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Complex Regional Pain Syndrome Fact Sheet

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What is complex regional pain syndrome?

Complex regional pain syndrome (CRPS) is a chronic (lasting greater than six months) pain condition that most often affects one limb (arm, leg, hand, or foot) usually after an injury. CRPS is believed to be caused by damage to, or malfunction of, the peripheral and central nervous systems. The central nervous system is composed of the brain and spinal cord; the peripheral nervous system involves nerve signaling from the brain and spinal cord to the rest of the body. CRPS is characterized by prolonged or excessive pain and changes in skin color, temperature, and/or swelling in the affected area.

CRPS is divided into two types: CRPS-I and CRPS-II. Individuals without a confirmed nerve injury are classified as having CRPS-I (previously known as reflex sympathetic dystrophy syndrome). CRPS-II (previously known as causalgia) is when there is an associated, confirmed nerve injury. As some research has identified evidence of nerve

injury in CRPS-I, it is unclear if these disorders will always be divided into two types. Nonetheless, the treatment is similar.

CRPS symptoms vary in severity and duration, although some cases are mild and eventually go away. In more severe cases, individuals may not recover and may have long-term disability.

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Who can get CRPS?

Although it is more common in women, CRPS can occur in anyone at any age, with a peak at age 40. CRPS is rare in the elderly. Very few children under age 10 and almost no children under age 5 are affected.

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What are the symptoms of CRPS?

The key symptom is prolonged severe pain that may be constant. It has been described as “burning,” “pins and needles” sensation, or as if someone were squeezing the affected limb. The pain may spread to the entire arm or leg, even though the injury might have only involved a finger or toe. In rare cases, pain can sometimes even travel to the opposite extremity. There is often increased sensitivity in the affected area, known as *allodynia*, in which normal contact with the skin is experienced as very painful.

People with CRPS also experience changes in skin temperature, skin color, or swelling of the affected limb. This is due to abnormal microcirculation caused by damage to the nerves controlling blood flow and temperature. As a result, an affected arm or leg may feel warmer or cooler compared to the opposite limb. The skin on the affected limb may change color, becoming blotchy, blue, purple, pale, or red.

Other common features of CRPS include:

- changes in skin texture on the affected area; it may appear shiny and thin
- abnormal sweating pattern in the affected area or surrounding areas
- changes in nail and hair growth patterns
- stiffness in affected joints
- problems coordinating muscle movement, with decreased ability to move the affected body part
- abnormal movement in the affected limb, most often fixed abnormal posture (called *dystonia*) but also tremors in or jerking of the limb.

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What causes CRPS?

It is unclear why some individuals develop CRPS while others with similar trauma do not. In more than 90 percent of cases, the condition is triggered by a clear history of trauma or injury. The most common triggers are fractures, sprains/strains, soft tissue injury (such as burns, cuts, or bruises), limb immobilization (such as being in a cast), surgery, or even minor medical procedures such as needle stick. CRPS represents an abnormal response that magnifies the effects of the injury. Some people respond excessively to a trigger that causes no problem for other people, such as what is observed in people who have food allergies.

Peripheral nerve abnormalities found in individuals with CRPS usually involve the small unmyelinated and thinly myelinated sensory nerve fibers (axons) that carry pain messages and signals to blood vessels. (Myelin is a mixture of proteins and fat-like substances that surround and insulate some nerve fibers.) Because small fibers in the nerves communicate with blood vessels, injuries to the fibers may trigger the many different symptoms of CRPS. Molecules secreted from the ends of hyperactive small nerve fibers are thought to contribute to inflammation and blood vessel abnormalities. These peripheral nerve abnormalities in turn trigger damage in the spinal cord and brain.

Blood vessels in the affected limb may dilate (open wider) or leak fluid into the surrounding tissue, causing red, swollen skin. The dilation and constriction of small blood vessels is controlled by small nerve fiber axons as well as chemical messengers in the blood. The underlying muscles and deeper tissues can become starved of oxygen and nutrients, which causes muscle and joint pain as well as damage. The blood vessels may over-constrict (clamp down), causing old, white, or bluish skin.

CRPS also affects the immune system. High levels of inflammatory chemicals (cytokines) have been found in the tissues of people with CRPS. These contribute to the redness, swelling, and warmth reported by many patients. CRPS is more common in individuals with other inflammatory and autoimmune conditions such as asthma.

Limited data suggest that CRPS also may be influenced by genetics. Rare family clusters of CRPS have been reported. Familial CRPS may be more severe with earlier onset, greater dystonia, and more than one limb being affected.

Occasionally CRPS develops without any known injury. In these cases, an infection, a blood vessel problem, or entrapment of the nerves may have caused an internal injury. A physician will perform a thorough examination in order to identify a cause.

In many cases, CRPS results from a variety of causes. In such instances, treatments are directed at all of the contributing factors.

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How is CRPS diagnosed?

Currently there is no specific test that can confirm CRPS. Its diagnosis is based on a person's medical history, and signs and symptoms that match the definition. Since other

conditions can cause similar symptoms, careful examination is important. As most people improve gradually over time, the diagnosis may be more difficult later in the course of the disorder.

Testing also may be used to help rule out other conditions, such as arthritis, Lyme disease, generalized muscle diseases, a clotted vein, or small fiber polyneuropathies, because these require different treatment. The distinguishing feature of CRPS is that of an injury to the affected area. Such individuals should be carefully assessed so that an alternative treatable disorder is not overlooked.

Magnetic resonance imaging or triple-phase bone scans may be requested to help confirm a diagnosis. While CRPS is often associated with excess bone resorption, a process in which certain cells break down the bone and release calcium into the blood, this finding may be observed in other illnesses as well.

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What is the prognosis?

The outcome of CRPS is highly variable. Younger persons, children, and teenagers tend to have better outcomes. While older people can have good outcomes, there are some individuals who experience severe pain and disability despite treatment. Anecdotal evidence suggests early treatment, particularly rehabilitation, is helpful in limiting the disorder, a concept that has not yet been proven in clinical studies. More research is needed to understand the causes of CRPS, how it progresses, and the role of early treatment.

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How is CRPS treated?

The following therapies are often used:

Rehabilitation and physical therapy. An exercise program to keep the painful limb or body part moving can improve blood flow and lessen the circulatory symptoms. Additionally, exercise can help improve the affected limb's flexibility, strength, and function.

Rehabilitating the affected limb also can help to prevent or reverse the secondary brain changes that are associated with chronic pain. Occupational therapy can help the individual learn new ways to work and perform daily tasks.

Psychotherapy. CRPS and other painful and disabling conditions often are associated with profound psychological symptoms for affected individuals and their families. People with CRPS may develop depression, anxiety, or post-traumatic stress disorder, all of which heighten the perception of pain and make rehabilitation efforts more difficult.

Treating these secondary conditions is important for helping people cope and recover from CRPS.

Medications. Several different classes of medication have been reported to be effective

for CRPS, particularly when used early in the course of the disease. However, no drug is approved by the U.S. Food and Drug Administration specifically for CRPS, and no single drug or combination of drugs is guaranteed to be effective in every person. Drugs to treat CRPS include:

- bisphosphonates, such as high dose alendronate or intravenous pamidronate
- non-steroidal anti-inflammatory drugs to treat moderate pain, including over-the-counter aspirin, ibuprofen, and naproxen
- corticosteroids that treat inflammation/swelling and edema, such as prednisolone and methylprednisolone (used mostly in the early stages of CRPS)
- drugs initially developed to treat seizures or depression but now shown to be effective for neuropathic pain, such as gabapentin, pregabalin, amitriptyline, nortriptyline, and duloxetine
- botulinum toxin injections
- opioids such as oxycodone, morphine, hydrocodone, and fentanyl. These drugs must be prescribed and monitored under close supervision of a physician, as these drugs may be addictive.
- N-methyl-D-aspartate (NMDA) receptor antagonists such as dextromethorphan and ketamine, and
- topical local anesthetic creams and patches such as lidocaine.

All drugs or combination of drugs can have various side effects such as drowsiness, dizziness, increased heartbeat, and impaired memory. Inform a healthcare professional of any changes once drug therapy begins.

Sympathetic nerve block. Some individuals report temporary pain relief from sympathetic nerve blocks, but there is no published evidence of long-term benefit. Sympathetic blocks involve injecting an anesthetic next to the spine to directly block the activity of sympathetic nerves and improve blood flow.

Surgical sympathectomy. The use of this operation that destroys some of the nerves is controversial. Some experts think it is unwarranted and makes CRPS worse, whereas others report a favorable outcome. Sympathectomy should be used only in individuals whose pain is dramatically relieved (although temporarily) by sympathetic nerve blocks.

Spinal cord stimulation. Placing stimulating electrodes through a needle into the spine near the spinal cord provides a tingling sensation in the painful area. Electrodes may be placed temporarily for a few days in order to assess whether stimulation is likely to be helpful. Minor surgery is required to implant all the parts of the stimulator, battery, and electrodes under the skin on the torso. Once implanted, the stimulator can be turned on and off, and adjusted using an external controller. Approximately 25 percent of individuals develop equipment problems that may require additional surgeries.

Other types of neural stimulation. Neurostimulation can be delivered at other locations

along the pain pathway, not only at the spinal cord. These include near injured nerves (peripheral nerve stimulators), outside the membranes of the brain (motor cortex stimulation with dural electrodes), and within the parts of the brain that control pain (deep brain stimulation). A recent option involves the use of magnetic currents applied externally to the brain (known as repetitive Transcranial Magnetic Stimulation, or rTMS). A similar method that uses transcranial direct electrical stimulation is also being investigated. These stimulation methods have the advantage of being non-invasive, with the disadvantage that repeated treatment sessions are needed.

Intrathecal drug pumps. These devices pump pain-relieving medications directly into the fluid that bathes the spinal cord, typically opioids, local anesthetic agents, clonidine, and baclofen. The advantage is that pain-signaling targets in the spinal cord can be reached using doses far lower than those required for oral administration, which decreases side effects and increases drug effectiveness. There are no studies that show benefit specifically for CRPS.

Emerging treatments for CRPS include:

- *Intravenous immunoglobulin (IVIG).* Researchers in Great Britain report low-dose IVIG reduced pain intensity in a small trial of 13 patients with CRPS for 6 to 30 months who did not respond well to other treatments. Those who received IVIG had a greater decrease in pain scores than those receiving saline during the following 14 days after infusion.
- *Ketamine.* Investigators are using low doses of ketamine—a strong anesthetic—given intravenously for several days to either reduce substantially or eliminate the chronic pain of CRPS. In certain clinical settings, ketamine has been shown to be useful in treating pain that does not respond well to other treatments.
- *Graded Motor imagery.* Several studies have demonstrated the benefits of graded motor imagery therapy for CRPS pain. Individuals do mental exercises including identifying left and right painful body parts while looking into a mirror and visualizing moving those painful body parts without actually moving them.

Several alternative therapies have been used to treat other painful conditions. Options include behavior modification, acupuncture, relaxation techniques (such as biofeedback, progressive muscle relaxation, and guided motion therapy), and chiropractic treatment.

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What research is currently being done on CRPS?

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. The NINDS is part of the National Institutes of Health (NIH), the leading supporter of biomedical research in the world.

NINDS-supported scientists are studying new approaches to treat CRPS and to intervene more aggressively to limit the symptoms and disability associated with the syndrome.

Other NIH institutes also support research on CRPS and other painful conditions.

Previous research has shown that CRPS-related inflammation is caused by the body's own immune response. Researchers hope to better understand how CRPS develops by studying immune system activation and peripheral nerve signaling using an animal model of the disorder. The animal model was developed to mimic certain CRPS-like features following fracture or limb surgery, by activating certain molecules involved in the immune system process.

Limb trauma, such as a fracture, followed by immobilization in a cast, is the most common cause of CRPS. By studying an animal model, researchers hope to better understand the neuroinflammatory basis of CRPS in order to identify the relevant inflammatory signaling pathways that lead to the development of post-traumatic CRPS. They also will examine inflammatory effects of cast immobilization and exercise on the development of pain behaviors and CRPS symptoms.

Peripheral nerve injury and subsequent regeneration often lead to a variety of sensory changes. Researchers hope to identify specific cellular and molecular changes in sensory neurons following peripheral nerve injury to better understand the processes that underlie neuroplasticity (the brain's ability to reorganize or form new nerve connections and pathways following injury or death of nerve cells). Identifying these mechanisms could provide targets for new drug therapies that could improve recovery following regeneration.

Children and adolescents with CRPS generally have a better prognosis than adults, which may provide insights into mechanisms that can prevent chronic pain. Scientists are studying children with CRPS given that their brains are more adaptable through a mechanism known as neuroplasticity. Scientists hope to use these discoveries in order to develop more effective therapies for CRPS.

NINDS-funded scientists continue to investigate how inflammation and the release of adenosine triphosphate (ATP) may induce abnormal connections and signaling between sympathetic and sensory nerve cells in chronic pain conditions such as CRPS. (ATP is a molecule involved with energy production within cells that can also act as a neurotransmitter. Neurotransmitters are chemicals used by nervous system cells to communicate with one another.) A better understanding of changes in nerve connections following peripheral nerve injury may offer greater insight to pain and lead to new treatments.

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Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain


Resources and Information Network (BRAIN) at:

BRAIN


P.O. Box 5801
Bethesda, MD 20824
800-352-9424
www.ninds.nih.gov

Information also is available from the following organizations:

[Reflex Sympathetic Dystrophy Syndrome Association \(RSDSA\)](#) 

P.O. Box 502
99 Cherry Street
Milford, CT 06460
203-877-3790
877-662-7737
<http://rsds.org> 

[International Research Foundation for RSD/CRPS](#) 

1910 East Busch Boulevard
Tampa, FL 33612
813-907-2312
www.rsdfoundation.org 

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[Complex Regional Pain Syndrome Brochure](#) (*pdf, 529 kb*)

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Prepared by:

Office of Communications and Public Liaison
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Bethesda, MD 20892

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