3 Laboratory Biomarkers of Inflammation: Peripheral Neurogenic

Peripheral neurogenic inflammation is believed to contribute significantly to the hyperalgesia, allodynia, and trophic abnormalities observed in CRPS. This pathway promotes cutaneous vasodilation primarily through the neuropeptide calcitonin gene-related peptide (CGRP) and increases vascular permeability through substance P (SP) (90,91). Both neuropeptides are measurable biomarkers and have been found to be elevated at various stages of the disease (Table 5).

Birklein et al (92) reported that serum CGRP levels were significantly elevated in CRPS patients compared to healthy controls and returned to normal levels after nine months, correlating with clinical improvement—though not directly with pain severity. Elevated CGRP levels were associated with the presence of nerve le-

Table 5. *Potential neurogenic inflammatory biomarkers of CRPS.*

Biomarker	Local vs. Systemic	Source	Finding	Additional Comments
SP	Systemic	Venous Blood	Conflicting evidence	-Higher levels in chronic CRPS vs. acute CRPS (95) -No difference in CRPS vs healthy control (96)
CGRP	Systemic	Venous Blood	Conflicting evidence	
MMP-2 (94)	Local	Skin biopsy	-Higher in CRPS limb vs. contralateral limb -Higher in CRPS limb and contralateral limb vs. healthy control limbs -Low level in CRPS limb associated with trophic changes -Levels in contralateral limb, inversely correlated to CRPS severity	Serum studies found no statistically significant differences
MMP- (94)	Local	Skin biopsy	Positive correlation with CRPS severity	Serum studies found no statistically significant differences

SP: substance P; CGRP: calcitonin gene-related peptide; MMP: Matrix metalloproteinase

sions and hyperhidrosis, but not with other clinical symptoms. In contrast, Schinkel et al (5) did not find elevated CGRP levels in patients with acute CRPS compared to healthy controls but noted significantly lower CGRP levels in those with chronic CRPS. These conflicting results from Birklein and Schinkel suggest variability in CGRP expression based on disease stage or patient characteristics.

Schinkel et al also examined venous SP levels and found them to be elevated in acute CRPS patients compared to controls, with even higher levels observed in chronic CRPS (87,93). However, Blair et al found no statistically significant difference in serum SP levels between CRPS patients and healthy controls. Despite these inconsistencies, both CGRP and SP remain frequently cited in the CRPS literature and are considered central to its pathophysiology. Their diagnostic and therapeutic relevance may become clearer with further research.

Another contributor to neurogenic inflammation is the family of matrix metalloproteinases (MMPs)—enzymes involved in neuropathic pain, mechanical allodynia, edema, inflammation, bone remodeling, and wound healing. MMPs are commonly upregulated in chronic wounds and inflammatory conditions. A study by Escolano-Lozano et al (94) found that low concentrations of MMP-2 in the affected CRPS limb were associated with trophic changes, while MMP-2 levels in the contralateral limb were inversely correlated with disease severity. Additionally, higher MMP-9 levels were linked to increased CRPS severity. However, the same study reported no statistically significant differences in serum levels of MMP-2 and MMP-9 between CRPS patients and controls, indicating that localized measurements may be more clinically meaningful than systemic ones.

6.4 Laboratory Biomarkers of Inflammation: Neuroinflammation

Neuroinflammation refers to inflammation within the central and/or peripheral nervous system, characterized by the activation of glial cells. It is believed to play a critical role in the transition from acute to chronic pain through central sensitization. This process is driven and sustained by the central release of pro-inflammatory mediators, which sensitize nociceptive pathways and amplify pain signaling.

Peptide neurotransmitters—such as bradykinin, calcitonin gene-related peptide (CGRP), and substance P (SP)—are involved in both central and peripheral sensitization, contributing to the heightened pain response observed in CRPS (95,96).

Jung et al (97) and Jeon et al (98) reported an increased distribution volume ratio (DVR) in specific regions of the central nervous system in CRPS patients compared to healthy controls, with a positive correlation between DVR and pain severity. These findings, obtained via positron emission tomography (PET), support the role of neuroinflammation in CRPS pathophysiology. However, due to the limited accessibility of PET imaging in routine clinical settings, its current utility remains primarily investigational.

6.5 Additional Laboratory/Histological Biomarkers (Table 6)

Additional biomarkers that may hold clinical value

in diagnosing CRPS include α_1-adrenoreceptors (α_1-AR), epidermal thickness, and keratinocyte proliferation.

Drummond et al (99) classified CRPS into three phases based on duration: acute (<12 months), intermediate (11–36 months), and chronic (>36 months). They examined cutaneous expression of α_1-AR, a G protein-coupled receptor (GPCR) implicated in CRPS-related pain. Their findings revealed that α_1-AR immunoreactivity was significantly higher in nerve bundles of patients with acute CRPS compared to those with intermediate or chronic CRPS. Additionally, α_1-AR expression was greater in the nerve bundles of the affected limb than in the contralateral limb across all subtypes. Increased α_1-AR expression on blood vessels was also observed in the acute phase compared to later stages.

In a separate study, Birklein et al defined CRPS duration more narrowly—acute (<3 months) and chronic (>3 months)—and reported that epidermal thickness and keratinocyte expression were both elevated in the affected limb compared to the contralateral side in patients with acute CRPS. In contrast, these markers were decreased in patients with chronic CRPS.

These findings suggest that α_1-AR expression, epidermal morphology, and keratinocyte activity may serve as useful biomarkers for distinguishing between stages of CRPS and guiding early diagnosis and management.

6.6 Nerve Conduction Studies and Electromyography

Peripheral neuropathic and myopathic changes contributing to the sensory and motor abnormalities observed in CRPS have been studied using nerve conduction studies (NCS) and electromyography (EMG). These diagnostic tools may reveal abnormalities supportive of CRPS Type II, which involves confirmed nerve injury; however, findings are typically normal in CRPS Type I, adding to the diagnostic challenge (100).

In cases where abnormalities are present, NCS may demonstrate impaired or absent conduction, indicative of axonal injury, while EMG findings may include positive sharp waves and decreased or absent motor unit recruitment (101). An EMG study focusing on chronic CRPS patients with abnormal hand and wrist posturing found that, although the posturing resembled dystonia, it was not due to excessive antagonistic muscle contraction, but rather a loss of voluntary muscle activation and structural alterations in muscle tissue (102).

Interestingly, neuromuscular disorders such as muscular dystrophy—where axial muscle weakness is common—abnormal posturing is not typically observed. In contrast, posturing is a clinical feature in CRPS and other conditions involving central nervous system dysfunction, such as cerebral palsy, suggesting that central nervous system involvement is a necessary factor in the development of abnormal posturing in CRPS.

Overall, these neurophysiological and structural changes are more commonly identified in chronic CRPS, further supporting the complexity and progressive nature of the disorder.

6.7 Brain Imaging Modalities

Macroscopic changes in the central nervous system have been identified in CRPS patients through advanced imaging modalities, including magnetic resonance imaging (MRI) (103), functional MRI (fMRI) (103–105), and single-photon emission computed tomography (SPECT) (106).

Structural imaging has shown reduced grey matter volume in regions such as the dorsal insula, left orbitofrontal cortex, and cingulate cortex, alongside

Table 6. *Additional potential laboratory biomarkers of CRPS.*

Biomarker	Local vs. Systemic	Source	Finding	Additional Comments
α1-AR (99) immunoreactivity	Local	Nerve bundle	-Greater in acute CRPS (<12 mo.) vs. intermediate (11-36 mo.) and chronic CRPS (>36 mo.) -Greater in CRPS limb vs. contralateral limb	
	Local	Blood vessel	-Greater in acute CRPS vs. Intermed and chronic CRPS	
	Local	Skin	-CRPS Type I: Greater in chronic b/l limbs (>36 mo.) vs. acute (<12 mo.) and intermediate (11-36 mo.) b/l limbs -CRPS Type II: Greater in acute (<12 mo.) and intermediate (11-36 mo.) in b/l limbs vs. chronic (>36 mo.) b/l limbs	
Epidermal thickness and keratinocyte expression (83)	Local	Skin	-Greater in acute CRPS (<3 mo.) limb vs. contralateral limb -Greater in acute CRPS (< 3 mo) vs. chronic CRPS (> 3 mo.)	

increased grey matter in the bilateral dorsal putamen and right hypothalamus (107). Functional imaging studies have demonstrated enhanced thalamocortical connectivity and altered activity in the ventromedial prefrontal cortex, anterior insula, and dorsal anterior cingulate cortex (106,108). One proposed mechanism involves impaired antinociceptive modulation within the periaqueductal grey, as shown in MRI studies, which may contribute to altered pain perception (109).

These structural and functional alterations are most commonly observed in chronic CRPS. They likely result from cortical atrophy due to disuse of the affected limb (110), disinhibition of cortical excitability, and neuroplastic changes associated with chronic pain and emotional regulation—processes that develop over months to years.

While these findings are of considerable academic and research interest, their clinical utility remains limited, largely due to the high cost and limited accessibility of fMRI in routine healthcare settings. Nonetheless, the presence of symptoms such as impaired emotional regulation or altered decision-making in CRPS patients should raise suspicion for chronic neuroplastic changes and may inform clinical judgment regarding disease progression.

6.8 Extremity Imaging Modalities

It is worth noting that while MRI of the central nervous system is being explored as a tool to differentiate acute versus chronic CRPS, the evidence supporting the use of MRI for distinguishing CRPS from non-CRPS etiologies in affected limbs remains conflicting.

One study found no significant differences in skin thickness, enhancement, bone marrow edema, or subcutaneous edema between patients with acutely presenting CRPS and those with non-CRPS conditions (103). In contrast, a small case series reported that gadolinium-enhanced MRIs revealed distinct T1 and T2 signal changes across different CRPS stages—acute, chronic, and recovery (111). Specifically, during the acute inflammatory phase, T2-weighted images showed hyperintense signals with gadolinium enhancement, indicating capillary hyperpermeability and muscular edema. In the chronic phase, gadolinium enhancement was absent; however, both T1 and T2 sequences remained hyperintense, consistent with muscle fibrosis or fatty infiltration.

Other imaging modalities such as computed tomography (CT) and bone scintigraphy also offer limited utility in evaluating soft tissue and bony morphology in CRPS. These techniques are more commonly used to identify neuropathic or osseous disorders adjacent to or mimicking CRPS. In chronic CRPS, these modalities may be helpful in detecting osseous changes, including demineralization and osteopenia, which are less apparent in earlier disease stages.

7.0 Proposal of Chronic CRPS Criteria and ASIPP's New Diagnostic Guidance for Chronic Complex Regional Pain Syndrome

Complex Regional Pain Syndrome (CRPS) is a chronic pain condition that predominantly affects the extremities, typically following surgery or injury—ranging from minor to major—but can also arise spontaneously without any identifiable inciting event. It is characterized by a constellation of sensory, motor, autonomic, and trophic abnormalities, and is broadly classified into two types:

- CRPS Type I: Diagnosed in the absence of a specific nerve injury
- CRPS Type II: Diagnosed in the presence of a specific nerve injury

Despite extensive research, significant gaps remain in the literature concerning the differentiation between acute and chronic CRPS. This article explores the clinical distinctions between the two, the limitations of applying acute-phase diagnostic criteria to chronic cases and highlights the need for time-dependent criteria for the accurate diagnosis of Chronic CRPS.

Informed by a comprehensive literature review and expert consensus among the authors, draft diagnostic criteria were developed to support the creation of ASIPP's Diagnostic Guidance for Chronic CRPS. These were circulated for feedback and refinement.

Because the clinical features of Chronic CRPS typically evolve over 6 to 12 months after the onset of acute CRPS, each author assumed the definition of Chronic CRPS as a condition persisting beyond 12 months, as per the Budapest criteria, and proposed clinically meaningful indicators to support diagnosis. The draft was generally well received, with feedback leading to revisions involving criteria consolidation, removal of redundancies, and clarification of emphasis. The resulting revised criteria are presented below:

1. General Criteria

To establish a diagnosis of Chronic CRPS, all three of the following must be met:

- The patient has met the Budapest criteria for CRPS for at least 12 months
- Chronic CRPS remains a diagnosis of exclusion
- Chronic CRPS Types I and II are regional conditions and must be differentiated from primary or secondary nociplastic conditions causing generalized pain

2. History-Based Criteria

At least three of the five historical features must be present:

- Sensory: Reports of allodynia, hyperesthesia, and/or hyperpathia
- Vasomotor: Reports of temperature asymmetry and/or skin color changes
- Sudomotor/Edema: Reports of asymmetric edema or sweating
- Motor/Trophic: Reports of decreased range of motion, motor dysfunction, and/or trophic changes (e.g., hair, nail, skin)
- Contralateral overutilization: Increased use of the unaffected limb due to pain or dysfunction in the affected limb

3. Physical Examination Criteria

A. General Physical Exam Findings

At least two of the three must be present:

- Avoidance of usage of the affected limb with contralateral dominance or overuse
- Evidence of allodynia, hyperesthesia, and/or hyperpathia, or reduced tactile acuity (e.g., decreased two-point discrimination) in the affected limb compared to the unaffected side
- Asymmetric limb girth, accounting for factors such as occupation, activity level, or hand dominance

B. Superficial Trophic Changes

At least two of the three must be present:

- Superficial trophic changes (e.g., skin thinning or breakdown, hair pattern differences, nail dystrophy)
- Vasomotor findings: Visible temperature asymmetry (>1°C) and/or skin color changes
- Sudomotor/Edema findings: Presence of asymmetric edema and/or diaphoresis

C. Musculoskeletal Trophic Changes

All three criteria must be present:

- Decreased range of motion, contractures, or fixed postures
- Motor dysfunction, including weakness, tremor, or dystonia
- Musculoskeletal changes, including atrophy, changes in limb girth, or joint abnormalities (e.g., frozen shoulder)

4. Diagnostic Testing (Optional Supportive Criteria)

These tests are not required but may support the

diagnosis when Criteria 1–3 are met:

- Reduced intraepidermal nerve fiber density on punch biopsy
- Bone demineralization in the affected limb (e.g., via X-ray, CT, or bone density testing)
- Positive response to sympathetic block, indicating sympathetically maintained pain

The Chronic CRPS Criteria were accepted by all contributing authors as a probable framework for identifying chronic CRPS. While the progression of CRPS may vary by individual and disease duration, both acute and chronic forms can be treatable, reversible, and potentially curable with timely intervention. Although the ultimate diagnosis remains at the discretion of the treating clinician, these criteria aim to reduce misdiagnosis and improve the objectivity of chronic CRPS identification by emphasizing measurable, stage-specific features.

8.0 Treatments

8.1 Acute vs. Chronic Phase Pharmacologic Treatments

Over recent decades, pharmacological treatments for CRPS have yielded mixed results, with outcomes typically assessed based on functional improvement and enhanced quality of life. Clinicians must perform a thorough evaluation of each patient's pain severity and functional limitations to determine the most appropriate therapeutic strategy (115). This often involves a multimodal approach—integrating pharmacologic and non-pharmacologic therapies, along with psychological support to address the emotional burden of chronic pain.

Pharmacologic management frequently includes prescribing multiple agents from different drug classes to achieve additive or synergistic effects in pain reduction. However, this strategy presents challenges, particularly in the geriatric population, where there is increased susceptibility to adverse drug interactions and heightened sensitivity to side effects.

As a general guideline, clinicians are encouraged to begin with non-opioid medications, given the high risk of opioid-related side effects and dependency. Moreover, initiating treatment with the lowest effective dose is advised to minimize adverse effects while still aiming for meaningful pain relief.

8.1.1 NSAIDs

NSAIDs are a commonly used class of medications that have been investigated for the treatment of CRPS, though results have generally been limited. Non-steroidal anti-inflammatory drugs (NSAIDs) are often considered a first-line option for general pain management; however, their use is cautioned or contraindicated in elderly patients due to the increased risk of side effects in this population. The route of administration is also an important consideration, as some elderly patients may have difficulty taking oral medications and may require alternative delivery methods.

Although CRPS is believed to involve an inflammatory component, NSAIDs have not demonstrated consistent clinical effectiveness in reducing pain in CRPS patients. In contrast, corticosteroids have shown more promising results, with several studies reporting pain reduction in patients with mild to moderately severe CRPS. However, a double-blind, randomized trial indicated that corticosteroids are less effective in treating severe or chronic cases of CRPS (116).

8.1.2 Ketamine

Ketamine is another treatment option that has been explored for CRPS (113,114). Current evidence from 14 studies involving ketamine infusions—ranging from 0.15 mg/kg to 7 mg/kg—suggests that it may be beneficial for patients who do not respond to more conservative measures (117). The overall quality of evidence from studies evaluating ketamine's effects on pain and functional improvement in CRPS is considered fair (118–121).

However, ketamine use is associated with psychotomimetic and dissociative side effects, which can be amplified when combined with other medications. This raises particular concern for elderly patients, as it may contribute to cognitive disturbances, impaired balance, and an increased risk of falls (122). Other NMDA receptor antagonists, such as dextromethorphan and memantine, have also been used in clinical settings for similar purposes.

8.1.3 Alpha Receptor Modulators

Alpha1 blockers, such as terazosin and phenoxybenzamine, and alpha2 agonists, including clonidine and dexmedetomidine, have been used in the treatment of CRPS to reduce sympathetic stimulation and alleviate pain. Notably, phenoxybenzamine may offer additional therapeutic benefits, including suppression of macrophage activity through cytokine modulation and inhibition of calmodulin (123).

8.1.4 Bisphosphonates

Bisphosphonates, commonly prescribed for the treatment of osteoporosis, have also been shown to reduce pain in both human and animal models of CRPS. Although the precise mechanism by which bisphosphonates alleviate pain remains unclear, agents such as clodronate and pamidronate have been used clinically in CRPS management (124,125). It is hypothesized that their analgesic effects may be related to the modulation of inflammatory mediator concentrations (124). Bisphosphonates are not only widely used and well tolerated but have also been reported to reduce pain and prevent bone degradation in patients with CRPS (126,127).

8.1.5 Anticonvulsants, Antidepressants, and Neuropathic Medications

Anticonvulsants, antidepressants, and other neuropathic agents are commonly used in the management of CRPS. Given the neurological component of CRPS,

neuropathic pain medications have been evaluated for their therapeutic potential. However, there is a lack of well-designed, double-blind prospective studies supporting their efficacy.

Lidocaine patches are another frequently used option, offering localized relief in some CRPS patients. Commonly prescribed neuropathic agents include gabapentin, amitriptyline, and carbamazepine (Table 7). While these medications can provide pain relief, their effectiveness is generally limited and inconsistent (116). Additional agents such as doxepin, duloxetine, venlafaxine, and milnacipran have also been utilized clinically, though evidence supporting their use in CRPS remains variable.

8.1.6 Immunotherapeutic Treatments

Immunotherapeutic treatments aimed at interrupting proinflammatory processes in CRPS have been the focus of recent research (128-134). The appeal of targeting regional inflammatory mediators and autoimmune components has grown as new immunomodulatory therapies undergo clinical evaluation (131). Examples of such therapies include TNFα inhibitors, immunoglobulins, IL-1 antagonists, and glucocorticoids. When selecting an immunotherapy regimen for CRPS patients, clinicians must consider the presence of chronic comorbidities and the patient's ability to comply with treatment protocols.

Other anti-inflammatory agents that function as free radical scavengers have also been explored. These include DMSO 50% cream, N-acetylcysteine, mannitol, and Vitamin C (132–134).

8.1.7 TNF-α Inhibitors

TNFα inhibitors are known to suppress inflammation in various autoimmune diseases such as rheumatoid arthritis and have been proposed as a potential treatment for CRPS due to their anti-inflammatory properties (135). Examples of TNFα inhibitors include etanercept, thalidomide, infliximab, and other monoclonal antibodies. While most of these agents require intravenous infusion, some, like adalimumab, are available for subcutaneous administration.

The optimal duration of TNFα inhibitor therapy for CRPS has not yet been clearly established. However, treatment is generally continued until symptomatic inflammation is reduced to a level aligned with patient-specific therapeutic goals (136). It is important to note that patients must be screened for latent tuberculosis prior to initiating TNFα inhibitor therapy, as these biologic agents carry a risk of reactivating latent TB infections.

8.1.8 Thalidomide/IL-10

Thalidomide-derived immunomodulators inhibit TNFα production by enhancing mRNA degradation (137). In animal models, thalidomide has been shown to reduce mechanical allodynia and thermal hyperalgesia in neuropathic pain conditions and to stimulate spinal expression of IL-10 and β-endorphins, suggesting a potential role in pain relief for conditions such as CRPS (138). Thalidomide exerts anti-inflammatory effects by upregulating IL-10 expression in the spinal cord (138). IL-10 is a key immunoregulatory cytokine primarily produced by macrophages, B cells, and regulatory T cells,

Table 7. *Comparison of neuropathic medications in CRPS, modified (128-130).*

	Gabapentin	Amitriptyline	Carbamazepine
Mechanism of Action	Inhibits release of excitatory neurotransmitters via binding of alpha-2-delta calcium channels	Tricyclic antidepressant blocks the reuptake of both 5-HT and norepinephrine neurotransmitters	Modulates voltage-gated sodium channels to decrease synaptic transmission and inhibit action potential
Clinical Utility *indicates FDA approval; all other listed are off-label uses **clinical utility lists are not exhaustive	-postherpetic neuralgia* -partial seizures* -restless leg syndrome* -fibromyalgia -essential tremors -diabetic neuropathy -migraine prophylaxis	-major depressive disorder* -anxiety -diabetic neuropathy -fibromyalgia -migraine prophylaxis -interstitial cystitis -postherpetic neuralgia	-epilepsy* -trigeminal neuralgia* -bipolar I disorder* -refractory schizophrenia -restless leg syndrome -fibromyalgia -diabetic neuropathy
Adverse Effects *adverse effects include the most common effects, lists are not exhaustive	Fatigue, dizziness, headache	Weight gain, constipation, xerostomia, dizziness, headache, somnolence, QT prolongation, decreased seizure threshold, serotonin syndrome	FDA black box: severe dermatologic reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis), drowsiness, ataxia, nausea, vomiting

and it contributes to antinociception via activation of the STAT3 phosphorylation pathway (139). This activation leads to the expression of the precursor molecule proopiomelanocortin (POMC), which is processed into β-endorphin. β-endorphin binds to μ-opioid receptors and produces an anti-allodynic effect (139).

In experimental rat models, the administration of intrathecal β-endorphin antibodies or μ-opioid receptor antagonists inhibited the pain-relieving effects mediated by IL-10, further supporting the pathway's role in analgesia. Despite its potential benefits, thalidomide is associated with significant risks, most notably teratogenicity. Additional adverse effects include constipation, hypothyroidism, ACTH stimulation, somnolence, sedation, and deep vein thrombosis (140).

Gabapentinoids are currently under investigation for their ability to increase IL-10 and β-endorphin mRNA expression. Similarly, cinobufagin is being studied for its dose-dependent antiallodynic effects through the IL-10/β-endorphin pathway (141).

8.1.9 Immunoglobulins

Intravenous immunoglobulin (IVIG) preparations closely resemble normal plasma immunoglobulins, consisting primarily of IgG, along with smaller amounts of IgA and various cytokines. Although the exact mechanism by which IVIG reduces pain remains unclear, one proposed explanation is its ability to neutralize proinflammatory autoantibodies (142). IVIG is typically administered via intramuscular injection or intravenous infusion (142).

As with other immunotherapeutic agents, IVIG administration may be associated with a range of side effects, including flu-like symptoms, dermatologic reactions, arrhythmias, hypotension, and, in rare cases, transfusion-related acute lung injury (143). It is important to recognize that different IVIG formulations may carry distinct side effect profiles, and many clinical trials evaluating immunoglobulin safety lack standardized definitions for adverse events.

8.1.10 IL-1 Modulation

Interleukin-1 (IL-1) has stimulatory effects on neuronal activity, and IL-1 receptor antagonists represent a potential therapeutic strategy for managing hyperalgesia. IL-1β plays a central role in mediating neuroinflammation, including the activation of microglia and astrocytes. Blocking IL-1 receptors not only directly inhibits IL-1's proinflammatory effects but may also interrupt the downstream amplification of autoimmune responses (144,145).

IL-1 receptor antagonists can include direct antibodies targeting IL-1R, combination therapies, or recombinant cytokine biologic agents. One notable limitation of these therapies is their large molecular weight, which poses challenges for drug formulation and delivery. As with other biologic agents, patients should be screened for latent tuberculosis prior to initiating treatment to avoid potential reactivation (136).

8.1.11 Glucocorticoids

Glucocorticoids act by targeting inflammatory pathways and exert immunomodulatory effects through the inhibition of IL-2 and NF-kB signaling, suppression of mast cell degranulation, and reduction in the release of immune cells from lymphoid tissues (146). Despite their effectiveness, glucocorticoid use is associated with several disadvantages, including dose- and time-dependent metabolic side effects and a range of other physiological complications (146).

Long-term glucocorticoid therapy is generally not recommended due to these risks. Tapering must be done under close medical supervision, requiring both physician oversight and thorough patient education to ensure safe discontinuation and favorable treatment outcomes.

8.2 Clinical Studies and Trials of Immunotherapy for CRPS

A 2015 retrospective case series evaluated 33 patients diagnosed with CRPS who had failed to respond to conventional non-immune therapies and subsequently received plasma exchange. Prior to treatment, participants underwent medical and pain evaluations, the McGill Pain Questionnaire, quantitative sensory testing, and punch biopsies of affected skin areas. Following an initial dose of plasma exchange, 24 patients demonstrated a biological response. These responders advanced in the study: 15 received additional plasma exchange, eight were treated with IVIG, and one was given oral therapy. Treatment was administered weekly for up to three weeks. The study reported an average initial pain reduction of 64% in those receiving plasma exchange, although three patients experienced no change in pain. The authors noted that the study design was retrospective, non-randomized, non-blinded, and uncontrolled (147). Notably, the greatest pain reduction occurred in patients with significant small fiber loss and pronounced sensory deficits. No adverse reactions were reported.

In a 2019 study, researchers investigated the

transferability of CRPS symptoms to mice using human autoantibodies, suggesting IL-1–mediated mechanisms. Plasma from CRPS patients was injected into mice grouped by injury and non-injury status. Behavioral pain responses were quantified to assess the impact of immunoglobulin transfer. Glucocorticoid prednisone provided only transient analgesic and anti-inflammatory effects, lasting approximately five hours per day and diminishing after two to three days. In contrast, anakinra, an IL-1 receptor antagonist, produced a more sustained reduction in immune-mediated pain behaviors and reduced glial cell activation in the brain (144). Due to the risk of serum sickness, the experiment was limited to thirteen days. Epidermal nerve fiber length and density were not measured, limiting conclusions on small fiber effects.

A separate study by Guo et al explored passive transfer autoimmunity in a mouse model of CRPS. Tibial fractures were surgically induced in rats and mice, followed by subcutaneous administration of buprenorphine, enrofloxacin, and saline. After three weeks, serum from the injured wild-type (WT) mice was transferred to B-cell-deficient muMT mice. Pain behavior was assessed using mesh platform testing and quantified by withdrawal or licking responses. The muMT mice developed von Frey allodynia over three weeks. However, serum testing showed that immunoglobulin levels declined over time, and pain responses diminished accordingly. When WT serum was given to other WT mice, no change in pain behavior was observed, suggesting that IgM autoantibodies generated in muMT mice—but already present in WT mice—contributed to pronociceptive activity. At 21 weeks, loss of pain behavior coincided with a confirmed reduction in pronociceptive autoantibodies via ELISA (148). The authors concluded that targeting IgM immunoglobulins may be a novel therapeutic approach for CRPS.

A 2017 randomized trial evaluated low-dose IVIG therapy in patients with long-standing CRPS. This multicenter, double-blind, placebo-controlled trial used a one-to-one randomization model over six weeks, with an optional six-week extension. A total of 111 participants with moderate to severe CRPS (within five years of diagnosis) were enrolled. Pain was assessed using an 11-point numerical scale from days 6 to 42. Participants received either IVIG (0.5 g/kg) or placebo (0.1% albumin in saline) on days 1 and 22. Of the initial group, 108 were eligible, and 103 completed the study. The mean pain score was 6.9 for placebo and 7.2 for IVIG. In the open-label extension phase, 18% of participants who received two IVIG doses reported a two-point reduction in pain. Adverse events occurred in one participant from the placebo group, one from the blinded IVIG group, and four in the open-label group. The study concluded that low-dose IVIG did not provide significant or lasting pain relief in CRPS patients (149).

Shoenfeld et al conducted a retrospective case review comparing intravenous and oral plasma therapies in CRPS patients unresponsive to other medical treatments. The study was based on patients meeting Budapest diagnostic criteria for CRPS. It found that those with the most severe small fiber loss and temperature sensory deficits benefited most from plasma exchange therapy (150).

To date, few high-quality randomized controlled trials have supported the efficacy of commonly used CRPS treatments (50,151). Given the immune system's significant role in CRPS pathophysiology, immunotherapy remains a promising area of investigation (152). Studies have explored the potential of immunomodulatory treatments, including IL-1 receptor antagonists, glucocorticoids, IVIG infusions, and TNF-α inhibitors (136,153–155).

In summary, immunomodulatory therapies—such as IL-1 receptor antagonists, glucocorticoids, IVIG, and TNF-α inhibitors—have shown promise in alleviating pain and improving function in CRPS patients (138,142,146,155,156). These treatments aim to regulate immune responses and reduce inflammation, addressing key mechanisms of CRPS. However, their use requires careful monitoring due to potential side effects (Tables 8 and 9).

8.3 Acute vs. Chronic Phase Interventional Treatments

The interventional management of CRPS begins with identifying the nature of the pain—whether it is nociceptive, neuropathic, or a combination of both (157,158). For the neuropathic component, it is essential to differentiate between sympathetically mediated pain (SMP) and sympathetically independent pain (SIP). This distinction is typically evaluated using sympathetic blockade. Von Gaza is credited with pioneering diagnostic sympathetic blockade in 1924, followed by contributions from White in 1930 and Steindler and Luck in 1938 (159). To diagnose and treat upper extremity SMP, stellate ganglion blocks (SGB) and thoracic sympathetic blocks (TSB) are commonly used, while lumbar sympathetic blocks (LSB) are preferred for lower extremity involvement (160).

Table 8. *Overview of immunotherapeutic agents in complex regional pain syndrome.*

Agent	Mechanism	Advantages	Comments
IL-1 decoy receptor (Rilonacept)	Inhibition of IL-1 activity by binding IL-1α and IL-1β	Selective agents for blood brain barrier penetration	Large molecular weight (155) -Prior to starting, patients must be tested for tuberculosis
IL-1Ra recombinants (Anakira)	-Competitive inhibition of IL-1α and IL-1β binding -Blocks intracellular signal transduction (A)		
IL-1R binding monoclonal antibody (MEDI-78998)	-Blocks IL-1β signaling pathways (A)		
Glucocorticoids	-Inhibition of IL-2 and NF-kB signaling, degranulation inhibition of mast cells, and impaired release of cells from lymphoid tissues (B)	-Various routes of administration -Well-studied, robust, and systemic anti-inflammatory capabilities	-Dose and time-dependent side effects
IVIG	-Exact mechanism for modulating reduction in pain is unknown; a proposed mechanism is IVIG neutralizing proinflammatory autoantibodies (C)	-Broad mechanism to suppress proinflammatory markers that stimulate neuropathic pain (142)	-Wide side effect profile varying in severity and timing
Thalidomide-derived immunomodulators (i.e., lenalidomide and pomalidomide)	-Inhibits TNFα production by enhancing mRNA degradation (D) -Increased IL-10/β-endorphin signaling pathway (E)	-Markedly effective anti-inflammatory agent (D)	-Teratogenic activity
Gabapentinoids	-Increased IL-10/β-endorphin signaling pathway (E)	-Gabapentinoids are approved and first-choice drugs for neuropathic pain (F)	-NA
Other TNFα inhibitors (i.e., infliximab and etanercept)	-Block physiological response to TNF-α	-Markedly effective anti-inflammatory agent (D). -Subcutaneous modalities available	-Increased risk of lymphoma -Increased risk of opportunistic infections -Prior to starting, patients must be tested for tuberculosis

For SGBs, the classic signs of Horner's syndrome—ptosis, miosis, and anhidrosis—indicate successful facial sympathetic blockade but do not confirm sympathetic denervation of the upper extremity. Additional markers of effective blockade include a temperature increase of at least 2°C in the affected limb, improved function and range of motion, and pain relief. The same criteria apply to LSBs. In cases of SIP, a temperature rise may be observed without corresponding pain or functional improvement (160,161). It is also common for pain relief to extend beyond the pharmacologic duration of the local anesthetic. Complete relief suggests that pain is entirely sympathetically mediated, while partial relief may reflect mixed components of SMP, SIP, and/or nociceptive pain. There is no standardized number of blocks required for diagnosis or treatment; typically, these are performed in a series based on the patient's response (161).

Tian et al conducted a 2024 systematic review and meta-analysis focusing on the efficacy of stellate ganglion blocks for CRPS (162). The authors searched multiple databases including PubMed, EMBASE, Web of Science, Google Scholar, CINAHL, the NIH Clinical Trials Registry, and the Cochrane Library from January 1967 to April 2023. From 8523 records, 747 full-text articles were reviewed, and 12 randomized controlled trials involving 422 patients aged 18–25 years were included. The meta-analysis found a weighted mean difference (WMD) in visual analog scale pain scores of -6.24 mm (95% CI, -11.45 to -1.03; P=0.019) using a random-effects model, and a numerical scale pain score reduction of -1.17 mm (95% CI, -2.42 to 0.08; P=0.067) using a fixed-effects model. No high risk of reporting bias was detected. The included studies had an average PEDro score of 7 (range, 5–9), indicating generally good methodological quality. However, the authors noted the small number of trials as a limitation. They concluded that SGB may reduce pain in CRPS patients, though more high-quality RCTs are needed.

In another 2024 systematic review, Her et al evaluated the current evidence on multiple treatment modalities for CRPS. Databases searched included Ovid MEDLINE, Ovid Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of System-

Table 9. *Overview of clinical studies and reviews for immunotherapy modulation modalities for complex regional pain syndrome (157).*

Title (Year):	Groups Studied and Intervention:	Results and Findings:	Conclusions:
Plasma Exchange Therapy in Patients with Complex Regional Pain Syndrome (2015) (147)	-33 previously diagnosed CRPS patients -IVIG, oral therapeutics, and plasma exchange	-After 3 weeks, 64% of plasma exchange participants reported pain reduction	-Those who lost an abundance of small fibers and have the most profound sensory deficits were the participants to experience the greatest pain reduction results
Transfer of Complex Regional Pain Syndrome (2019) (144)	-Mice -Human plasma transfer, anakinra, and glucocorticoids	-Glucocorticoids did not provide lasting results or reduce inflammation -Anakinra reduced immune responses, leading to pain.	-Anakinra – an interleukin – 1 receptor antagonist was given and showed a reduction in IgG-related immune actions spanning the entire experiment and reduced glial cell activation parts of the brain
Low-Dose Intravenous Immunoglobulin Treatment for Long-Standing Complex Regional Pain Syndrome (2017) (158)	-111 previously diagnosed CRPS patients -Low dose IVIG	-The average for pain score was 6.9 for those taking the placebo and 7.2 for those on IVIG -18% of those in the open phase of the study that received IVIG x 2 doses reported a two-point reduction in pain levels	-There was no positive and lasting effect on those with CRPS taking low dose IVIG 0.5g/kg
Passive transfer autoimmunity in a mouse model of complex regional pain syndrome (2017) (148)	-Rats and mice -Fracturing and casting tibias and cross-administering serum IgM	-IgM played a role in allodynia but subsided by week 21 or serum administration from previously injured specimen	-IgM is responsible for pro-nociception, and specifically targeting these immunoglobulins can serve as an advancement in new treatment modalities for CRPS.
The spinal microglial IL-10/β-endorphin pathway accounts for cinobufagin-induced mechanical antiallodynia in bone cancer pain following activation of α7-nicotinic acetylcholine receptors (2020) (141)	-Rat bone cancer model treated with activation of α7-nicotinic acetylcholine receptor	-Intrathecal cinobufagin stimulated expression of IL-10 and β-endorphin in the spinal cords of bone cancer pain model rats in a dose-dependent manner with a maximum effect value (Emax) of 90% of the maximum possible effect (%MPE) and a half-effective concentration (ED50) of 6.4 μg	-Cinobufagin via activation of α7-nicotinic acetylcholine receptors and expression of IL-10 and β-endorphin inhibited mechanical allodynia in rats with bone cancer.

atic Reviews, and Scopus, covering publications from 1990 to April 26, 2023. Eligible studies included English-language RCTs and observational studies reporting changes in pain intensity following conservative, pharmacologic, or interventional therapies.

Four RCTs addressed SGB for upper extremity CRPS. Naskar et al found no significant difference between SGB with ropivacaine plus clonidine versus methylprednisolone. Another study comparing SGB with T2 paravertebral block (PVB) showed that PVB was more effective in pain reduction, duration of relief, and patient satisfaction. Toshniwal et al demonstrated that continuous SGB and continuous infraclavicular brachial plexus block had similar effects on pain, edema, and range of motion. Rocha et al assessed TSB and reported significant pain relief and improved scores on the McGill Pain Questionnaire, Neuropathic Pain Symptom Inventory, and depression inventories compared to a sham procedure.

Three RCTs evaluated LSB for lower extremity CRPS. Meier et al compared intravenous lidocaine combined with LSB versus saline and found lidocaine more effective in reducing allodynia and pain. Yoo et al showed that botulinum toxin A injected into the lumbar sympathetic ganglion produced greater pain reduction than local anesthetic. Freitas et al reported that pulsed radiofrequency ablation of the lumbar sympathetic plexus was as effective as LSB in reducing pain (163). The systematic review concluded that sympathetic ganglion blocks are associated with meaningful pain relief in CRPS.

Only one RCT has examined sympathectomy for CRPS, in which 20 patients were randomized to receive either radiofrequency or phenol lumbar sympathectomy. Although both groups experienced significant pain relief up to four months post-procedure, there was no statistically significant difference between the two approaches. A recent Cochrane review highlighted

the ongoing lack of high-quality evidence supporting most CRPS treatments in adults, underscoring the need for larger, more rigorous trials and systematic reviews to guide clinical decision-making (164).

8.4 Behavioral Treatments of CRPS

The relationship between CRPS and psychological factors remains complex and poorly understood, largely due to methodological inconsistencies. There is no clear consensus on which psychological factors are relevant or how these constructs should be reliably measured. Furthermore, it remains unclear whether psychological sequelae arise as a consequence of CRPS or whether preexisting psychological conditions contribute to the onset and progression of the disorder, potentially in conjunction with biological and social factors (26). Given evidence suggesting that pain, disability, and psychological distress in CRPS may perpetuate one another (165), the need for high-quality research into behavioral interventions is both evident and urgent.

While most CRPS treatment guidelines recommend "interdisciplinary" or "multidisciplinary" approaches, they often fail to clearly define the role or specific components of behavioral therapies within these frameworks (57,166). Additionally, there is limited guidance on when in the disease course such interventions should be implemented (28,166,167). The UK Royal College of Physicians guideline (168) identifies psychological treatment as one of the four essential pillars of CRPS management—alongside pharmacologic, interventional, and physical rehabilitative therapies—yet even this widely cited guideline lacks specificity regarding which behavioral approaches are most appropriate for CRPS patients (169).

A critical distinction must be made between early-stage CRPS and the chronic condition, as each involves different pathophysiological and molecular mechanisms (170). Consequently, findings from studies focused on persistent CRPS may not be applicable to the early stages of the disorder. Recent data also indicate significant symptom heterogeneity among early CRPS patients (171), further complicating treatment efforts. Although various behavioral treatments have been recommended, their efficacy is far from universal (26).

Much of the existing literature misleadingly suggests that there is little benefit to initiating behavioral treatment during the early stages of CRPS. On the contrary, some studies advocate for early psychological intervention. For example, Lima Pessôa and colleagues stated, "Psychological therapy is crucial, particularly for patients with prolonged symptoms, poor response to initial therapies, or suspected psychological comorbidities" (p. 5) (172). However, 8-year follow-up data from a prospective study suggest that early interventions to reduce anxiety may improve mobility and long-term pain outcomes (173). Similarly, a systematic review hypothesized that addressing pain-related fear and anxiety early in the disease course may prevent chronification (174).

Perhaps the strongest case for early behavioral intervention comes from a 2015 prospective study of patients with recent-onset CRPS (<12 weeks), who were followed for one year. The study found that lower baseline anxiety and pain-related fear predicted better outcomes, leading the authors to recommend investigating the impact of early cognitive behavioral therapy (CBT) in CRPS (175). Unfortunately, further studies in this area have not been conducted. A follow-up study by the same research group in 2016, though cross-sectional in nature, found that depression scores were associated with increased disability and work absenteeism. The authors suggested that early psychotherapy and pharmacotherapy might help disrupt this cycle (176).

The lack of specific guidance in current CRPS treatment guidelines may have contributed to underutilization of behavioral services. A study of clinical practice patterns revealed significant disparities in referrals for behavioral treatment between acute and chronic CRPS patients. Although the supporting literature remains limited, the existing evidence is strong enough to justify the earlier inclusion of behavioral therapies in CRPS treatment plans. Given the potential benefits, including reductions in pain, disability, and psychological distress, this approach merits further research and broader implementation.

9.0 Summary

While there is a clear clinical distinction between acute and chronic CRPS, the current literature does not sufficiently address these differences—particularly regarding diagnostic criteria for chronic CRPS, which this article seeks to clarify. In developing guidance for chronic CRPS, our objective was to enhance diagnostic specificity and improve clinical recognition of the chronic phase. Nonetheless, further research is essential to establish more precise diagnostic criteria and to investigate the mechanisms underlying the transition from acute to chronic CRPS. Advancing this line of research will be vital for improving both the accuracy of diagnosis and the effectiveness of management strategies, ensuring that patients receive timely and appropriate care.

10.0 Author Contributions

The article was designed by CG, MD, and LM. All authors contributed to the preparation of this article, reviewed and approved the content with the final version.

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