

Different Types of Pain in Complex Regional Pain Syndrome Require a Personalized Treatment Strategy

Thomas JP Mangnus , Maaïke Dirckx , Frank JPM Huygen 

Department of Anesthesiology, Center for Pain Medicine, Erasmus MC University Medical Center, Rotterdam, the Netherlands

Correspondence: Thomas JP Mangnus, Email t.mangnus@erasmusmc.nl

Abstract: Complex regional pain syndrome (CRPS) is a debilitating painful state of an extremity that can develop after trauma. CRPS is diagnosed by the new International Association for the Study of Pain (IASP) diagnostic criteria for CRPS. The syndrome is characterized by continuing regional pain with abnormal sensory, motor, sudomotor, vasomotor, edema, and/or trophic signs. The clinical presentation of CRPS can be very heterogeneous because CRPS is a multi-mechanism syndrome. Therefore, mechanism-based subgroups have been suggested to personalize treatment for CRPS. Additionally, the presentation of symptom pain may also be able to identify different subgroups of CRPS. In this review, the types of pain recognized by the IASP—nociceptive, neuropathic, and nociplastic pain—will be discussed as possible subgroups for CRPS. Each pain type should be identified in CRPS patients, with a thorough history taking, physical examination, and diagnostic tests or (novel) biomarkers to optimize treatment effectiveness. Over the course of the syndrome, patients with CRPS probably experience more than one distinct pain type. Therefore, pain specialists should be alert to not only adjust their treatment if underlying pathophysiologic mechanisms tend to change but also to personalize the treatment of the associated type of pain in the CRPS patient.

Keywords: CRPS, nociceptive pain, neuropathic pain, nociplastic pain, mixed pain, personalized medicine

Introduction

Complex Regional Pain Syndrome (CRPS) is a syndrome that is initiated by trauma to an extremity. This results in continuous regional pain that is disproportionate to the extent and healing of the trauma.¹ Besides continuous pain, patients have additional clinical signs such as disturbed blood flow or abnormal sudomotor activity, motor dysfunction, and trophic changes in the affected CRPS extremity. CRPS is a clinical diagnosis based on the new International Association for the Study of Pain (IASP) diagnostic criteria for CRPS,² that were validated in 2010 and adopted by the IASP in 2012. Nowadays, CRPS is considered a multi-mechanism syndrome, and the experienced continuous pain can be linked to mechanisms such as inflammation, vasomotor disturbances, and peripheral and central sensitization.^{3–6} The presentation of symptoms and signs of CRPS patients can be heterogeneous, because a combination of the underlying mechanisms may be more prominent. Rather than a one-size-fits-all treatment approach, pain specialists nowadays specifically determine the most prominent underlying mechanism(s). These mechanisms are targeted with different pharmacologic treatment categories in order to improve treatment efficacy.^{6–8}

To personalize the management of CRPS, several subgroups have been suggested. The subgroups CRPS type 1 (without nerve lesion) and CRPS type 2 (with nerve lesion) are recognized by the IASP.⁹ In addition, different subgroups have been proposed based on clinical presentation (warm/cold¹⁰), syndrome duration (early/persistent⁹), and underlying pathophysiological mechanisms (peripheral/central¹¹ and florid/sensory/vasomotor¹²). Recently, our research group suggested creating subgroups on the mechanisms that are targeted by the pharmacotherapeutic options for CRPS: 1) inflammation; 2) peripheral and central sensitization; 3) vasomotor disturbances and 4) motor disturbances.⁶ Unfortunately, there is no consensus yet on which classification of CRPS subtypes is best to use.⁹

Different presentations of symptom pain in CRPS can potentially also identify possible subgroups of CRPS that require a distinct treatment strategy. The IASP recognizes nociceptive (tissue damage), neuropathic (nerve injury), and nociplastic pain (sensitized nervous system) as distinct pain types driven by different mechanisms.¹³ In this article, we describe a strategy to phenotype CRPS patients based on the three types of chronic pain defined by the IASP because this classification affects the work-up and treatment decisions in chronic pain.¹³ Diagnostic tests and biomarkers are developed for nociceptive and neuropathic pain. However, especially to differentiate nociplastic pain, diagnostic tests have to be further developed.¹⁴

Hence, the aim of this narrative review is threefold: 1) to describe the types of pain in CRPS and link these pain types to pathophysiological underlying mechanisms in CRPS; 2) to explain how these pain types can be differentiated by history taking, physical examination, and diagnostic tests; 3) to illustrate how these pain types can be specifically targeted to optimize treatment effectiveness. Ultimately, a personalized treatment plan should be made for each CRPS patient. For this purpose, the differentiation of symptom pain in nociceptive, neuropathic, and nociplastic pain may be an additional helpful tool to optimize the management of CRPS.

Nociceptive Pain

According to the IASP, nociceptive pain is defined as “pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.”¹⁵ Nociceptive pain serves as a physiologic warning system as it helps sensing noxious stimuli in peripheral tissues.¹⁶ Noxious stimuli are detected by nociceptors, which are primary sensory neurons made up of both unmyelinated C-fibers and myelinated A δ -fibers.¹⁷ Specific receptors and transducer-proteins on the nociceptors cause a depolarization and generate an action-potential via the C-fibers or A δ -fibers to the central nervous system.¹⁷ When these fibers are activated, pronociceptive neuropeptides and inflammatory mediators are secreted.^{17,18} Inflammation is included in the category of nociceptive pain because trauma to tissue initiates an active inflammatory response and inflammatory mediators directly activate and sensitize nociceptors.^{18,19} Similarly, hypertonic states such as dystonia and contractures can directly activate and sensitize muscle nociceptors through mechanical stimuli and pain-producing substances after muscle damage.²⁰ Mechanical, thermal, and chemical stimuli reduce the threshold for neurons to generate action potentials and result in peripheral sensitization.^{17,18} Peripheral sensitization is a local, self-limiting protective mechanism that ends as inflammation diminishes and tissues recover.

Nociceptive Pain in CRPS

Nociceptive pain in CRPS can be the result of persistent inflammation. Increasing evidence suggests that persistent inflammation after trauma causes CRPS.^{10,21,22} Peripheral trauma initiates an immune cascade with cytokines,²³ and these cytokines sensitize peripheral nerve endings that release pronociceptive neuropeptides (eg substance P and calcitonin gene-related peptide).^{24,25} In the immune dysregulation of CRPS, both disturbances in the innate and adaptive immune system play a role.²⁶ Regarding the innate immune system, elevated levels of proinflammatory cytokines are detected in serum, cerebrospinal fluid and blister fluid.^{23,27,28} Dysregulation of the adaptive immune system is reflected by altered T-cell activity and higher prevalence of autoantibodies.^{29–31} Nociceptive pain can also be the result of motor disturbances caused by excitation of muscle nociceptors in, for instance, contractures and dystonia.³² Both can be characterized by fixed flexion postures of the fingers, wrist, or feet, but the mechanisms of these motor disturbances are different.³² Contractures are probably caused by proliferation of connective tissue cells, if the extremity is not moved properly during the early inflammatory phase of CRPS.³³ Dystonia is thought to be caused by spinal or supraspinal changes in the motor circuitry.³²

To differentiate nociceptive pain from other pain types, a combination of physical examination and inflammation-specific biomarkers should be used. Nociceptive pain is typically local and can for instance be triggered by specific movements and may be accompanied by local inflammatory signs (tumor, dolor, calor, rubor, and functio laesa). Although these inflammatory signs are informative, objective biomarkers are needed because, for instance, cold CRPS patients can still have active inflammation.³⁴ Therefore, biomarkers for detecting inflammation in CRPS are being studied.^{35,36} By contrast, physical examination is sufficient for detecting flexion postures. Contractures can be distinguished from dystonia by passive stretching of the affected digits. In dystonia, this should incite a contraction of the

stretched muscle implying stretch reflex hyperexcitability.³² This does not happen in contractures because the range of motion is impaired because of overstimulated fibroblast growth during acute inflammation.

In general, if nociceptive pain is suspected in the early phase of CRPS, pain medication from the World Health Organization (WHO) analgesic ladder can be used concurrently with active mobilization therapy.^{37,38} If inflammation is confirmed with an inflammation biomarker, specific immunomodulating drugs such as corticosteroids or bisphosphonates could be considered.^{6,39,40}

Neuropathic Pain

According to the IASP, the definition of neuropathic pain is “pain caused by a lesion or disease of the somatosensory nervous system.”^{15,41} The IASP notes that “Neuropathic pain is a clinical description which requires a demonstrable lesion or a disease that satisfies established neurological diagnostic criteria.”¹⁵ In 2016, an updated grading system for neuropathic pain was introduced categorizing neuropathic pain into three grades of certainty: 1) possible neuropathic pain; 2) probable neuropathic pain; 3) definite neuropathic pain.⁴² For possible neuropathic pain, there should be “history of a relevant neurological lesion or disease and the pain distribution should be neuroanatomically plausible.”⁴² Pain descriptors such as burning, electric shooting, numbness, and tingling may be suggestive of neuropathic pain but cannot be used alone for identifying neuropathic pain. Of note, several questionnaires such as the PainDETECT⁴³ and DN4 questionnaire⁴⁴ are developed because a combination of these descriptors can be distinctive for neuropathic pain versus nociceptive pain. Neuropathic pain is classified as probable if “the pain is associated with sensory signs in the same neuroanatomically plausible distribution during physical examination.”⁴² During physical examination, sensory loss is usually experienced and can be examined with light touch, vibration, pinprick, cold, or warm stimuli. Sensory gain is less specific for neuropathic pain, especially when it does not follow a neuroanatomical distribution. A more detailed profile of the sensory-discriminative dimensions of pain, including the function of A β -, A δ -, and C-fibers, can be obtained by quantitative sensory testing. Quantitative sensory testing is a set of tests that assesses pain thresholds and thermal, pressure, and mechanical sensation with special brushes, calibrated filaments, pinpricks, pressure algometry, and electrical stimulation.⁴⁵ Neuropathic pain is definite if “diagnostic testing confirmed a lesion or disease of the somatosensory nervous system that explains the pain.”⁴² Diagnostic tests include magnetic resonance imaging (MRI), electromyography, heat and laser evoked potentials, and skin biopsies for small fiber neuropathy.⁴²

Neuropathic Pain in CRPS

CRPS can be categorized as CRPS type 1 and CRPS type 2. In CRPS type 1, there is no verified nerve lesion, excluding CRPS type 1 from neuropathic pain. Approximately 90% of CRPS patients are categorized as CRPS type 1.⁴⁶ In CRPS type 2, there is a demonstrable nerve lesion, thus fulfilling the definition of neuropathic pain. Knowledge of trauma that causes CRPS type 2 increased because of experience from soldiers who encountered injuries with clear nerve lesions from blasts and gunshots.⁴⁷ In these cases, nerve lesions could be detected by electromyography or MRI and CRPS type 2 can be diagnosed. However, if the grading system by Finnerup et al is used,⁴² CRPS type 2 may fail to qualify for neuropathic pain because the glove- or stocking-like distribution of CRPS has no clear neuroanatomically plausible distribution.⁴⁸

Interestingly, small nerve lesions were also detected in some CRPS type 1 patients without severe trauma. In 1998, van der Laan et al studied amputated CRPS legs and were the first to show histopathologic degeneration of C-fibers in 4 out of 8 sural nerves.⁴⁹ In addition, skin biopsies were used of 18 CRPS patients to investigate the innervation density of CRPS-affected extremities.⁵⁰ In the CRPS-affected extremities, C-fibers and A δ -fiber density were reduced by 29% compared to control sites. Furthermore, skin samples of two CRPS-affected amputated limbs showed a decrease in epidermal, sweat gland, and vascular innervation and a reduction in dermal innervation by C- and A δ -fibers was reported.⁵¹ Because of these findings, Oaklander and Fields hypothesized that dysfunction of small fibers was causal to the onset of CRPS, as many symptoms and signs of CRPS can be related to small fiber neuropathy.⁴⁶ However, the most recent skin biopsy study in CRPS showed that only a subset of 20% of 43 CRPS patients had changes in skin innervation.⁵² Because small fiber neuropathy is only seen in a subset of CRPS type 1 patients,⁵² small fiber neuropathy is probably the consequence of the syndrome activity and not causal to CRPS type 1.⁵

Small fiber neuropathy is of clinical importance because a decrease in small fibers after trauma can change neighboring fibers to a state with reduced depolarization thresholds and ectopic firing.⁴⁶ Reduced thresholds and increased firing in the peripheral nervous system can trigger central sensitization. It is also believed that catecholamines can stimulate upregulated adrenergic receptors in damaged or regenerating nociceptive fibers and result in local pain.⁵³ Furthermore, neuropeptides can be released from damaged nociceptive C-fibers and induce vasodilation, sweating, recruitment of local immune cells, and allodynia and hyperalgesia.²⁵ This condition is called peripheral neurogenic inflammation and is implicated, alongside neuroinflammation, as a source of inflammation linked to the nervous system in CRPS.³⁵ Neuroinflammation refers to inflammation in the nervous system and can be initiated by enhanced neuronal activity of primary afferent nerve fibers or higher-order neurons that activate microglia and release proinflammatory mediators.⁵⁴

Unfortunately, small fiber neuropathy cannot be detected by electromyography or MRI, and invasive skin biopsies that can detect small fiber neuropathy are not regularly conducted. Therefore, neuropathic pain is underdiagnosed and specific treatment for neuropathic pain may be falsely left out of the treatment plan. A solution could be to implement quantitative sensory testing in clinical practice to detect small fiber neuropathy. If a nerve lesion is detected or the CRPS patient is highly suspected for having neuropathic pain by history taking, physical examination, and neuropathic pain questionnaires, it seems suitable to start with an anticonvulsant or antidepressant.^{6,55}

Nociplastic Pain

Nociplastic pain was introduced in 2016 to categorize chronic pain patients without any evidence of tissue damage or neuropathy.⁵⁶ Nociplastic pain is defined by the IASP as “pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.”¹⁵ Although the underlying mechanisms of nociplastic pain are not completely understood, it is suggested that in the nervous system, the processing of painful stimuli is amplified or the inhibition of painful stimuli is decreased.¹⁴ The nervous system becomes hypersensitive, which results in, for instance, a wider spread of pain than would be expected from tissue or nerve damage. Furthermore, symptoms may also include central changes such as fatigue, sleep, memory and mood problems.¹⁴ Although nociplastic pain is not a synonym for the neurophysiological term central sensitization, central sensitization is probably dominating underlying mechanisms of nociplastic pain.⁵⁶ Central sensitization was introduced to illustrate increased excitability and synaptic efficacy of the neurons in nociceptive pathways after ongoing noxious input.⁵⁷ The induction and maintenance of central sensitization was shown to be dependent on the N-Methyl-D-aspartic acid (NMDA) receptor and the neurotransmitter glutamate⁵⁸ and is also driven by neuroinflammation.⁵⁴

Clinical criteria and a grading system are formulated for nociplastic pain.⁵⁹ To classify pain as possible nociplastic pain, the following conditions must be met: 1) pain duration should be more than 3 months; 2) pain must be regional, rather than discrete, in distribution; 3) pain cannot entirely be explained by nociceptive or neuropathic pain mechanisms and 4) clinical signs of pain hypersensitivity are present in the region of pain.⁵⁹ Hypersensitivity should be objectified by static or dynamic mechanical allodynia, heat or cold allodynia or painful after-sensations reported after testing allodynia. For probable nociplastic pain, a history of pain hypersensitivity in the region of pain and defined comorbidities such as sensitivity to light or sound, sleep disturbance, fatigue, or cognitive problems have to be present.⁵⁹ However, these comorbidities are still under debate.⁶⁰

Several tools exist to help distinguish nociplastic pain. A body map such as the Michigan Body Map can be used to visualize body areas with allodynia.⁶¹ Another tool is the Central Sensitization Inventory, which is a questionnaire that gives an indication of central sensitization and has focus on the comorbidities according to the IASP criteria for nociplastic pain.⁶² Other diagnostic tests are still mostly used in the research setting. For instance, quantitative sensory testing and conditioned pain modulation are used to examine amplified pain processing and decreased inhibition.^{63,64} An example of facilitative activity is temporal summation, which is an enhanced spinal neuron response after repetitive noxious C-fiber stimulation and thus a marker for central sensitization.⁶³ Conditioned pain stimulation examines the endogenous pain inhibitory pathway.⁶³ This test is conducted by applying a painful stimulus that is followed by a second painful stimulus and at the same time a conditioning stimulus such as immersion of a limb in cold water. Furthermore, brain imaging showed structural brain changes due to neuroplasticity, increased glutamatergic activity or decreased gamma-aminobutyric acid (GABA)-ergic activity in pain regions, glial cell involvement in neuroinflammation, increased connectivity in pain brain regions, and decreased activity in descending analgesic pathways.¹⁴

Nociplastic Pain in CRPS

An indication for nociplastic pain in CRPS is that allodynia and hyperalgesia are not necessarily restricted to the affected CRPS extremity.^{65–70} This is illustrated by, for instance, hemi-lateral distribution of allodynia and hyperalgesia in CRPS patients.^{66,69} Evidence that central sensitization contributes to the pathophysiology of CRPS, is that temporal summation is increased in the affected CRPS extremity.^{65,71} In addition, CRPS patients with an extended pain pattern had a more prominent temporal summation in the CRPS extremity and were associated with more disturbance of body perception.⁶⁵ The wider spread of allodynia and hyperalgesia in CRPS could be the result of increased excitability in the brainstem or higher brain centers and a deficient endogenous pain inhibition system.^{66,72} To visualize the wider spread of allodynia, the Michigan Body Map is suggested to be added as a clinical outcome parameter in CRPS studies.⁷³

Several imaging studies have studied the structural, functional, and chemical changes of the brain in CRPS patients. For instance, a reduced representation of the affected CRPS extremity and an increased representation of the contralateral unaffected extremity are shown.^{74,75} These changes in representation can return to normal in patients that respond to their treatment.^{76,77} Functional changes are shown by increased activity in pain regions such as the somatosensory cortex, insula, frontal cortex, and anterior cingulate cortex during pinprick hyperalgesia and an increased resting state activity and connectivity is reported between the thalamus and somatosensory cortex.^{78–80} In addition, impaired endogenous pain inhibitory pathways and the reorganization of the somatosensory cortex correlated with pain severity.^{81–83} Unexpectedly, a recent magnetic resonance spectroscopy study showed that CRPS was not associated with altered GABA or glutamate concentrations.⁸⁴ Furthermore, two positron emission tomography studies confirmed neuroinflammation in CRPS and this underlines the facilitation of central sensitization in CRPS.^{85,86}

Regarding pharmacotherapeutic treatment, pain medication from the WHO analgesic ladder is less effective for nociplastic pain than for nociceptive pain. Opioids should be avoided because of the risk of tolerance, induced hyperalgesia and the known mortality and morbidity of chronic opioid use.⁷ Drugs that target central sensitization may be used for nociplastic pain such as gabapentin and intravenous ketamine.^{6,87,88}

Mixed Pain

Some CRPS patients may experience substantial overlap between nociceptive, neuropathic, and nociplastic pain. Although mixed pain is not recognized by the IASP, Freynhagen et al defined mixed pain as follows: “mixed pain is a complex overlap of the different known pain types (nociceptive, neuropathic, nociplastic) in any combination, acting simultaneously and/or concurrently to cause pain in the same body area.”⁸⁹ The term mixed pain was introduced to help clinicians with the challenge of the management of mixed pain states. However, the authors question whether mixed pain is simply a combination of nociceptive, neuropathic, or nociplastic pain, or whether mixed pain is a new clinical entity on its own.⁸⁹ An example of mixed pain could, for instance, be a patient with spinal disc herniation. When a spinal disc starts to bulge out and the nerve route is hampered by the mass of the herniation and the local inflammatory process, we call this nociceptive pain. The nerve route can get impinged and damaged, which will result in neuropathic pain. When these processes occur simultaneously—disc bulging, inflammation, and the nerve impingement—the pain can be characterized as mixed pain.

At present, there is no diagnostic test for mixed pain, but it can be pragmatically diagnosed by history taking, physical examination and by using the diagnostic criteria for nociceptive, neuropathic, and nociplastic pain.⁹⁰ Freynhagen et al developed nine key questions to help identify the most dominant pain type of the patient.⁹⁰ Physicians must be aware that mixed pain states are common, but we acknowledge that the phenotype of mixed pain is challenging.

Mixed Pain in CRPS

In CRPS, combinations of nociceptive, neuropathic, and nociplastic are possible because CRPS is a multi-mechanism syndrome. For instance, pain caused by ischemia in CRPS is probably a combination of nociceptive and neuropathic pain because hypoperfusion can cause tissue damage and nerve lesions. Hypoperfusion in CRPS can be the result of sympathetic dysregulation and endothelial dysfunction.⁹¹ In early CRPS, an altered sympathetic function was shown to result in a reduction in catecholamine release.⁹² As a response to the reduction of catecholamines, upregulated

adrenoreceptors, and an enhanced binding affinity of catecholamines to adrenoreceptors resulted in vasoconstriction in persistent CRPS.^{93,94} Furthermore, endothelial dysfunction was shown by increased levels of the endogenous vasoconstrictor endothelin-1 and a decreased level of the vasodilator nitric oxide, which was shown in blister fluid of CRPS patients.⁹⁵ Vasoconstriction can cause a cascade of hypoxia, acidosis, and inflammation and can result in nociceptive pain.⁹⁶ Vasoconstriction can also cause endoneurial hypoperfusion and neuropathic pain.⁹⁷ Especially, the small distal nerves are vulnerable because they rely on the perfusion of a few capillaries. In chronic post-ischemia pain models in rodents, small nerve fibers spontaneously discharge and show intraepidermal degeneration.⁹⁸ This corresponds with the observed small fiber degeneration and decreased nerve density seen in CRPS.⁵⁰

Another example of mixed pain in CRPS is the inflammation induced overlap of nociceptive, neuropathic, and nociplastic pain.⁹⁹ Nociceptive inflammatory pain is triggered by peripheral trauma and tissue damage in CRPS. Inflammation may damage small nerve fibers and can induce neuropathic pain. In addition, partial peripheral nerve lesions may cause a release of neuropeptides like nerve growth factor, substance P, and calcitonin-gene related peptide.²⁴ These neuropeptides released from damaged C-fibers recruit immune cells and can initiate neurogenic inflammation.^{24,25} Furthermore, in neuroinflammation, glial cells are activated in the dorsal root ganglia and spinal cord and drive central sensitization and nociplastic pain.⁵⁴

Altogether, it is crucial to detect mixed pain in CRPS and to consider early treatment, with a multimodal treatment plan targeting nociceptive, neuropathic, and nociplastic pain.⁹⁰ For example, ischemic pain may be targeted with a vasodilator or a sympathetic blockade to treat vasoconstriction and hypoxia.^{6,100} In addition, an anticonvulsant can be prescribed for neuropathic pain.^{6,55} For different types of inflammation, emerging treatments have been developed that specifically target neurogenic inflammation or neuroinflammation,^{99,101} but these therapies have not yet been studied in CRPS.

Expert Opinion

According to the new IASP diagnostic criteria for CRPS, all patients with CRPS experience continuous debilitating pain.² Our research group suggests that symptom pain in CRPS should not be generalized into one distinct pain type but should be differentiated into nociceptive, neuropathic, and nociplastic pain (see [Table 1](#) for definitions/criteria). CRPS is a multi-mechanism syndrome, and over time CRPS patients have probably suffered nociceptive, neuropathic, and

Table 1 Definition and Grading System of Nociceptive, Neuropathic, and Nociplastic Pain

	Nociceptive Pain	Neuropathic Pain	Nociplastic Pain
Definition	Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors ¹⁵ Pain associated with active inflammation falls into the category of nociceptive pain ¹⁹	Pain caused by a lesion or disease of the somatosensory nervous system ^{15,41}	Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain ^{15,56}
Grading system: Possible		<ul style="list-style-type: none"> • History of relevant neurological lesion or disease • Pain distribution neuroanatomically plausible⁴² 	<ul style="list-style-type: none"> • Pain >3 months • Regional rather than discrete • No nociceptive or neuropathic pain • Evoked pain hypersensitivity phenomena⁵⁹
Grading system: Probable		Sensory signs in neuroanatomically plausible distribution during physical examination ⁴²	History of pain hypersensitivity and comorbidities ⁵⁹
Grading system: Definite		Confirmed lesion or disease of the somatosensory nervous system by a diagnostic test ⁴²	

nociceptive pain. The pain experienced by CRPS patients could be seen as a continuum and typically starts with nociceptive pain because of peripheral tissue damage and persistent inflammation after trauma. Trauma can either directly result in a nerve lesion or it can initiate inflammation that may result in small fiber neuropathy and neurogenic inflammation. Ongoing pain facilitation through peripheral sensitization and neuroinflammation may result in central sensitization. When there is no clear evidence of tissue damage or nerve damage causing the activation of nociceptors, the experienced pain can be the result of a hypersensitive pain system. This pain state can be characterized as nociplastic pain. When this continuum of pain types— from nociceptive, neuropathic to nociplastic pain— in CRPS exists, it seems logical that mixed pain pictures are present and that initiating treatment as early as possible is mandatory to break the vicious circle. The pain types in CRPS and the linked underlying pathophysiological mechanisms are displayed in Figure 1.

For personalized medicine, pain types should be differentiated from each other by history taking, physical examination, and (novel) diagnostic tests (see Table 2). Our research group encourages implementing mechanism-specific biomarkers for each pain type in CRPS research. Nociceptive pain due to inflammation may be supported with inflammation signs during physical examination and with specific inflammation biomarkers.^{35,36} For nociceptive pain, our research group uses the serum soluble interleukin-2 receptor (sIL-2R) level to determine the inflammation involved

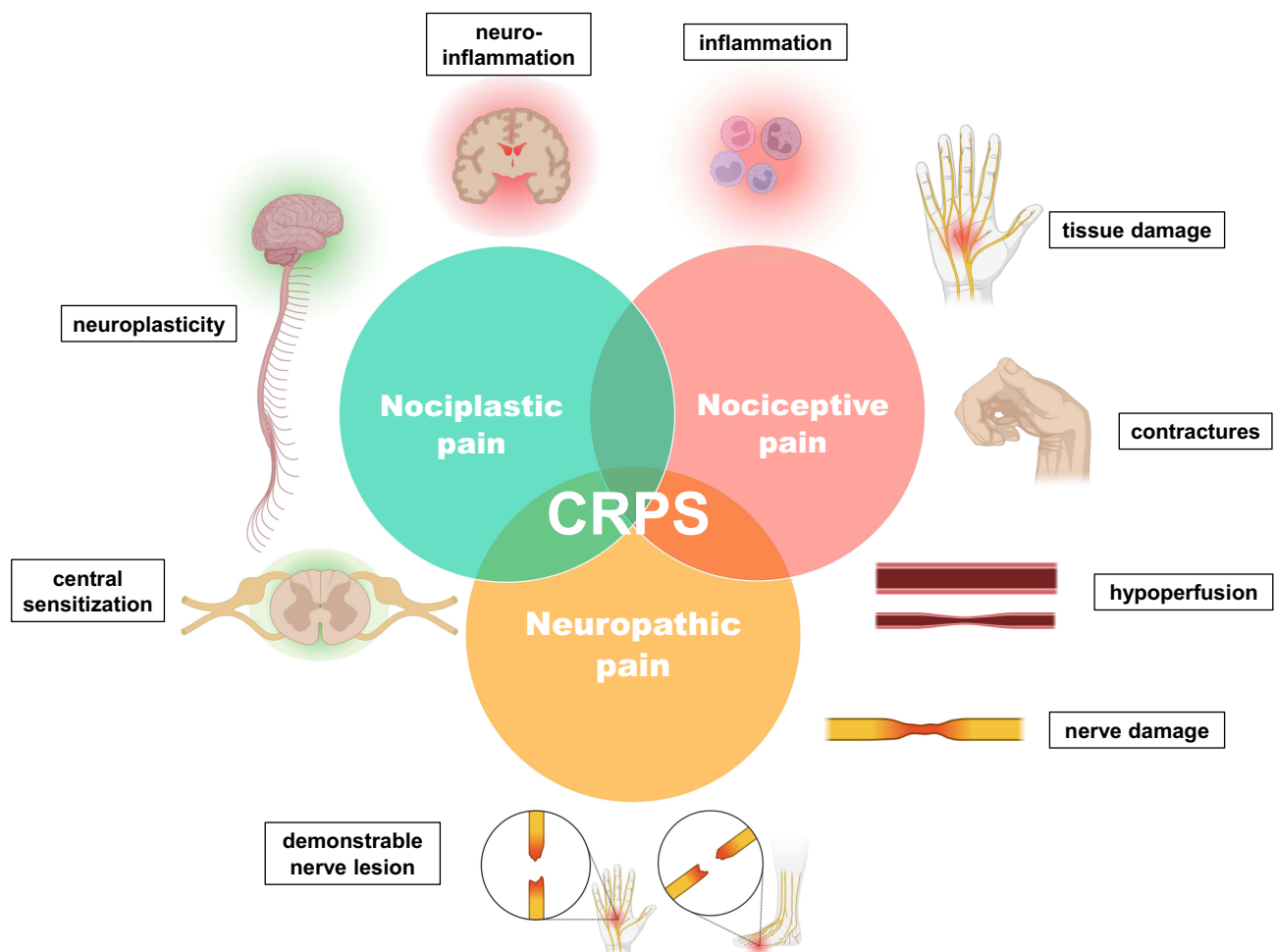


Figure 1 Pain types in Complex Regional Pain Syndrome.

Notes: Pain types experienced by CRPS patients can be differentiated in the pain types that are recognized for chronic pain by the International Association for the Study of Pain: nociceptive, neuropathic and nociplastic pain. The most prominent pain type should be targeted to optimize the treatment effectiveness. Nociceptive, neuropathic and nociplastic pain are linked to underlying pathophysiological mechanisms that contribute to Complex Regional Pain Syndrome.

Table 2 Underlying Mechanisms, Diagnostic Instruments, and Treatments That Can Be Linked to Nociceptive, Neuropathic, and Nociplastic Pain in CRPS

Types of Pain Recognized by IASP	Evidence in CRPS	Diagnostic Instruments	Treatment
Nociceptive pain	Inflammation ^{23,26}	Physical examination: tumor, dolor, calor, rubor and functio laesa	<ul style="list-style-type: none"> Physical therapy and rehabilitation^{7,104} Psychological treatment^{7,105}
		Inflammation biomarkers ³⁵	<ul style="list-style-type: none"> World Health Organization analgesic ladder medication³⁸ Immunomodulating drugs^{39,40}
	Contractures ³²	Physical examination: fixed flexion postures	<ul style="list-style-type: none"> Physical therapy and rehabilitation^{7,104} Psychological treatment^{7,105}
	Dystonia ³²	Physical examination: fixed flexion postures. Passive stretching of the affected digits should incite a contraction of the stretched muscle implying stretch reflex hyperexcitability ³²	<ul style="list-style-type: none"> Physical therapy and rehabilitation^{7,104} Anti-spasmolytics³² Psychological treatment^{7,105}
Neuropathic pain	<ul style="list-style-type: none"> Major nerve lesions 	<ul style="list-style-type: none"> Physical examination: pain in neuroanatomical distribution PainDETECT⁴³ and DN4 questionnaire⁴⁴ Electromyography, magnetic resonance imaging 	<ul style="list-style-type: none"> Physical therapy and rehabilitation^{7,104} Psychological treatment^{7,105} Antidepressants or anticonvulsants⁵⁵ Neurostimulation^{106–108}
	<ul style="list-style-type: none"> Small fiber neuropathy⁵⁰ 	<ul style="list-style-type: none"> Quantitative sensory testing, skin biopsy 	
Nociplastic pain	Central sensitization ^{65,66}	<ul style="list-style-type: none"> Physical examination: more widespread allodynia/hyperalgesia Michigan Body Map⁶¹ Quantitative sensory testing, temporal summation^{65,71} Conditioned pain modulation⁷² 	<ul style="list-style-type: none"> Physical therapy and rehabilitation^{7,104} Psychological treatment^{7,105} Antidepressants or anticonvulsants⁵⁵ Intravenous ketamine⁸⁸ Neurostimulation^{106–108}

with T-cell activity.¹⁰² The serum sIL-2R level was shown to be elevated in CRPS and may be used to monitor T-cell mediated inflammatory activity in CRPS.^{29,103} Our research group suggests that inflammation should be treated in an early stage with immunomodulating drugs.^{6,103} If inflammation is adequately treated, the damage caused by the inflammatory process will be diminished. This will probably result in a lower CRPS severity due to a loss of contribution of central sensitization and (vaso)motor disturbances to the syndrome severity.^{6,103}

Neuropathic pain due to peripheral nerve lesions can be diagnosed using electromyography or MRI. Small fiber neuropathy can be detected with skin biopsies or quantitative sensory testing. Furthermore, neuropathic pain can be supported by dermatomal spreading and questionnaires. A typical treatment for neuropathic pain is the prescription of anticonvulsants or antidepressants, which may also be used in nociplastic pain. Nociplastic pain can be supported by clinical pain spreading expressed in a body map and enhanced temporal summation or impaired conditioned pain modulation. Quantitative sensory testing and conditioned pain modulation may be useful to predict treatment response. For instance, in diabetic neuropathy, a deficient pain modulation system measured by conditioned pain modulation, predicted that duloxetine was more effective.¹⁰⁹ It is suggested that duloxetine boosted the endogenous descending inhibitory pathway. In addition, higher temporal summation predicted a positive treatment response for ketamine and pregabalin in neuropathic pain patients and patients with chronic pancreatitis.^{110,111} Currently, an ongoing RCT on ketamine treatment for CRPS uses quantitative sensory testing and conditioned pain modulation to predict treatment of response in certain subgroups of CRPS.¹¹² Other parameters, such as quality of life, mood, and functionality can be assessed using the COMPACT questionnaires.¹¹³

Some interventions can be beneficial for multiple pain types in CRPS such as patient education, psychological interventions, and physical therapy. These therapies should be considered as part of a comprehensive interdisciplinary treatment program. Patient education should highlight a biopsychosocial model that addresses physical exercise, fatigue, stress reduction, and cognitive difficulties.¹³ Regarding psychological interventions for CRPS, there are only few small studies testing their efficacy for CRPS.⁷ Given the efficacy of cognitive-behavioral therapy for chronic pain in general,^{13,105} its utility for the management of CRPS might also be expected.⁷ Furthermore, clinical experience indicates that mobilization and active physiotherapy play an important role in functional restoration,⁷ but the evidence about the effect of physical therapy on CRPS is still very uncertain.¹⁰⁴ Our research groups recommend that the management of CRPS should be based on biopsychosocial model and psychological support and physical therapy should be integrated as early as possible and continued during the course of the syndrome (Table 2). Additional pharmacological treatment should target the most prominent pain type at clinical presentation and target specific underlying pathophysiological mechanisms of CRPS.⁶ When patients do not respond to conservative and pharmacological treatment, neurostimulation can be considered.^{106–108} Neurostimulation may target multiple mechanisms including neuropathic pain, ischemic pain, and inflammation.^{114–116} We suggest that neurostimulation also affects nociplastic pain, as it is described that neurostimulation inhibits pain transmission and neuron hyperactivity in the dorsal horn and activates descending modulatory pathways that suggest supraspinal involvement.^{116,117} A consensus-based e-health tool can help physicians in selecting CRPS patients for neurostimulation.¹¹⁸

Conclusion

Pain experienced by CRPS patients should be differentiated between nociceptive, neuropathic, and nociplastic pain to optimize the management of CRPS. Pain should be seen as a continuum in which nociceptive, neuropathic, and nociplastic pain can shift over the course of the syndrome due to a change in underlying pathophysiological mechanisms of CRPS. Precision medicine—by subgrouping CRPS patients based on history taking, physical examination, and diagnostic testing on the most prominent pain type—may tailor a more specific and effective treatment for individual CRPS patients.

Abbreviations

COMPACT questionnaires, Core Outcome Measurement set for complex regional Pain syndrome Clinical sTudies;¹¹³ CRPS, Complex Regional Pain Syndrome; DN4, douleur neuropathique 4 questionnaire;⁴⁴ GABA, gamma-aminobutyric acid; IASP, International Association for the Study of Pain; MRI, magnetic resonance imaging; NMDA, N-Methyl-D-aspartic acid; PainDETECT, pain detect questionnaire;⁴³ WHO analgesic ladder, World Health Organization analgesic ladder.³⁸

Funding

No funding for this research has been received.

Disclosure

Prof. Dr. FJPM Huygen reports personal fees for educational work and grants from ABBOTT, Saluda, and Boston Scientific outside the submitted work. Prof. Dr. Frank JPM Huygen also has patents P121304EP00 and P121304NL00 pending to DRG stimulation for spasticity. The authors report no other conflicts of interest in this work.

References

- Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. *Lancet*. 1993;342(8878):1012–1016. doi:10.1016/0140-6736(93)92877-V
- Harden RN, Bruhl S, Perez RSGM, et al. Validation of proposed diagnostic criteria (the “Budapest Criteria”) for complex regional pain syndrome. *Pain*. 2010;150(2):268–274. doi:10.1016/j.pain.2010.04.030
- Gierthmühlen J, Binder A, Baron R. Mechanism-based treatment in complex regional pain syndromes. *Nat Rev Neurol*. 2014;10(9):518–528. doi:10.1038/nrneurol.2014.140
- Birklein F, Schlereth T. Complex regional pain syndrome—significant progress in understanding. *Pain*. 2015;156:S94–S103. doi:10.1097/01.j.pain.0000460344.54470.20
- Bruhl S. Complex regional pain syndrome. *BMJ*. 2015;351:h2730. doi:10.1136/bmj.h2730
- Mangnus TJP, Bharwani KD, Dirckx M, Huygen FJPM. From a symptom-based to a mechanism-based pharmacotherapeutic treatment in complex regional pain syndrome. *Drugs*. 2022;82:511–531. doi:10.1007/s40265-022-01685-4
- Harden RN, McCabe CS, Goebel A, et al. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 5th edition. *Pain Med*. 2022;23(Supplement_1):S1–S53. doi:10.1093/pm/pnac046
- Ferraro MC, Cashin AG, Wand BM, et al. Interventions for treating pain and disability in adults with complex regional pain syndrome- an overview of systematic reviews. *Cochrane Database Syst Rev*. 2023;6. doi:10.1002/14651858.CD009416.pub3
- Goebel A, Birklein F, Brunner F, et al. The Valencia consensus-based adaptation of the IASP complex regional pain syndrome diagnostic criteria. *Pain*. 2021;162(9):2346–2348. doi:10.1097/j.pain.0000000000002245
- Bruhl S, Maihofner C, Stanton-Hicks M, et al. Complex regional pain syndrome: evidence for warm and cold subtypes in a large prospective clinical sample. *Pain*. 2016;157(8):1674–1681. doi:10.1097/j.pain.0000000000000569
- Dimova V, Herrnberger MS, Escolano-Lozano F, et al. Clinical phenotypes and classification algorithm for complex regional pain syndrome. *Neurology*. 2020;94(4):e357–e367. doi:10.1212/WNL.0000000000008736
- Bruhl S, Harden RN, Galer BS, Saltz S, Backonja M, Stanton-Hicks M. Complex regional pain syndrome: are there distinct subtypes and sequential stages of the syndrome? *Pain*. 2002;95(1–2):119–124. doi:10.1016/S0304-3959(01)00387-6
- Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. *Lancet*. 2021;397(10289):2082–2097. doi:10.1016/S0140-6736(21)00393-7
- Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Hauser W. Nociceptive pain: towards an understanding of prevalent pain conditions. *Lancet*. 2021;397(10289):2098–2110. doi:10.1016/S0140-6736(21)00392-5
- Loeser JD. IASP terminology. International Association For The Study Of Pain; 2022. Available from: <https://www.iasp-pain.org/resources/terminology/>. Accessed December 2, 2023.
- Woolf CJ. What is this thing called pain? *J Clin Invest*. 2010;120(11):3742–3744. doi:10.1172/JCI45178
- Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. *Cell*. 2009;139(2):267–284. doi:10.1016/j.cell.2009.09.028
- Pinho-Ribeiro FA, Verri WA Jr, Chiu IM. Nociceptor sensory neuron–immune interactions in pain and inflammation. *Trends Immunol*. 2017;38(1):5–19. doi:10.1016/j.it.2016.10.001
- Loeser JD, Treede R-D. The Kyoto protocol of IASP basic pain terminology. *Pain*. 2008;137(3):473–477. doi:10.1016/j.pain.2008.04.025
- Mense S, Masi AT. Increased muscle tone as a cause of muscle pain. In: Mense S, Gerwin RD, editors. *Muscle Pain: Understanding the Mechanisms*. Springer Berlin Heidelberg; 2010:207–249.
- Birklein F, Ajit SK, Goebel A, Perez R, Sommer C. Complex regional pain syndrome - phenotypic characteristics and potential biomarkers. *Nat Rev Neurol*. 2018;14(5):272–284. doi:10.1038/nrneurol.2018.20
- Lenz M, Uceyler N, Frettlöh J, et al. Local cytokine changes in complex regional pain syndrome type I (CRPS I) resolve after 6 months. *Pain*. 2013;154(10):2142–2149. doi:10.1016/j.pain.2013.06.039
- Huygen FJ, De Bruijn AG, De Bruin MT, Groeneweg JG, Klein J, Zijlstra FJ. Evidence for local inflammation in complex regional pain syndrome type 1. *Mediators Inflamm*. 2002;11(1):47–51. doi:10.1080/09629350210307
- Birklein F, Schmelz M. Neuropeptides, neurogenic inflammation and complex regional pain syndrome (CRPS). *Neurosci Lett*. 2008;437(3):199–202. doi:10.1016/j.neulet.2008.03.081
- Littlejohn G. Neurogenic neuroinflammation in fibromyalgia and complex regional pain syndrome. *Nat Rev Rheumatol*. 2015;11(11):639–648. doi:10.1038/nrrheum.2015.100
- David Clark J, Tawfik VL, Tajerian M, Kingery WS. Autoinflammatory and autoimmune contributions to complex regional pain syndrome. *Mol Pain*. 2018;14:1744806918799127. doi:10.1177/1744806918799127
- Alexander GM, Peterlin BL, Perreault MJ, Grothusen JR, Schwartzman RJ. Changes in plasma cytokines and their soluble receptors in complex regional pain syndrome. *J Pain*. 2012;13(1):10–20. doi:10.1016/j.jpain.2011.10.003
- Alexander GM, van Rijn MA, van Hilten JJ, Perreault MJ, Schwartzman RJ. Changes in cerebrospinal fluid levels of pro-inflammatory cytokines in CRPS. *Pain*. 2005;116(3):213–219. doi:10.1016/j.pain.2005.04.013

29. Bharwani KD, Dirckx M, Stronks DL, Dik WA, Schreurs MWJ, Huygen F. Elevated plasma levels of sIL-2R in complex regional pain syndrome: a pathogenic role for T-lymphocytes? *Mediators Inflamm.* 2017;2017:2764261. doi:10.1155/2017/2764261
30. Heyn J, Azad SC, Luchting B. Altered regulation of the T-cell system in patients with CRPS. *Inflamm Res.* 2019;68(1):1–6. doi:10.1007/s00011-018-1182-3
31. Dirckx M, Schreurs MW, de Mos M, Stronks DL, Huygen FJ. The prevalence of autoantibodies in complex regional pain syndrome type I. *Mediators Inflamm.* 2015;2015:718201. doi:10.1155/2015/718201
32. van Hilten JJ. Movement disorders in complex regional pain syndrome. *Pain Med.* 2010;11(8):1274–1277. doi:10.1111/j.1526-4637.2010.00916.x
33. Birklein F, Dimova V. Complex regional pain syndrome—up-to-date. *Pain Rep.* 2017;2(6). doi:10.1097/PR.0000000000000624
34. Dirckx M, Stronks DL, van Bodegraven-Hof EA, Wesseldijk F, Groeneweg JG, Huygen FJ. Inflammation in cold complex regional pain syndrome. *Acta Anaesthesiol Scand.* 2015;59(6):733–739. doi:10.1111/aas.12465
35. Bharwani KD, Dik WA, Dirckx M, Huygen F. Highlighting the role of biomarkers of inflammation in the diagnosis and management of complex regional pain syndrome. *Mol Diagn Ther.* 2019;23(5):615–626. doi:10.1007/s40291-019-00417-x
36. Russo MA, Georgius P, Pires AS, et al. Novel immune biomarkers in complex regional pain syndrome. *J Neuroimmunol.* 2020;347:577330. doi:10.1016/j.jneuroim.2020.577330
37. Perez R, Geertzen JHB, Dijkstra PU, Dirckx M, Van Eijs F, Frölke JP. *Updated Guidelines Complex Regional Pain Syndrome Type I.* Utrecht, Netherlands: The Dutch Pain Society; 2014.
38. Jadad AR, Browman GP. The WHO analgesic ladder for cancer pain management: stepping up the quality of its evaluation. *JAMA.* 1995;274(23):1870–1873. doi:10.1001/jama.1995.03530230056031
39. Chevreau M, Romand X, Gaudin P, Juvin R, Baillet A. Bisphosphonates for treatment of complex regional pain syndrome type I: a systematic literature review and meta-analysis of randomized controlled trials versus placebo. *Joint Bone Spine.* 2017;84(4):393–399. doi:10.1016/j.jbspin.2017.03.009
40. van den Berg C, de Bree PN, Huygen FJPM, Tiemensma J. Glucocorticoid treatment in patients with complex regional pain syndrome: a systematic review. *Eur J Pain.* 2022;26(10):2009–2035. doi:10.1002/ejp.2025
41. Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain. *Neurology.* 2008;70(18):1630. doi:10.1212/01.wnl.0000282763.29778.59
42. Finnerup NB, Haroutounian S, Kamerman P, et al. Neuropathic pain: an updated grading system for research and clinical practice. *Pain.* 2016;157(8):1599. doi:10.1097/j.pain.0000000000000492
43. Freynhagen R, Baron R, Gockel U, Tölle TR. Pain DETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin.* 2006;22(10):1911–1920. doi:10.1185/030079906X132488
44. Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain.* 2005;114(1–2):29–36. doi:10.1016/j.pain.2004.12.010
45. Rolke R, Magerl W, Campbell KA, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain.* 2006;10(1):77–88. doi:10.1016/j.ejpain.2005.02.003
46. Oaklander AL, Fields HL. Is reflex sympathetic dystrophy/complex regional pain syndrome type I a small-fiber neuropathy? *Ann Neurol.* 2009;65(6):629–638. doi:10.1002/ana.21692
47. Nelson CN, Glauser G, Kessler RA, Jack MM. Causalgia: a military pain syndrome. *Neurosurg Focus.* 2022;53(3):E9. doi:10.3171/2022.6.FOCUS22270
48. Naleschinski D, Baron R. Complex regional pain syndrome type I: neuropathic or not? *Curr Pain Headache Rep.* 2010;14(3):196–202. doi:10.1007/s11916-010-0115-9
49. van der Laan L, ter Laak HJ, Gabreels-Festen A, Gabreels F, Goris RJ. Complex regional pain syndrome type I (RSD): pathology of skeletal muscle and peripheral nerve. *Neurology.* 1998;51(1):20–25. doi:10.1212/WNL.51.1.20
50. Oaklander AL, Rissmiller JG, Gelman LB, Zheng L, Chang Y, Gott R. Evidence of focal small-fiber axonal degeneration in complex regional pain syndrome-I (reflex sympathetic dystrophy). *Pain.* 2006;120(3):235–243. doi:10.1016/j.pain.2005.09.036
51. Albrecht PJ, Hines S, Eisenberg E, et al. Pathologic alterations of cutaneous innervation and vasculature in affected limbs from patients with complex regional pain syndrome. *Pain.* 2006;120(3):244–266. doi:10.1016/j.pain.2005.10.035
52. Kharkar S, Venkatesh YS, Grothusen JR, Rojas L, Schwartzman RJ. Skin biopsy in complex regional pain syndrome: case series and literature review. *Pain Physician.* 2012;15(3):255–266.
53. Finch PM, Drummond ES, Dawson LF, Phillips JK, Drummond PD. Up-regulation of cutaneous α 1-adrenoceptors in complex regional pain syndrome type I. *Pain Med.* 2014;15(11):1945–1956. doi:10.1111/pme.12548
54. Ji RR, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and central sensitization in chronic and widespread pain. *Anesthesiology.* 2018;129(2):343–366. doi:10.1097/ALN.0000000000002130
55. Javed S, Abdi S. Use of anticonvulsants and antidepressants for treatment of complex regional pain syndrome: a literature review. *Pain Manag.* 2021;11(2):189–199. doi:10.2217/pmt-2020-0060
56. Kosek E, Cohen M, Baron R, et al. Do we need a third mechanistic descriptor for chronic pain states? *Pain.* 2016;157(7):1382–1386. doi:10.1097/j.pain.0000000000000507
57. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain.* 2011;152(3 Suppl):S2–S15. doi:10.1016/j.pain.2010.09.030
58. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain.* 1991;44(3):293–299. doi:10.1016/0304-3959(91)90100-C
59. Kosek E, Clauw D, Nijs J, et al. Chronic nociplastic pain affecting the musculoskeletal system: clinical criteria and grading system. *Pain.* 2021;162(11):2629–2634. doi:10.1097/j.pain.0000000000002324
60. Cohen ML. Proposed clinical criteria for nociplastic pain in the musculoskeletal system are flawed. *Pain.* 2022;163(4):e604. doi:10.1097/j.pain.0000000000002505
61. Brummett CM, Bakshi RR, Goesling J, et al. Preliminary validation of the Michigan body map. *Pain.* 2016;157(6):1205–1212. doi:10.1097/j.pain.0000000000000506

62. Mayer TG, Neblett R, Cohen H, et al. The development and psychometric validation of the central sensitization inventory. *Pain Pract.* 2012;12(4):276–285. doi:10.1111/j.1533-2500.2011.00493.x
63. Arendt-Nielsen L, Morlion B, Perrot S, et al. Assessment and manifestation of central sensitisation across different chronic pain conditions. *Eur J Pain.* 2018;22(2):216–241. doi:10.1002/ejp.1140
64. Treede R-D, Hoheisel U, Wang D, Magerl W. Central sensitization: clinical utility of a physiological concept for the International Statistical Classification of Diseases and Related Health Problems and for nociplastic pain. *Pain.* 2022;163(S1). doi:10.1097/j.pain.0000000000002740
65. De Schoenmacker I, Mollo A, Scheuren PS, et al. Central sensitization in CRPS patients with widespread pain: a cross-sectional study. *Pain Med.* 2023;24:974–984. doi:10.1093/pm/pnad040
66. Drummond PD, Finch PM, Birklein F, Stanton-Hicks M, Knudsen LF. Hemisensory disturbances in patients with complex regional pain syndrome. *Pain.* 2018;159(9):1824–1832. doi:10.1097/j.pain.0000000000001280
67. Reimer M, Rempel T, Diedrichs C, Baron R, Gierthmühlen J. Sensitization of the nociceptive system in complex regional pain syndrome. *PLoS One.* 2016;11(5):e0154553. doi:10.1371/journal.pone.0154553
68. Drummond PD, Finch PM. Sensory changes in the forehead of patients with complex regional pain syndrome. *Pain.* 2006;123(1–2):83–89. doi:10.1016/j.pain.2006.02.013
69. Knudsen L, Finch PM, Drummond PD. The specificity and mechanisms of hemilateral sensory disturbances in complex regional pain syndrome. *J Pain.* 2011;12(9):985–990. doi:10.1016/j.jpain.2011.03.001
70. van Rooijen DE, Marinus J, van Hilten JJ. Muscle hyperalgesia is widespread in patients with complex regional pain syndrome. *Pain.* 2013;154(12):2745–2749. doi:10.1016/j.pain.2013.08.004
71. Sieweke N, Birklein F, Riedl B, Neundörfer B, Handwerker HO. Patterns of hyperalgesia in complex regional pain syndrome. *Pain.* 1999;80(1–2):171–177. doi:10.1016/S0304-3959(98)00200-0
72. Seifert F, Kiefer G, DeCol R, Schmelz M, Maihöfner C. Differential endogenous pain modulation in complex-regional pain syndrome. *Brain.* 2009;132(3):788–800. doi:10.1093/brain/awn346
73. Llewellyn A, Buckle L, Grieve S, et al. Delphi study to define core clinical outcomes for inclusion in a complex regional pain syndrome international research registry and data bank. *Pain.* 2023;164(3):543–554. doi:10.1097/j.pain.0000000000002729
74. Di Pietro F, McAuley JH, Parkitny L, et al. Primary somatosensory cortex function in complex regional pain syndrome: a systematic review and meta-analysis. *J Pain.* 2013;14(10):1001–1018. doi:10.1016/j.jpain.2013.04.001
75. Di Pietro F, Stanton TR, Moseley GL, Lotze M, McAuley JH. Interhemispheric somatosensory differences in chronic pain reflect abnormality of the healthy side. *Hum Brain Mapp.* 2015;36(2):508–518. doi:10.1002/hbm.22643
76. Pleger B, Tegenthoff M, Ragert P, et al. Sensorimotor returning in complex regional pain syndrome parallels pain reduction. *Ann Neurol.* 2005;57(3):425–429. doi:10.1002/ana.20394
77. Maihöfner C, Handwerker HO, Neundörfer B, Birklein F. Cortical reorganization during recovery from complex regional pain syndrome. *Neurology.* 2004;63(4):693–701. doi:10.1212/01.WNL.0000134661.46658.B0
78. Maihöfner C, Forster C, Birklein F, Neundörfer B, Handwerker HO. Brain processing during mechanical hyperalgesia in complex regional pain syndrome: a functional MRI study. *Pain.* 2005;114(1):93–103. doi:10.1016/j.pain.2004.12.001
79. Di Pietro F, Lee B, Henderson LA. Altered resting activity patterns and connectivity in individuals with complex regional pain syndrome. *Hum Brain Mapp.* 2020;41(13):3781–3793. doi:10.1002/hbm.25087
80. Schwenkreis P, Maier C, Tegenthoff M. Functional imaging of central nervous system involvement in complex regional pain syndrome. *Am J Neuroradiol.* 2009;30(7):1279–1284. doi:10.3174/ajnr.A1630
81. Klega A, Eberle T, Buchholz HG, et al. Central opioidergic neurotransmission in complex regional pain syndrome. *Neurology.* 2010;75(2):129–136. doi:10.1212/WNL.0b013e3181e7ca2e
82. Freund W, Wunderlich AP, Stuber G, et al. The role of periaqueductal gray and cingulate cortex during suppression of pain in complex regional pain syndrome. *Clin J Pain.* 2011;27(9):796–804. doi:10.1097/AJP.0b013e31821d9063
83. Maihöfner C, Handwerker HO, Neundörfer B, Birklein F. Patterns of cortical reorganization in complex regional pain syndrome. *Neurology.* 2003;61(12):1707–1715. doi:10.1212/01.WNL.0000098939.02752.8E
84. Lee B, Henderson LA, Rae CD, Di Pietro F. CRPS is not associated with altered sensorimotor cortex GABA or glutamate. *Eneuro.* 2020;7(1). doi:10.1523/ENEURO.0389-19.2020
85. Jeon SY, Seo S, Lee JS, et al. [11C]-(R)-PK11195 positron emission tomography in patients with complex regional pain syndrome: a pilot study. *Medicine (Baltimore).* 2017;96(1):e5735. doi:10.1097/MD.0000000000005735
86. Jung Y-H, Kim H, Jeon SY, et al. Brain metabolites and peripheral biomarkers associated with neuroinflammation in complex regional pain syndrome using [11C]-(R)-PK11195 positron emission tomography and magnetic resonance spectroscopy: a pilot study. *Pain Med.* 2019;20(3):504–514. doi:10.1093/pm/pny111
87. van de Vusse AC, Stomp-van den Berg SG, Kessels AH, Weber WE. Randomised controlled trial of gabapentin in complex regional pain syndrome type 1 [ISRCTN84121379]. *BMC Neurol.* 2004;4(1):13. doi:10.1186/1471-2377-4-13
88. Zhao J, Wang Y, Wang D. The effect of ketamine infusion in the treatment of complex regional pain syndrome: a systemic review and meta-analysis. *Curr Pain Headache Rep.* 2018;22(2):12. doi:10.1007/s11916-018-0664-x
89. Freynhagen R, Parada HA, Calderon-Ospina CA, et al. Current understanding of the mixed pain concept: a brief narrative review. *Curr Med Res Opin.* 2019;35(6):1011–1018. doi:10.1080/03007995.2018.1552042
90. Freynhagen R, Rey R, Argoff C. When to consider “mixed pain”? The right questions can make a difference! *Curr Med Res Opin.* 2020;36(12):2037–2046. doi:10.1080/03007995.2020.1832058
91. Kortekaas MC, Niehof SP, Stolker RJ, Huygen FJ. Pathophysiological mechanisms involved in vasomotor disturbances in complex regional pain syndrome and implications for therapy: a review. *Pain Pract.* 2016;16(7):905–914. doi:10.1111/papr.12403
92. Wasner G, Heckmann K, Maier C, Baron R. Vascular abnormalities in acute reflex sympathetic dystrophy (CRPS I): complete inhibition of sympathetic nerve activity with recovery. *Arch Neurol.* 1999;56(5):613–620. doi:10.1001/archneur.56.5.613
93. Drummond ES, Dawson LF, Finch PM, Bennett GJ, Drummond PD. Increased expression of cutaneous α 1-adrenoceptors after chronic constriction injury in rats. *J Pain.* 2014;15(2):188–196. doi:10.1016/j.jpain.2013.10.010

94. Arnold JM, Teasell RW, MacLeod AP, Brown JE, Carruthers SG. Increased venous alpha-adrenoceptor responsiveness in patients with reflex sympathetic dystrophy. *Ann Intern Med.* 1993;118(8):619–621. doi:10.7326/0003-4819-118-8-199304150-00008
95. Groeneweg JG, Huygen FJ, Heijmans-Antonissen C, Niehof S, Zijlstra FJ. Increased endothelin-1 and diminished nitric oxide levels in blister fluids of patients with intermediate cold type complex regional pain syndrome type 1. *BMC Musculoskelet Disord.* 2006;7(1):91. doi:10.1186/1471-2474-7-91
96. Koban M, Leis S, Schultze-Mosgau S, Birklein F. Tissue hypoxia in complex regional pain syndrome. *Pain.* 2003;104(1–2):149–157. doi:10.1016/S0304-3959(02)00484-0
97. Coderre TJ, Bennett GJ. A hypothesis for the cause of complex regional pain syndrome-type I (reflex sympathetic dystrophy): pain due to deep-tissue microvascular pathology. *Pain Med.* 2010;11(8):1224–1238. doi:10.1111/j.1526-4637.2010.00911.x
98. Laferrière A, Millecamps M, Xanthos DN, et al. Cutaneous tactile allodynia associated with microvascular dysfunction in muscle. *Mol Pain.* 2008;4:1744–8069-4–49. doi:10.1186/1744-8069-4-49
99. Matsuda M, Huh Y, Ji -R-R. Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. *J Anesth.* 2019;33(1):131–139. doi:10.1007/s00540-018-2579-4
100. Cepeda MS, Lau J, Carr DB. Defining the therapeutic role of local anesthetic sympathetic blockade in complex regional pain syndrome: a narrative and systematic review. *Clin J Pain.* 2002;18(4). doi:10.1097/00002508-200207000-00002
101. Seidel MF, Hügle T, Morlion B, et al. Neurogenic inflammation as a novel treatment target for chronic pain syndromes. *Exp Neurol.* 2022;356:114108. doi:10.1016/j.expneurol.2022.114108
102. Dik WA, Heron M. Clinical significance of soluble interleukin-2 receptor measurement in immune-mediated diseases. *Neth J Med.* 2020;78(5):220–231.
103. Mangnus TJP, Bharwani KD, Dik WA, Baart SJ, Dirckx M, Huygen FJPM. Is there an association between serum soluble interleukin-2 receptor levels and syndrome severity in persistent complex regional pain syndrome? *Pain Med.* 2023;24:1234–1243. doi:10.1093/pm/pnad081
104. Smart KM, Ferraro MC, Wand BM, O'Connell NE. Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II. *Cochrane Database Syst Rev.* 2022;5(5):CD010853. doi:10.1002/14651858.CD010853.pub3
105. de C Williams AC, Fisher E, Hearn L, Eccleston C. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev.* 2020;8:1.
106. Kemler MA, Barendse GAM, van Kleef M, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med.* 2000;343(9):618–624. doi:10.1056/NEJM200008313430904
107. Deer TR, Levy RM, Kramer J, et al. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. *Pain.* 2017;158(4):669–681. doi:10.1097/j.pain.0000000000000814
108. Geurts JW, Smits H, Kemler MA, Brunner F, Kessels AG, van Kleef M. Spinal cord stimulation for complex regional pain syndrome type I: a prospective cohort study with long-term follow-up. *Neuromodulation.* 2013;16(6):523–9; discussion 529. doi:10.1111/ner.12024
109. Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. *Pain.* 2012;153(6):1193–1198. doi:10.1016/j.pain.2012.02.021
110. Olesen SS, Graversen C, Bouwense SAW, van Goor H, Wilder-Smith OHG, Drewes AM. Quantitative sensory testing predicts pregabalin efficacy in painful chronic pancreatitis. *PLoS One.* 2013;8(3):e57963. doi:10.1371/journal.pone.0057963
111. Bosma RL, Cheng JC, Rogachov A, et al. Brain dynamics and temporal summation of pain predicts neuropathic pain relief from ketamine infusion. *Anesthesiology.* 2018;129(5):1015–1024. doi:10.1097/ALN.0000000000002417
112. Mangnus TJP, Dirckx M, Bharwani KD, et al. Intermittent versus continuous esketamine infusions for long-term pain modulation in complex regional pain syndrome: protocol of a randomized controlled non-inferiority study (KetCRPS-2). *BMC Musculoskelet Disord.* 2023;24(1):239. doi:10.1186/s12891-023-06258-4
113. Grieve S, Perez R, Birklein F, et al. Recommendations for a first core outcome measurement set for complex regional Pain syndrome Clinical sTudies (COMPACT). *Pain.* 2017;158(6):1083–1090. doi:10.1097/j.pain.0000000000000866
114. Kriek N, Schreurs MWJ, Groeneweg JG, et al. Spinal cord stimulation in patients with complex regional pain syndrome: a possible target for immunomodulation? *Neuromodulation.* 2018;21(1):77–86. doi:10.1111/ner.12704
115. Linderth B, Foreman RD. Physiology of spinal cord stimulation: review and update. *Neuromodulation.* 1999;2(3):150–164. doi:10.1046/j.1525-1403.1999.00150.x
116. Knotkova H, Hamani C, Sivanesan E, et al. Neuromodulation for chronic pain. *Lancet.* 2021;397(10289):2111–2124. doi:10.1016/S0140-6736(21)00794-7
117. Sivanesan E, Maher DP, Raja SN, Linderth B, Guan Y. Supraspinal mechanisms of spinal cord stimulation for modulation of pain: five decades of research and prospects for the future. *Anesthesiology.* 2019;130(4):651–665. doi:10.1097/ALN.0000000000002353
118. Thomson S, Huygen F, Prangnell S, et al. Appropriate referral and selection of patients with chronic pain for spinal cord stimulation: European consensus recommendations and e-health tool. *Eur J Pain.* 2020;24(6):1169–1181. doi:10.1002/ejp.1562