



# Complex Regional Pain Syndrome

U.S. DEPARTMENT OF HEALTH  
AND HUMAN SERVICES  
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## What is complex regional pain syndrome?

**C**omplex regional pain syndrome (CRPS) is a broad term describing excess and prolonged pain and inflammation that follows an injury to an arm or leg. CRPS has acute (recent, short-term) and chronic (lasting greater than six months) forms. CRPS used to be known as reflex sympathetic dystrophy (RSD) and causalgia. People with CRPS have changing combinations of spontaneous pain or excess pain that is much greater than normal following something as mild as a touch. Other symptoms include changes in skin color, temperature, and/or swelling on the arm or leg below the site of injury. Although CRPS improves over time, eventually going away in most people, the rare severe or prolonged cases are profoundly disabling.

Most CRPS illnesses are caused by improper function of the peripheral C-fiber nerve fibers that carry pain messages to the brain. Their excess firing also triggers inflammation designed to promote healing and rest after injury. In some people the nerve injury is obvious but in others a specialist may be needed to locate and treat the injury.

- Historically, people were classified as having CRPS-I (previously called RSD) when there was uncertainty about the exact nerve injured.
- After a doctor identifies the specific nerve injured, people are diagnosed as having CRPS-II (previously known as causalgia). Many people labeled with CRPS-II have more extensive injuries that also damage nerves going to muscles (motor nerves) to cause weakness and muscle shrinkage in certain areas, making it easier to identify. Motor nerves control the movement of muscles under conscious control, such as those used for walking, grasping things, or talking.

Since both types of CRPS have identical symptoms, both may be caused by nerve injury, although nerve injuries in CRPS I are typically more subtle and go unnoticed.

CRPS is more common in women but can occur in anyone at any age, with a peak around age 40. It is rare in the elderly, who have less inflammation after injury, and in young children who heal so quickly and completely.

The outcome of CRPS is highly variable:

- Most illnesses are mild and recover over months to a few years as the injured nerve regrows. If this doesn't happen, symptoms can linger to cause long-term disability.
- The outcome depends not only on the severity of the original injury, but also on the person's underlying general and nerve health. Younger people, children, and teenagers almost always recover, as

do older adults with good circulation and nutrition. Smoking is a major impediment to nerve regeneration as is diabetes and previous chemotherapy. Removing barriers to healing increases the chance and speed of recovery.

- Rare individuals experience prolonged severe pain and disability despite treatment. This may indicate underlying separate problems interfering with healing, requiring additional testing and treatment.

Because of the varied symptoms, the fact that symptoms may change over time, and the difficulty finding a positive cause in some cases, CRPS is hard to treat. There is no treatment that rapidly cures CRPS.

## What are typical symptoms of CRPS?

**M**ost individuals do not have all of these symptoms, and the number of symptoms typically reduces during recovery.

- **Unprovoked or spontaneous pain that can be constant or fluctuate with activity.** Some say it feels like a “burning” or “pins and needles” sensation, or as if the affected limb was being squeezed. Over time, if nerves remain chronically inflamed, pain can spread to involve most or all of the arm or leg, even if the originally affected area was smaller. In rare cases, pain and other symptoms occur in a matching location on the opposite limb. This “mirror pain” is thought to reflect secondary involvement of spinal cord neurons (nerve cells). Mirror pain is less severe and resolves as the injured nerves recover.

**Excess or prolonged pain after use or contact.** There is often increased sensitivity in the affected area, known as *allodynia*, in which light touch, normal physical contact, and use is felt by the person to be very painful. Some notice severe or prolonged pain after a mildly painful stimulus such as a pin prick, known as *hyperalgesia*.

- **Changes in skin temperature, skin color, or swelling of the affected limb.** The injured arm or leg may feel warmer or cooler than the opposite limb. Skin on the affected limb may change color, becoming blotchy, blue, purple, gray, pale, or red. These skin symptoms typically fluctuate as they indicate abnormal blood flow in the area. Opening and closing the small blood vessels under the skin is controlled by the C-nerve fibers that are injured in CRPS.
- **Changes in skin texture.** Over time, insufficient delivery of oxygen and nutrients can cause skin in the affected limb to change texture. In some cases, it becomes shiny and thin, in others thick and scaly. Avoiding contact or washing painful skin contributes to this build-up.
- **Abnormal sweating and nail and hair growth.** On the affected limb, hair and nails may grow abnormally rapidly, or not at all, and people may notice patches of profuse sweating or no sweating. All are under neural control and influenced by local blood circulation.
- **Stiffness in affected joints.** This common problem is that reduced movement leads to reduced flexibility of tendons and

ligaments. Tight ligaments or tendons sometimes rub or pinch nerves to provide an internal cause of CRPS in people who do not have external injuries.

- **Wasting away or excess bone growth.** In CRPS-affected limbs, bones that receive signals from the damaged nerves rarely become affected. These abnormalities are often visible on X-rays or other imaging where they help specialists pinpoint the location of nerve damage and identify best treatments. Rough or enlarged areas of bone, such as after a poorly healed fracture or from a bone cyst, can irritate passing nerves and initiate or prolong CRPS.
- **Impaired muscle strength and movement.** Most people with CRPS do not have direct injury to the nerve fibers that control the muscles coordinating muscle movement. However, most report reduced ability to move the affected body part. This is usually due to pain and abnormalities in the sensory input that helps coordinate movements. Also, the excess inflammation and poor circulation are not healthy for muscles. Rare patients report abnormal movement in the affected limbs, fixed abnormal posture called dystonia, and tremors in or jerking. These can reflect secondary spread of disturbed neural activity to the brain and spinal cord. Most resolve by themselves during CRPS healing, but some people require orthopedic surgery to lengthen contracted tendons and restore normal flexibility and position.

## What causes CRPS?

**M**ost CRPS is caused by damage to, or dysfunction of, injured peripheral sensory neurons, which then has secondary effects on the spinal cord and brain. 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 all other parts of the body.

It is unclear why some people develop CRPS while others with similar trauma do not. **In more than 90 percent of cases, CRPS is triggered by nerve trauma or injury to the affected limb that damages the thinnest sensory and autonomic nerve fibers.** These “**small fibers**”—which lack insulating thick myelin sheaths (a protective coating, like insulation that surrounds a wire)—transmit pain, itch, and temperature sensations and control the small blood vessels and health of almost all surrounding cells.

### The most common actions or activities that lead to CRPS are:

- **Fractures.** This is the most common cause, particularly wrist fractures. Nerves can become injured from a displaced or splintered bone, or pressure from a tight cast. Very tight or painful casts must be immediately cut off and replaced to prevent this complication.
- **Surgery.** A surgical incision, retractors, positioning, sutures, or post-operative scarring can cause nerve injury. Sometimes the cause can be identified and repaired, but CRPS can develop even after surgery goes well.



- **Sprains/strains.** Connective tissues ruptures, or the causal trauma, can permit excess movement of a joint that stretches nearby nerves.
- **Lesser injuries** such as burns or cuts. These are the visible signs of injuries that may also have damaged underlying nerves.
- **Limb immobilization** (often from casting). In addition to rarely pressing on nerves and restricting blood flow to the hands and feet as above, casts force prolonged disuse of a limb and deprive it of sensory input. After a cast is removed neurons need time to readapt to normal signaling.
- **Very rare penetrations**, such as from a cut or needle stick, can accidentally pierce a superficial sensory nerve. Nerve specialists help locate the injured nerve by mapping the sensory changes on the skin. Larger penetrating nerve injuries are ideally surgically repaired immediately to permit the cut nerve fibers to regrow into the farther nerve portion to reconnect with target tissues.
- Less than 10% of individuals with CRPS report no causal injury of trauma. Here, the cause is often an undiagnosed internal nerve injury. These include nerve rubbing or tethering against hard internal structures or scars. Tiny clots sometimes block blood flow to a nerve and injure it. Very rarely, a new tumor, infection (such as leprosy), or abnormal blood vessels irritate a nerve. New CRPS without evident cause requires thorough evaluation to check for internal problems.

**Poor circulation can impede nerve and tissue healing.** Damage to the small fibers that control blood flow causes many symptoms of CRPS. Blood vessels in the affected limb can dilate (open wider) to leak fluid into the surrounding tissue, causing red, swollen skin. This can deprive underlying muscles and deeper tissues of oxygen and nutrients, which can cause muscle weakness and joint pain. When skin blood vessels over-constrict (clamp down), the skin becomes cold, white, gray, or bluish.

CRPS develops only in the limbs because circulation is constrained there. Arterial blood pumped down to the hands and feet must fight gravity to return upwards in the veins to the heart. C-fiber damage can impede this, permitting blood fluids to remain in the limb where the swelling then further blocks return blood flow. Slowed circulation impedes delivery of oxygen and nutrients needed for healing and sometimes causes spreading of cellular injury. Breaking the cycle by reducing limb swelling and restoring circulation is often the key that permits recovery to begin.

- People should keep CRPS-affected arms and legs elevated when resting or sleeping to help excess fluid return to the heart.
- Exercise every day—even if only for a few minutes—is critical to improve circulation and oxygenation. Physical therapists can help devise an exercise regimen.
- For some individuals, compression stockings or sleeves can limit the swelling, particularly when standing.

## Other influences on CRPS include:

**Poor nerve health.** Conditions such as diabetes or exposure to nerve toxins can leave the nerves less resilient. Individuals with generalized peripheral neuropathies may be unable or slow to regrow their nerve cells from an injury or stress that wouldn't cause problems in healthy nerves. A key to CRPS recovery is improving general nerve health by removing or improving conditions that slow nerve regrowth.

**Immune system involvement.** The C-fiber nerve cells also communicate with immune cells to help us heal from injury. Excess or prolonged nerve signaling can dysregulate immune cells in the affected limb, as does CRPS-associated poor circulation. Some people with CRPS have elevated local levels of inflammatory chemicals called cytokines that contribute to the redness, swelling, and warmth in the CRPS-affected limb. CRPS is more common in individuals with other inflammatory and autoimmune conditions such as asthma. Some individuals with CRPS may have abnormal antibodies that promote an immune attack on small fibers.

**Genetics.** Genetics, along with environment, influence each person's ability to recover from injury. Rare family clusters of CRPS have been reported. Familial CRPS may be more severe with earlier onset, greater dystonia, and the involvement of more than one limb.

## How is CRPS diagnosed?

**N**o specific test can confirm CRPS and identify the injured nerve. Diagnosis includes:

- Detailed examination by a physician such as a neurologist, orthopedist, or plastic surgeon familiar with normal patterns of sensory nerve anatomy. Having patients draw the outline of their most abnormal skin often reveals the affected nerve.
- Nerve conduction studies detect some but not all CRPS-associated nerve injuries (some injuries involve tiny nerve branches of that cannot be detected this way).
- imaging nerves by ultrasound or magnetic resonance imaging (MRI), also called magnetic resonance neurography (MRN), sometimes reveals underlying nerve damage. Characteristic bone and bone marrow abnormalities on MRI can help identify the injured nerve.
- Triple-phase bone scans (using a dye) sometimes shows CRPS-associated excess bone resorption (the normal breakdown and absorption of bone tissue back into the body), which can help with diagnosis and localization.

Since CRPS generally improves over time, diagnosis is easiest early in the disorder and should not be delayed.

## How is CRPS treated?

**M**ost early or mild cases recover on their own. Treatment is most effective when started early.

### **Primary therapies that are widely used include:**

**Rehabilitation and physical therapy.** This is the single most important treatment for CRPS. Keeping the painful limb or body part moving improves blood flow and lessens circulatory symptoms, as well as maintains flexibility, strength, and function. Rehabilitating the affected limb helps prevent or reverse secondary spinal cord and brain changes associated with disuse and chronic pain. Occupational therapy can help people learn new ways to become active and return to work and daily tasks.

**Psychotherapy.** People with severe CRPS often develop secondary psychological problems including depression, situational anxiety, and sometimes post-traumatic stress disorder. These heighten pain perception, further reduce activity and brain function, and make it hard for patients to seek medical care and engage in rehabilitation and recovery. Psychological treatment helps people with CRPS to feel better and better recover from CRPS.

**Graded motor imagery.** Individuals are taught mental exercises including how to identify left and right painful body parts while looking into a mirror and visualizing moving those painful body parts without actually moving them. This is thought to provide non-painful sensory signals to the brain that helps reverse brain changes that are prolonging CRPS.

**Medications.** Several classes of medication have been reported as effective for CRPS, particularly when given early in the disease. However, none are approved by the U.S. Food and Drug Administration (FDA) to be marketed specifically for CRPS, and no single drug or combination is guaranteed to be effective in everyone. Drugs often used to treat CRPS include:

- Acetaminophen to reduce pain associated with inflammation and bone and joint involvement
- Non-steroidal anti-inflammatory drugs (NSAIDS) to treat moderate pain and inflammation, including over-the-counter aspirin, ibuprofen, and naproxen in sufficient doses
- Drugs proven effective for other neuropathic pain conditions, such as nortriptyline, gabapentin, pregabalin, and duloxetine. Amitriptyline, an older treatment, is effective but causes more side effects than nortriptyline, which is very similar chemically.
- Topical local anesthetic ointments, sprays, or creams such as lidocaine and patches such as fentanyl. These can reduce allodynia, and skin coverage by patches can provide additional protection.
- Bisphosphonates, such as high dose alendronate or intravenous pamidronate, that reduce bone changes
- Corticosteroids that treat inflammation/swelling and edema, such as prednisolone and methylprednisolone

- Botulinum toxin injections can help in severe cases, particularly for relaxing contracted muscles and restoring normal hand or foot positions
- Opioids such as oxycodone, morphine, hydrocodone, and fentanyl may be required for individuals with the most severe pain. However, opioids can convey heightened pain sensitivity and run the risk of dependence.
- N-methyl-D-aspartate (NMDA) receptor antagonists such as dextromethorphan and ketamine are controversial unproven treatments

**Spinal cord stimulation.** Stimulating electrodes are threaded through a needle into the spine outside the spinal cord. They create tingling sensations in the painful area that helps block pain sensations and normalize signaling into the spinal cord and brain. Electrodes can be placed temporarily for a few days to assess if stimulation is likely to be helpful. Minor surgery is required to implant the stimulator, battery, and electrodes under the skin on the torso. Once implanted, stimulators can be turned on and off and adjusted with an external controller.

**Other types of neural stimulation.**

Implanted neurostimulation can be delivered at other locations including near injured nerves (peripheral nerve stimulators), under the skull (motor cortex stimulation with electrodes), and within brain pain centers (deep brain stimulation). Recent noninvasive commercially available treatments include nerve stimulation at the peroneal nerve at the knee. Another is repetitive Transcranial

Magnetic Stimulation or rTMS, a noninvasive form of brain stimulation that uses a magnetic field to change electrical signaling in the brain. Similar at-home use of small transcranial direct electrical stimulators is also being investigated. These stimulation methods have the advantage of being non-invasive; however, repeated treatment sessions are needed to maintain benefit, so they require time.

**Spinal-fluid drug pumps.** These implanted devices deliver pain-relieving medications directly into the fluid that bathes the nerve roots and spinal cord. Typically, these are mixtures of opioids, local anesthetic agents, clonidine, and baclofen. The advantage is that very low doses can be used that do not spread beyond the spinal canal to affect other body system. This decreases side effects and increases drug effectiveness.

**Alternative and holistic therapies.** Based on studies from other painful conditions, some individuals are investigating accessible treatments such as medical marijuana, behavior modification, acupuncture, relaxation techniques (such as biofeedback, progressive muscle relaxation, and guided motion therapy), and chiropractic treatment. These do not benefit the primary cause of CRPS, but some people find them useful. They are generally accessible and not dangerous to try.

**Limited use therapy for the most severe or non-resolving pain that has not responded to conventional treatment,** such as ketamine. Some investigators report benefit from low doses of ketamine—a strong anesthetic—given intravenously for several days.



In certain clinical settings, ketamine has been shown to be useful in treating pain that does not respond well to other treatments. However, it can cause delusions and other symptoms of psychosis with long-lasting impact.

### **Rarely used former treatments include:**

**Sympathetic nerve block.** Previously, sympathetic blocks—in which an anesthetic is injected next to the spine to directly block the activity of sympathetic nerves and improve blood flow—were used. More recent studies demonstrate no long-lasting benefit after the injected anesthetic wears off and there is the risk of injury from needle injections, so this approach has fallen from favor.

**Surgical sympathectomy.** This destroys some of the nerves that carry pain signals. Use is controversial; some experts think it is unwarranted and makes CRPS worse, while others report occasional favorable outcome. Sympathectomy should be used only in individuals whose pain is temporarily dramatically relieved by sympathetic nerve blocks.

**Cutting injured nerves or nerve roots.** People with CRPS often ask if cutting the damaged nerve above the site of injury would end the pain. In fact, this causes a larger nerve lesion that will affect a larger area of the limb. Also, the spinal cord and brain react badly to being deprived of stimulation which can result in central pain syndromes. Other than in exceptional circumstances such as palliative care, this should not be performed.

**Amputating the painful lower limb.** This is an even more drastic and disabling form of nerve cutting, and the consequences are irreversible, whereas CRPS almost always improves over time, albeit sometimes slowly. Amputation is thus not appropriate for pain control alone, but it is rarely required to manage bone infection or to permit use of a prosthesis for long-affected non-recovering individuals. This last resort should not be performed without input from several specialists along with psychological counseling.

## What research is being done on CRPS?

**T**he 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 it to reduce the burden of neurological disease. NINDS is part of the National Institutes of Health (NIH), the leading supporter of biomedical research in the world, and leads NIH research on CRPS.

The NIH HEAL (Helping to End Addiction Long-term<sup>SM</sup>) Initiative is an ambitious trans-agency effort to speed scientific solutions to stem the national opioid public health crisis. Through the Initiative, NIH supports research to enhance pain management and improve treatment for opioid misuse and addiction. The NIH HEAL Initiative includes research focus areas led by 12 NIH Institutes and Centers supporting hundreds of projects that reflect the full spectrum of research

from basic science to implementation research. In Fiscal Year 2019, NIH awarded \$945 million in funding for grants, contracts, and cooperative agreements across 41 states through the HEAL Initiative. For more information, see [www.heal.nih.gov](http://www.heal.nih.gov).

NINDS-supported scientists are studying new approaches to understand and treat CRPS, and to intervene to limit the symptoms and disability associated with the syndrome. Other NIH institutes also support research on CRPS and other painful conditions. Research efforts include:

- understanding how CRPS develops by studying immune system activation and peripheral nerve signaling using model systems of the disease
- genetic and other approaches to investigate the contribution of peripheral inflammatory cells and central nervous system non-neuronal cells peripherally and centrally to the acute phase of CRPS and its transition to the disorder's chronic phase
- examining serum and skin biopsies to better understand changes in immunity that are seen in post-traumatic CRPS. Such studies may provide support for future CRPS clinical trials using intravenous immunoglobulin (IVIG), rituximab B cell antibodies, and other FDA approved treatments for autoimmune diseases.

- studying neuroplasticity in children and adolescents with CRPS—who generally have a better prognosis than adults—to gain insights into mechanisms that may prevent chronic pain and develop more effective therapies for the disease
- experimentally evaluating the use of ketamine (which has been used in adults as an add-on therapy to treat adult chronic pain) and dexmedetomidine (which has sedative and analgesic properties) to treat pain in children; and
- investigating the effectiveness of transcranial magnetic stimulation in reducing CRPS-related pain and associated cognitive, physical, and emotional symptoms.

More information about research on CRPS supported by NINDS and other NIH Institutes and Centers can be found using NIH RePORTER ([www.projectreporter.nih.gov](http://www.projectreporter.nih.gov)), a searchable database of current and past research projects supported by NIH and other federal agencies. RePORTER also includes links to publications and resources from these projects. Enter “CRPS” to start your search.

## Where can I get more information?

**F**or 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](http://www.ninds.nih.gov)

Information also is available from the following organizations:

### **NeuropathyCommons.org**

(information on peripheral nerves for patients, professionals, and researchers hosted by Harvard University)  
<https://neuropathycommons.org>

### **Reflex Sympathetic Dystrophy Syndrome Association (RSDSA)**

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

### **International Research Foundation for RSD/CRPS**

1910 East Busch Boulevard  
Tampa, FL 33612  
813-907-2312  
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