



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Reflex Sympathetic Dystrophy/Complex Regional Pain Syndrome Treatment

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Coverage Policy

Services provided by a psychiatrist, psychologist or other behavioral health professional are subject to the provisions of the applicable behavioral health benefit.

Please refer to the CIGNA Coverage Policies on Occupational Therapy and Physical Therapy for specific coverage criteria for these therapies.

CIGNA covers the following treatments as medically necessary for complex regional pain syndrome (CRPS) when conservative measures (e.g., physiotherapy, pharmacological, or psychological, if applicable) have been tried and failed or judged to be unsuitable or contraindicated:

- spinal cord stimulator
- peripheral nerve stimulator
- intrathecal drug delivery with subcutaneous pump
- sympathectomy

Note: Refer to the CIGNA Coverage Policy Spinal Cord Stimulation for specific criteria on spinal cord stimulators and the Coverage Policy Implantable Infusion Pumps for specific criteria on implantable intrathecal or epidural infusion pumps to administer analgesics.

CIGNA does not cover the following procedures/services for the treatment of CRPS because each is considered experimental, investigational or unproven for this indication (this list may not be all-inclusive):

- acupuncture
- biofeedback
- electromagnetic field treatment
- hyperbaric oxygen
- hypnosis
- interferential stimulators
- ketamine administration
- mirror box therapy
- motor cortex stimulation
- radiofrequency ablation

General Background

Complex regional pain syndrome (CRPS) is a neuropathic pain condition. The older term for this condition is reflex sympathetic dystrophy (RSD). In 1994, the International Association for the Study of Pain (IASP) established new terms and criteria for this condition. CRPS is the standard term that is currently used, although the older term is still seen in the literature and used in discussions regarding this condition. Other terms that have been used in the past include: post-traumatic pain syndrome, Sudeck's dystrophy, reflex neurovascular dystrophy, post-traumatic spreading neuralgia, sympathalgia, and shoulder-hand syndrome (Ghai and Dureja, 2004). CRPS is divided into two types:

- CRPS type I: This type corresponds to what was previously referred to as RSD.
- CRPS type II: This type corresponds to the condition previously referred to as causalgia.

The diagnostic criteria for these conditions established by the IASP include the following (Stanton-Hicks, 2003):

CRPS type I	CRPS type II
1. The presence of an initiating noxious event or a cause of immobilization	This condition follows a nerve injury. It is similar in other respects to type I
2. Continuing pain, allodynia, or hyperalgesia occurs that is disproportionate to the inciting event	1. The presence of continuing pain, allodynia or hyperalgesia after a nerve injury and not necessarily limited to the distribution of the injured nerve
3. Evidence at some point of edema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain	2. Evidence at some point of edema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain
4. The diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction	3. The diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction
Note: criteria two through four must be satisfied	Note: all three criteria must be satisfied

The primary difference between CRPS type I and CRPS type II is the evidence of an identifiable nerve lesion with CRPS II. Concerns have been raised regarding the above criteria. It has been noted that, although the sensitivity was quite high, the specificity was poor (Ghai and Dureja, 2004). Modified criteria were proposed for the purpose of improving the external validity and differentiating between CRPS and non-CRPS neuropathic pain conditions. The modified criteria include the following (Harden, 2001):

1. There is presence of continuing pain, which is disproportionate to any inciting event
2. The patient must report at least one symptom in each of the four categories: <ul style="list-style-type: none"> • sensory: reports of hyperesthesia • vasomotor: reports of temperature symmetry and/or skin color changes and/or skin color asymmetry • sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry • motor/trophic: reports of decreased range of motion and/or motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic (hair, nails, or skin)
3. The patient must display at least one sign in two or more of the following categories: <ul style="list-style-type: none"> • sensory: evidence of hyperalgesia (i.e., to pinprick) and/or allodynia (i.e., to light touch) • vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry • sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry • motor/trophic: evidence of decreased range of motion and/or motor dysfunction (i.e., weakness, tremor, dystonia) and/or trophic (i.e., hair, nails, or skin)

CRPS most often affects the hand or foot but may occur in other parts of the body. There may be recurrence or spread to another extremity or region. The hallmark symptom of this condition is intense pain that is out of proportion to the severity of the precipitating event, and worsens over time. The pain is often described as burning and stinging, and may be associated with hyperalgesia (i.e., heightened sensitivity to pain) or allodynia (i.e., when an ordinarily painless stimulus is perceived as being painful). Not all patients with CRPS present with the same collection of signs and symptoms to the same degree. There is a large amount of variation in the symptoms and degree of severity. Other signs and symptoms that are associated with this condition may include (Harden, 2001; Stanton-Hicks, 2003):

- Hyperaesthesia: This is a sense of heightened sensation. It may be experienced with stimulus that occurs in daily living (i.e., clothing resting on the affected part or air blowing on the limb).
- Sensitivity to temperature changes: The involved body area may be hotter or colder than the contralateral body area. There may also be fluctuations in the abnormal skin temperature.
- Skin temperature change: There may be asymmetry of the color or temperature of the affected limb.
- Sudomotor symptoms: There may be either hyperhidrosis (i.e., excessive sweating) or dryness.
- Trophic changes: There may be an increase or a decrease in nail and hair growth, and skin changes such as thinning of the epidermis, or a shiny patina.
- Motor dysfunction: This symptom includes tremors, weakness, decreased range of motion, dystonia, or myoclonic action in the affected body part.
- Edema of the affected extremity: Most patients will experience edema, and it may be exacerbated by evoked pain such as physical activity and extreme changes in temperature.
- Atrophy of muscles: This may occur later in the disease process and be associated with tendon contractures.

The diagnosis of CRPS is a clinical diagnosis made through history, physical examination, and observation of signs and symptoms. There is no specific diagnostic test that is conclusive for this condition. Laboratory testing is not necessary for diagnostic purposes, nor is it useful in defining appropriate therapies (Harden, et al., 2010). There are some tests that may be performed in order to provide information regarding the patient's condition, but they are not specific to CRPS. These tests may include (Harden, et al., 2010; Mehta and Lindenfeld, 2003):

- Radiologic testing: Findings of bony demineralization may be noted on x-ray in patients with CRPS; however, this finding is not specific to CRPS, and most patients do not exhibit this abnormality.
- Bone scan: There may be changes seen in a bone scan, including distinctive patterns of radiotracer uptake; however, the clinical utility of bone scan in CRPS has not been demonstrated.
- Electrodiagnostic studies: Electrophysiologic studies, electromyography and nerve conduction testing can confirm the presence of large fiber peripheral nerve injury. The clinical relevance of this testing in CRPS is not known.
- Thermography: Asymmetric skin temperature in the painful region may be noted with CRPS; however, thermography is not a necessity for diagnosing or treating the condition.
- Sympathetic block: Traditionally, these measures are used to determine if there is the presence of sympathetically maintained pain (SMP). It is generally recommended that a patient receive one

sympathetic nerve block to assess whether SMP is present. If the patient does not report significant pain relief from one block, further sympathetic blocks are not recommended.

The pathophysiology of CRPS is uncertain. There is scant information known regarding the pathophysiologic events that result in the development of CRPS (Harden, et al., 2010). In some cases, the cause of CRPS is unknown, or it may arise after a microscopic trauma such as an immunization (Stanton-Hicks, 2003). The symptoms may appear after an injury or a surgery. There may be recurrence or spread to another extremity or region.

Treatment

Early diagnosis and treatment of CRPS is recommended for optimal management of this condition. Treatment is often multidisciplinary, including rehabilitation, psychological and pain therapies. The goal of the psychological and pain-management interventions is to allow optimal functional restoration. In 1998, expert panel consensus guidelines were developed and published. The guidelines noted that (Stanton-Hicks, et al., 1998):

- Treatment should be developed around functional restoration.
- Most patients will improve as long as sufficient analgesia and symptomatic control can be provided to support exercise therapy.

An expert panel in 2002 reviewed and updated the guidelines (Stanton-Hicks, et al., 2002). The updated consensus treatment guidelines centered on the same three domains of rehabilitation, psychological and pain therapies, but noted that they should be addressed simultaneously, with advanced approaches in each area applied according to the patient's response to the treatment. The guidelines are based on the premise that rehabilitation is fundamental to the treatment of CRPS. The path in the treatment algorithm moves from more basic, less intense treatment to more advanced techniques. If a patient does not advance in therapy, then other interventions should be progressively added to give the patient greater comfort in order to proceed. If the pain level is too high for a patient to participate in therapy, it is recommended that stronger medications or interventions should be utilized. Although the guidelines do not contain recommendations on timing of treatments, it noted that "there is widespread agreement among experts that patients who do not respond to an acceptable level of treatment by 12 to 16 weeks should be given a trial of more interventional therapies." It is further noted that the proposed CRPS clinical pathway presented in the guidelines will require validation through the conduction of randomized controlled trials (Stanton-Hicks, et al., 2002).

In general, most patients with CRPS will respond well to conservative measures. Patients who prove refractory to conservative treatment or who develop unforeseen and rapid changes will require a flexible therapeutic response to keep them engaged in the rehabilitation process.

Conservative measures include the following noninvasive or minimally invasive treatments (Stanton-Hicks, et al., 2002):

- pharmacological treatment with oral and topical drugs
- physiotherapy
- transcutaneous electrical stimulation (TENS)
- psychological therapy (e.g., cognitive-behavioral therapy, assessment of Axis 1 disorders, pain coping skills)
- regional anesthetic nerve blocks (e.g., sympathetic nerve block, intravenous regional block)

If there is an inadequate or partial response, or a failure to progress in rehabilitation, then the following more invasive treatments should be attempted (Stanton-Hicks, et al., 2002):

- epidural block
- neurostimulation (i.e., spinal cord stimulation [SCS] or peripheral nerve stimulation [PNS])
- injectable and/or intravenous drug therapy
- intrathecal drug therapy

If there is continued inadequate or partial response to the above treatment, or failure to progress in rehabilitation, then the following more invasive treatment should be attempted (Stanton-Hicks, et al., 2002):

- sympathectomy

Rehabilitation: Rehabilitation is the core of treatment for CRPS. If the patient does not progress, it is important to utilize the pain management and psychological modalities that will assist in the progress. Occupational therapy (OT) and physical therapy (PT) are both utilized in rehabilitation. Therapy should emphasize physical activity in the affected limb and involve a steady progression of motion from very gentle movements on an active basis to gentle weight-bearing (Burton, et al., 2005). Modalities may include: desensitization, stress loading, exercises, range of motion, stretching, and electrical stimulation.

It has been noted in a literature review that the body of evidence regarding the efficacy of functional restoration is small but persuasive; in various uncontrolled studies, CRPS patients have shown benefit from physiotherapeutic modalities such as stress loading and isometric techniques (Harden, 2005). Oerlemans et al. (2000) conducted a prospective, randomized controlled trial of one hundred and thirty-five patients with a one-year follow-up for the purpose of investigating the effectiveness and cost of PT or OT in patient with CRPS. Patients were assigned to PT, OT or a control group (i.e., social work). The researchers noted that PT, and to a lesser extent, OT, resulted in significant and more rapid improvement as compared with the control group. On a disability level, a positive trend was found in favor of OT. The authors concluded that PT and OT each contributed in different ways to the recovery from CRPS of the upper extremity.

TENS may be used during physiotherapy or by the patient in the home. A review of the literature noted that use of TENS has been found to be effective in 50–90% of pediatric patients with CRPS (Hord and Oaklander, 2003). It is noted that since it is noninvasive and does not have apparent side effects, it is a conservative treatment option that is worth attempting.

Interferential stimulation has been proposed as a treatment for pain. There is insufficient evidence in the medical literature that this treatment is effective for CRPS or neuropathic pain.

Psychological Treatment: The focus of psychological treatment for CRPS is to improve quality of life, development of pain coping skills, provide cognitive-behavioral therapy and facilitate progress in other treatment modalities (Stanton-Hicks, et al., 2002). For patients in the early stages of CRPS, psychological intervention is usually minimal. As the disease progresses, the psychological factors may play a greater role. If there is an inadequate or partial response to initial treatment, then there may be need for an increase in frequency and intensity of psychotherapy. It is noted that there are few clinical trials that have examined the use of psychological treatments for neuropathic pain conditions; however, there is literature published regarding the effectiveness of multidisciplinary interventions for heterogeneous pain conditions, and the findings suggest that psychological interventions would be comparably effective for neuropathic pain conditions (Haythornthwaite and Benrud-Larson, 2001). Specific treatment interventions may include biofeedback, hypnosis, operant-behavioral interventions and cognitive-behavioral treatment, which may include stress management techniques and lifestyle modifications. Although biofeedback and hypnosis are mentioned as adjuncts to the more traditional cognitive-behavioral psychotherapy, it is noted that most of the literature regarding these treatments is limited by small sample size or are single case reports (Harden, et al., 2010).

Biofeedback provides information about a physiologic parameter through a monitoring instrument to enable an individual to learn how to control a physiologic response. There is insufficient evidence found in the peer-reviewed literature regarding the efficacy of biofeedback and CRPS or neuropathic pain.

Hypnosis has also been mentioned as a treatment in reducing the symptoms associated with CRPS. However, there is insufficient evidence found regarding this treatment in CRPS or neuropathic pain.

Mirror Box Therapy: Mirror box therapy, also referred to as mirror therapy, which utilizes visual feedback, has recently been proposed as a treatment for CRPS. It may be combined with cognitive behavioral therapy. This treatment was first proposed as treatment for phantom limb pain and stroke and is now being studied in other conditions, including CRPS. It is based on the theory that visual feedback provides a substitute for missing proprioceptive feedback to reduce pain. In mirror box therapy, the limbs are positioned in a box separated by a mirror placed sagittally; the patient looks into the mirror at the unaffected side, thereby thinking that the affected limb is moving effortlessly. Cacchio et al. (2009) conducted a randomized, controlled study to compare the effectiveness of mirror therapy on pain and upper limb function on patients with CRPS type 1 after acute stroke.

The study included 48 patients who were assigned to either mirror therapy group or placebo control group. The primary endpoints were a reduction in the visual analogue scale score of pain at rest, on movement and brush-induced tactile allodynia. Secondary endpoint was improvement in motor function. The mean scores of both the primary and secondary end points were found to improve significantly in the mirror group ($p < .001$). There was no statistically significant improvement seen in any of the control group values ($p > .001$). There were significant differences after treatment ($p < .001$) and at the six-month follow-up were found between the two groups. Limitations of the study include lack of evidence of brain reorganization after mirror therapy using imaging techniques (e.g., functional magnetic resonance imaging), lack of follow-up time sufficient to determine the long term effects.

Vladimir Tichelaar et al. (2007) reported on three case reports of patients with CRPS type I who were treated with cognitive behavioral therapy combined with mirror box therapy. Assessment was performed before, during and at follow-up and included the following measurements: pain (visual analog scale, 0–100), range of motion, muscle strength and the areas of allodynia and of hyperalgesia. In addition, patients were questioned regarding their feelings and thoughts about mirror box therapy and the affected limb. The therapy took place over four to six weeks with follow-up at five weeks, eight weeks or 14 weeks. A decrease was noted in pain at rest, pain after measuring allodynia/hyperalgesia and pain after measuring strength. Improvement in range of motion was noted in two patients, and strength in one patient was noted. An increase of area hyperalgesia was noted for all three patients, with the area of allodynia remaining stable in two and decreased in one patient. Selles et al. (2008) reported on two cases where mirror therapy was used in CRPS type II. In one case, a reduction in pain was found during and directly after the exercised, but the overall level of pain did not decrease. In the second case, mirror therapy for a three month period decreased the pain. These case studies suggest that there may be a role for this type of therapy; however, further research is needed regarding mirror box therapy for CRPS.

Pain Management

Pain management may be seen as a range from pharmacological to more invasive interventional pain techniques.

Pharmacologic Treatment: There are many medications that have been used and reported to be helpful but few that have been tested in double-blind, randomized controlled trials (Harden, 2001). There are trials that have been conducted and systematic reviews that have been published regarding drug therapy for related neuropathic pain conditions, and the results have been extrapolated to clinical use for CRPS (Harden, 2005). The choice of medication is usually based on the symptoms and presentation of the patient.

The primary types of medications used in treatment of CRPS may include anti-inflammatories, anticonvulsants and antidepressants (Harden, 2005.) Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used to treat the inflammatory symptoms of CRPS. A short course of corticosteroids early in the treatment of CRPS may be useful to manage the inflammatory components. Opioids have been used in the treatment of chronic neuropathic pain. The use of opioids may be appropriate in specific situations, such as when pain is not controlled by more conservative measures, including antidepressants, anticonvulsants, heat, ice, and the pain is preventing participation in physiotherapy.

The anticonvulsant group appears to be among some of the best-studied drugs in the area of neuropathic pain (Harden, 2001). Gabapentin has been studied in large, randomized controlled trials in post-herpetic neuralgia and diabetic peripheral neuropathy. Gabapentin has been used widely for neuropathic pain. The mechanism of action is not completely understood. A Cochrane systematic review was conducted for the purpose of evaluating the analgesic effectiveness and adverse effects of gabapentin for pain management in clinical practice (Wiffen, et al., 2005). The review noted that “gabapentin is now widely used as the drug of choice for neuropathic pain.” The conclusion states that gabapentin is effective for the treatment of a variety of neuropathic pain and that it should be considered along with other proven treatments such as carbamazepine and tricyclic antidepressants.

Tricyclic antidepressants have been a traditional choice in the treatment of neuropathic conditions, in particular, diabetic neuropathy and post-herpetic neuralgia (Harden, 2005). It appears to be partially effective in CRPS, although it has never been properly studied for this condition. It is thought that the analgesic effect appears to be related to several known actions of these drugs, including the enhancement of noradrenergic descending inhibitory pathways and partial sodium-channel blockade (Hord and Oaklander, 2003). The efficacy of the medications for pain reduction in chronic pain appears to be independent of the antidepressant effect and may take place at a lower dose than those typically used to treat depression. The novel antidepressants, including

venlafaxine (Effexor) and duloxetine (Cymbalta) appear to be effective in the treatment of neuropathic pain (Maizels and McCarberg, 2005).

Local anesthetics, lidocaine and its oral analog, mexiletine, have been used to treat neuropathic pain (Mehta and Lindenfeld, 2003). Lidocaine has been administered through different routes (i.e., oral, subcutaneous, topical and intravenous). A Cochrane review was conducted with the objective of evaluating pain relief and adverse effect rates between systemic local anesthetic-type drugs and other control interventions (Challapalli, et al., 2005). Thirty-two articles met selection criteria. The treatment drugs included in these studies were: lidocaine, mexiletine, lidocaine plus mexiletine and tocainide. It was noted that "in these trials, systemic local anesthetics were safe, with no deaths or life-threatening toxicities." The authors concluded that local anesthetic drugs can relieve pain in selected patients with neuropathic pain, compared to placebo.

Ketamine Administration: Ketamine infusion, an anesthetic, has gained active interest in the treatment of CRPS. Preliminary studies have been performed on this treatment utilizing anesthetic and subanesthetic doses of the drug. It has been noted that the use of ketamine at higher doses is limited by psychotropic side effects. The incidence and severity of ketamine side effects are dose-dependent as are its analgesic potency and duration of action (Kiefer, et al., 2009). Schwartzman et al. (2009) conducted a randomized double-blind placebo controlled trial that was designed to evaluate the effectiveness of intravenous ketamine in the treatment of CRPS. Nineteen subjects were randomized into a ketamine (n=9) or a placebo infusion group (n=10). All patients met CRPS criteria with intractable pain for at least six months. The patients were evaluated for at least 2 weeks prior to treatment and for 3 months following treatment. They were infused intravenously with normal saline with or without ketamine for 4 hours a day for 10 days. A pain reduction was seen in the ketamine treated group ($p < 0.05$) in several pain measurements. The patients in the placebo group did not demonstrate significant improvement in these parameters. Limitations of the study identified by the authors included: small size; non-stratification of patients either by length of time with the illness or by the temperature of the affected area; and lack of a crossover arm. The authors concluded that these results warrant a larger randomized placebo controlled trial using higher doses of ketamine and longer follow-up period.

Sigtermans et al. reported on a randomized, double-blind trial of 60 patients to evaluate if intravenous ketamine improves pain in CRPS patients. Ketamine was administered in a 4.2-day intravenous infusion of low-dose ketamine (n=30) or placebo (n=30) utilizing an individualized stepwise tailoring of dosage based on effect (pain relief) and side effects (nausea/vomiting/psychomimetic effects). A pain score (numerical rating score: 0-10) was the primary outcome of the study during the 12-week study period. Pain scores over the 12-week study period in patients receiving ketamine were significantly lower than those in patients receiving placebo ($p < 0.001$). The lowest pain score was at the end of week 1: ketamine 2.68 ± 0.51 , placebo 5.45 ± 0.48 . In week 12, significance in pain relief between groups was lost ($p = 0.07$). Treatment did not cause functional improvement. The patients in the ketamine group more often experienced mild to moderate psychomimetic side effects during drug infusion (76% versus 18%, $p < 0.001$). The authors conclude that, in a population of mostly chronic CRPS-1 patients with severe pain at baseline, a multiple day ketamine infusion resulted in significant pain relief without functional improvement.

Kiefer et al. (2008) conducted a study to investigate the efficacy of ketamine in anesthetic dosage in refractory CRPS patients that had failed available standard therapies. The study included 20 patients suffering from refractory CRPS who received ketamine in anesthetic dosage over 5 days. Outcome criteria included pain relief, effect on the movement disorder, quality of life, and ability to work at baseline and up to 6 months following treatment. Significant pain relief was noted at one, three, and six months following treatment ($93.5 \pm 11.1\%$, $89.4 \pm 17.0\%$, $79.3 \pm 25.3\%$; $p < 0.001$). Complete remission from CRPS was observed at one month in all patients, at three months in 17, and at six months in 16 patients. If relapse occurred, significant pain relief was still realized at three and six months ($59.0 \pm 14.7\%$, $p < 0.004$; $50.2 \pm 10.6\%$, $p < 0.002$). Quality of life, the associated movement disorder, and the ability to work were noted to be improved in the majority of patients at three and six months. The authors note that a randomized, controlled trial will be necessary to prove its efficacy.

A prospective pain journal evaluation of a 10-day infusion of intravenous ketamine was conducted for the objective of reporting on the efficacy of low-dose outpatient ketamine infusion for the treatment of CRPS in patients who have failed conservative treatment (Goldberg, et al., 2005). The study involved 40 patients with a primary diagnosis of CRPS refractory to conventional therapy. The patients were asked to rate their pain intensity using a verbal analog pain scale of 0–10 and the affective component using a verbal scale of 0–4. It was noted that there was an improvement in pain by day ten and an increase in mobility. Two weeks post-

treatment, it was reported that four patients had a return to pre-infusions level of pain. Twenty-five patients had at least a 70% reduction in pain for six weeks and were back to baseline pain by nine weeks post-treatment. At 15 months post-treatment, three patients remained CRPS-free.

A retrospective chart review was conducted by Webster and Walker (2006) to study the safety and efficacy of prolonged, low-dose, continuous intravenous or subcutaneous ketamine infusions in non-cancer outpatients. Thirteen patients were included in the study. Using a ten-point verbal analog score, 11 of the 13 patients (85%) reported a decrease in pain from the start of infusion treatment to the end. Side effects were noted to be minimal. A retrospective case review of 33 patients who had been treated with intravenous infusion of ketamine was performed for the purpose of determining if the use of ketamine provides a meaningful improvement in pain scores for patients with CRPS (Correll, et al., 2004). The immediate response to therapy was complete pain relief in 25 of the 33 patients. Due to relapse, 12 patients received a second course of therapy, and two patients received a third. Following the first course of therapy, 54% of the 33 patients remained pain-free for more than three months, and 31% remained pain-free for over six months. After the second infusion, 58% of the 12 patients experienced pain relief for over one year, and 33% remained pain-free for over three years.

An evidence-based review of the use of ketamine in chronic pain management was performed (Hocking and Cousins, 2003). The authors note that the review is based on evidence that would generally not be included in a systematic review; due to the variation in the study objectives and design and the small number of randomized controlled trials, a meta-analysis of published data was thought to be inappropriate. The review noted that there were two reports that described pain relief using ketamine by the epidural route in three patients. In two of the patients, there was intensive rehabilitation that may have explained the results. The authors note that "we probably do not yet have sufficient evidence to advocate the routine use of ketamine in chronic pain." It is noted in the review that "there are few good-quality studies with adequate numbers of patients to clearly delineate the place of this drug in chronic pain medicine." In addition, the review noted that there is evidence that this treatment can cause significant side effects.

Intrathecal Drug Delivery: Intrathecal drug delivery with a subcutaneous pump is a treatment that is considered when conservative measures have been tried, failed or there is a contraindication. The purpose of this route of drug delivery is to improve the therapeutic ratio of these medications by administering a higher concentration of medication near the spinal cord and less in the brain and periphery. The two most common medications that are used are morphine and baclofen (Hord and Oaklander, 2003). Intrathecal administration with subcutaneous pump is a treatment that should be considered when pain associated with CRPS is intractable and other conservative measures have been attempted and have failed, or when there is a contraindication.

Baclofen has been proposed when CRPS is associated with the presence of severe dystonia, which is a rare development in CRPS. Baclofen has been considered an effective treatment for patients with spasticity. A double-blind, randomized, controlled crossover trial was performed to evaluate treatment with intrathecal baclofen (van Hilten, et al., 2000). The study included seven women with CRPS with severe multifocal or generalized tonic dystonia. A crossover trial of bolus injection of 25, 50 and 75 mcg of baclofen and placebo was administered. Changes in the severity of dystonia were assessed by the women and an investigator. In the second phase of the study, six of the women received a subcutaneous pump for continuous intrathecal administration of baclofen and were followed for 0.5 to three years. In six of the women, bolus injections of 50 and 75 mcg of baclofen resulted in complete or partial resolution of focal dystonia of the hands but little improvement in the legs. During continuous infusion of baclofen, three of the women regained normal hand function, and two of these three women regained the ability to walk. In two of the women, the spasms decreased but without a change in the dystonia. The authors concluded that, in some patients, the dystonia associated with CRPS responds markedly to intrathecal baclofen. It is noted that the study is small and preliminary regarding the treatment with intrathecal baclofen for dystonia associated with CRPS.

Ziconotide (Prialt®) (Elan Pharmaceuticals, Inc., San Diego, CA) is in a class of non-opioid analgesics known as N-type calcium channel blockers. It is the synthetic equivalent of a naturally occurring conopeptide found in a marine snail known as *Conus magus*. It is administered intrathecally through appropriate programmable micro-infusion pumps that can be implanted or external, and which release the drug into the fluid surrounding the spinal cord. This medication received U.S. Food and Drug Administration (FDA) approval in December 2004 for management of severe chronic pain not relieved by systemic analgesics, adjunctive therapies, or intrathecal morphine in patients who are appropriate candidates for intrathecal therapy (Lynch, et al., 2006). Ziconotide has

a novel mechanism of action, and it offers a unique analgesic therapy for patients with severe intractable pain. However, its use should be limited to only those patients not responding to other therapies because it has the potential to produce serious neurologic and psychiatric side effects.

Acupuncture: Acupuncture has been mentioned in the literature as a treatment for pain of CRPS. A review of the peer-reviewed literature does not indicate that there is data that support the use of acupuncture in the treatment of CRPS. A double-blind, placebo-controlled study was conducted with fourteen patients suffering from CRPS of an upper limb lasting more than one but less than six months (Korpan, et al., 1999). Patients were randomly assigned either to a classical acupuncture or sham acupuncture group. Treatment was applied five times a week for three weeks for 30 minutes. The state of pain was assessed with a visual analog scale. Both groups also received the same basic therapy, consisting of a home therapy program with elevation, ice and therapeutic exercise. During the therapy, the state of pain as well as clinical parameters improved in both groups and reached nearly normal levels after six months. There was no difference noted between the acupuncture and sham groups.

Electromagnetic Field Treatment: Electromagnetic field treatment has been proposed as a treatment for CRPS type I. Durmus et al. (2004) conducted a randomized, double-blind, placebo-controlled study for the purpose of assessing whether or not electromagnetic field treatment administered with calcitonin and exercise has positive effects on clinical improvement, scintigraphic assessment and bone markers compared to calcitonin and exercise administration. The study involved 40 patients with CRPS type I that developed after a Colles fracture. All patients were administered calcitonin and exercise treatment for six weeks. Half of the patients received electromagnetic field treatment, and the other half received a placebo treatment by being placed in the same device without it being switched on. Patients were evaluated at the beginning and end of treatment with clinical parameters, scintigraphic assessment and biochemical markers. It was noted that there was not a significant statistical difference between groups. The authors concluded that the absence of a significant difference between the two groups has been interpreted as evidence that electromagnetic field treatment does not provide additional benefit to calcitonin and exercise treatment.

Hyperbaric Oxygen (HBO): HBO has been proposed as a treatment for the pain associated with CRPS. Kiralp et al. (2004) conducted a double-blind, randomized, placebo-controlled study to assess the effectiveness of HBO for treating patients with CRPS. The study included 71 patients. They were allocated alternately to receive HBO therapy or normal air, receiving fifteen 90-minute therapy sessions of either HBO or normal air. The time period between the diagnosis and the trauma was approximately 1.5 months, and the patient had not yet received any treatment for CRPS. Pain was evaluated using a visual analog scale. Range of motion evaluation included goniometric assessment of wrist extension and wrist flexion. Edema was assessed by measuring the wrist circumference. The visual analog scale score indicated that pain decreased starting from the first day until day 45. An increase in wrist flexion was observed with the HBO group after 15 therapy sessions. A decrease in wrist circumference in the HBO group was noted between end of treatment and day 45. There was a statistically significant difference for all variables except wrist extension. It does not appear that there was long-term follow-up of this group. This may be considered a preliminary study regarding HBO treatment for CRPS.

Regional Anesthetic Techniques: Regional anesthetic techniques have long been widely used in the management of CRPS. They have been used for provision of analgesia along with a functional restoration program and provided in cases where regional sympathetic block has demonstrated evidence of SMP (Stanton-Hicks, et al., 1998). Regional anesthetic, also known as nerve blocks, involves the injection of local anesthetic alone or in combination with steroids into a peripheral nerve or sympathetic ganglion. The site of the injection is determined by the location of the pain. It is noted that there is scant evidence regarding the proper timing, number, necessity or appropriateness of nerve blocks for diagnosis or treatment of CRPS. Techniques for regional nerve blocks include: selective sympathetic ganglion blockade, stellate ganglion block for the upper extremity and lumbar sympathetic block for the lower extremity, intravenous regional guanethidine/bretylum block, and intravenous phentolamine infusion (Harden, et al., 2010). Blocks may be used primarily to provide a pain-free period so that patients may progress in the functional restoration portion of treatment (Harden, 2001).

A Cochrane review was performed regarding the use of regional anesthetic for CRPS with three objectives: to determine the likelihood of pain alleviation after sympathetic blockade with local anesthetics in the patient with CRPS; to assess how long any benefit persists; and to evaluate the incidence of adverse effects of the procedure (Cepeda, et al., 2005). The review included two small randomized, double-blind cross-over studies that incorporated 23 subjects. Due to the small sample size, the authors determined that "no conclusion

concerning the effectiveness of this procedure could be drawn.” The authors note that sympathetic blockade is considered the gold standard for treatment of CRPS, but the efficacy is unknown.

Several case studies have been performed to study the effects of regional anesthetic, or nerve blocks in patients with CRPS (Meier, et al., 2009; Ackerman, et al., 2006; Dadure, et al., 2005). These studies indicate that short-term pain relief may be obtained with this treatment.

Spinal Cord Stimulation (SCS) and Peripheral Nerve Stimulation (PNS): SCS and PNS have been used in the treatment of CRPS. These modalities are recommended for patients who have tried and failed, who have been judged to be unsuitable, or when there is a contraindication for conservative treatment modalities. SCS, also known as dorsal column stimulation, involves surgical implantation of electrodes in the epidural space on the dorsal aspect of the spinal cord; electrical current from the electrode induces paresthesias, a sensation that suppresses the pain (Kemler, et al., 2000). SCS may be considered for CRPS type I, while PNS is considered a treatment for CRPS type II, providing relief from pain that is limited to the distribution of a major nerve (Ghai and Dureja, 2004). A review of the literature indicates that there is some evidence that these procedures can reduce pain in patients with CRPS.

In 2007, the European Federation of Neurological Societies (EFNS) published evidenced-based guidelines for use of neurostimulation for neuropathic pain (Cruccu, et al., 2007). Regarding the use of SCS for CRPS type I, they noted that based on the evidence, this treatment appears to be effective. With regard to CRPS type II, they noted that the available evidence is positive but “still requires confirmatory comparative trials before the use of SCS can be unreservedly recommended in these conditions” (Cruccu, et al., 2007).

Olsson et al. (2007) reported on a retrospective case study of the use of SCS in adolescents with CRPS type I. The study involved seven girls, 11–14 years of age, who presented with severe, incapacitating and therapy-resistant CRPS type I. Outcome measures included: spontaneous pain, evoked pain (allodynia), ability to bear weight, pain at bearing weight, dysautonomic signs, sensitivity to cold, analgesic consumption, and school attendance. It was noted that although instructions were provided to evaluate the patient using a visual analog scale, it was not always possible to obtain regular assessment data to the extent that it could be utilized for objective evaluation. The study relied on patients’ and parents’ unstructured evaluations of the effects and reported on weight-bearing and activity level. Five of the seven were noted to have complete pain relief, and in two there was a partial, but useful decrease in pain. The authors concluded that this may be a useful treatment in severely incapacitated, otherwise therapy-resistant pediatric cases of CRPS type I; however, further studies are needed before SCS can be recommended for use in both children and adolescents.

A Cochrane review was performed to assess the efficacy of SCS in relieving certain types of chronic pain and the complications and adverse effects of this procedure (Mailis-Gagnon, et al., 2004). Two randomized controlled trials, with 81 patients, were included in the review. It was noted that both studies reported that SCS was effective; however, no meta-analysis was undertaken due to the small number of patients and heterogeneity of the study population. The diagnosis in the studies included CRPS type I and failed back surgery syndrome. The reviewers note that at the present time, there is limited evidence that spinal cord stimulators are effective for some types of chronic pain (i.e., failed back syndrome and CRPS type I) and that patient selection should be thorough and indications for SCS need to be clear before treatment is provided. SCS might be effective for certain patients, but there is little evidence available to assess the benefits and harms of this treatment. The authors reported that, although there is limited evidence in favor of SCS for failed back surgery syndrome and CRPS type I, more trials are needed to confirm whether SCS is an effective treatment for certain types of chronic pain. In addition, there needs to be a debate about trial designs that will provide the best evidence for assessing this type of intervention.

A systematic review of the literature was performed for the purpose of reviewing the clinical and cost-effectiveness of SCS in the management of patients with CRPS and identifying the potential predictors of SCS outcome (Taylor, et al., 2006). One randomized controlled trial, 25 case series and one cost-effectiveness study were included in the review. The authors concluded that SCS appears to be an effective therapy in the management of patients with CRPS type I and type II. It is recommended that patients considered for SCS be psychologically appropriate and have responded well to a test period of neurostimulation prior to permanent implantation.

Kemler et al. (2004) performed a randomized trial involving patients who had CRPS for at least six months. The group receiving the SCS reported a reduction in the intensity of pain at six months, as compared with an increase in the group assigned to receive physical therapy alone. Forouzanfar et al. (2004) conducted a prospective study of 36 patients to investigate the long-term effects of cervical and lumbar SCS in the treatment of patients with CRPS type I. It was noted that pain intensity was reduced at six months, one year, and two years after implantation. Forty-two percent of cervical SCS patients and 47% of the lumbar SCS patients reported at least “much improvement.”

Sympathectomy: Sympathectomy has been used for patients with sympathetically maintained pain who have responded to regional anesthetic techniques; however, the role of this procedure in treatment of CRPS is controversial (Ghai and Dureja, 2004). The purpose of a sympathectomy is to disrupt the sympathetic nervous system. It can be performed by a surgical ablation of the sympathetic chain or through a chemical sympathectomy, using alcohol or phenol injections to destroy the sympathetic chain. The surgical procedure can be performed by open or endoscopic procedure. The chemical ablation results in a prolonged but not permanent denervation. This procedure should be utilized as a last resort in chronic refractory cases only (Mehta and Lindenfeld, 2003).

A Cochrane review was performed for the purpose of assessing the effects of both chemical and surgical sympathectomy with no treatment, placebo or conventional treatment, and to evaluate whether the technique of sympathectomy influences the outcomes of the procedure (Mailis-Gagnon and Furlan, 2005). The review notes that “despite the fact that the evidence for the effectiveness of sympathectomy for neuropathic pain derives mainly from uncontrolled studies and reports of personal experience, sympathectomy continues to be considered an appropriate indication for the treatment of neuropathic pain syndromes in many centers around the world.” Five articles reporting on four studies were included in the review. The authors noted that the practice of sympathectomy is based on very weak evidence. In addition, there may be complications from this procedure, which may be significant in terms of worsening of the pain or producing a new pain syndrome, or abnormal forms of sweating. The authors suggest that, “in light of the findings of the review, the practice of sympathectomy should be considered very carefully in terms of its usefulness, effectiveness and the potential risk of adverse effects.”

Motor Cortex and Deep Brain Stimulation: Motor cortex and deep brain stimulation have been proposed as a treatment option for intractable neuropathic pain, but at this time the procedure is considered an experimental option for treatment of CRPS (Ghai and Dureja, 2004). A review of the literature indicates that there are no clinical trials that evaluate this treatment for CRPS. Further research and data are needed to establish the efficacy of this procedure for CRPS (Stanton-Hicks, et al., 2002).

The EFNS evidenced-based guidelines for use of neurostimulation for neuropathic pain have the following notation regarding deep brain stimulation for CRPS that the “results are equivocal and require further comparative trials.” With regard to motor cortex stimulation for CRPS, the guidelines indicate that “evidence is insufficient” (Cruccu, et al., 2007).

Radiofrequency Ablation: Radiofrequency ablation (RFA) has been proposed as a treatment for CRPS. RFA is a procedure in which nerves are destroyed with the use of heat generated by an electric current. Evidence in the published peer-reviewed scientific literature on the use of RFA for CRPS appears to be limited to case series. Forouzanfar et al. (2000) reported on a retrospective analysis of clinical efficacy of radiofrequency (RF) of stellate ganglion (SG) in 86 patients with different chronic pain syndromes. They noted that the review indicates that an RF-SG block is most likely to be of benefit for patients suffering from CRPS type II, ischemic pain, cervicobrachialgia, or post-thoracotomy pain; however clinical efficacy remains to be proven in a randomized controlled trial. The Reflex Sympathetic Dystrophy Syndrome Association (RSDSA) treatment guidelines note, “The radiofrequency ablative techniques are much more controllable than neurolytic solution injections, and less invasive than surgical ablation. Preliminary reports in the form of case series are promising, but the exact role of RF ablation sympathectomy versus periodic blockade versus neurostimulation is uncertain.” (RSDSA, 2006) Well-designed controlled trials are needed before conclusions can be drawn regarding this intervention as a treatment for CRPS.

Complex Regional Pain Syndrome in Children

CRPS may also occur in children and adolescents. It has been noted that children are more likely to be responsive to conservative treatment. The consensus guidelines note that only a few children will require the

intensity and scope of treatment needed in the case of adults (Stanton-Hicks, et al., 1998). It has been noted that in children, the lower extremities are affected more frequently than the upper extremities; there is a marked female predominance, and the prognosis is excellent in most cases (Berde and Lebel, 2005). Most of the literature published regarding CRPS is geared to adolescents and adults (Bukhalo and Mullin, 2003).

Summary

Expert panel consensus guidelines recommend that treatment for complex regional pain syndrome/reflex sympathetic dystrophy (CRPS/RSD) include rehabilitation, pain management and psychological treatment. Functional restoration should be the primary goal of treatment. The symptoms may vary, and treatment needs are multidisciplinary and individualized to the patient. Conservative treatment includes physiotherapy, transcutaneous electrical stimulation (TENS), oral and topical medications, psychological treatment and regional aesthetic nerve blocks. If there is no improvement, or a failure or contraindication to conservative measures, then more invasive measures should be used, which may include: spinal cord stimulator, peripheral nerve stimulator, intrathecal drug delivery with subcutaneous pump, and sympathectomy.

Currently, there is insufficient evidence in the published, peer-reviewed scientific literature to support the use of acupuncture, biofeedback, electromagnetic field treatment, hyperbaric oxygen, hypnosis, interferential stimulators, ketamine administration, mirror box therapy, motor cortex stimulation, and radiofrequency ablation in the treatment of CRPS. Well-designed, randomized clinical trials are needed to determine the role of these interventions in the treatment of CRPS.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT [®] * Codes	Description
32664	Thoracoscopy, surgical; with thoracic sympathectomy
62360	Implantation or replacement of device for intrathecal or epidural drug infusion; subcutaneous reservoir
62361	Implantation or replacement of device for intrathecal or epidural drug infusion; nonprogrammable pump
62362	Implantation or replacement of device for intrathecal or epidural drug infusion; programmable pump, including preparation of pump, with or without programming
63650	Percutaneous implantation of neurostimulator electrode array, epidural
63655	Laminectomy for implantation of neurostimulator electrodes, plate/paddle, epidural
63685	Insertion or replacement of spinal neurostimulator pulse generator or receiver, direct or inductive coupling
64555	Percutaneous implantation of neurostimulator electrodes; peripheral nerve (excludes sacral nerve)
64802	Sympathectomy, cervical
64804	Sympathectomy, cervicothoracic
64809	Sympathectomy, thoracolumbar
64818	Sympathectomy, lumbar

HCPCS Codes	Description
C1816	Receiver and/or transmitter, neurostimulator (implantable)
C1820	Generator, neurostimulator (implantable), with rechargeable battery and charging system
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator

L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension

ICD-9-CM Diagnosis Codes	Description
337.20-337.29	Reflex sympathetic dystrophy
354.4	Causalgia of upper limb
355.71	Causalgia of lower limb

Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
90880	Hypnotherapy
90901 [†]	Biofeedback training by any modality
97810 [†]	Acupuncture, 1 or more needles; without electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient
97811 [†]	Acupuncture, 1 or more needles; without electrical stimulation, each additional 15 minutes of personal one-on-one contact with the patient, with re-insertion of needle(s) (List separately in addition to code for primary procedure)
97813 [†]	Acupuncture, 1 or more needles; with electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient
97814 [†]	Acupuncture, 1 or more needles; with electrical stimulation, each additional 15 minutes of personal one-on-one contact with the patient, with re-insertion of needle(s) (List separately in addition to code for primary procedure)
	Multiple/varied

HCPCS Codes	Description
C1300 [†]	Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval
	Multiple/varied

[†]**Note: Experimental/investigational/Unproven/Not Covered when used to report Biofeedback, Acupuncture or Hyperbaric Oxygen for the treatment of Reflex Sympathetic Dystrophy/Complex Regional Pain Syndrome.**

ICD-9-CM Diagnosis Codes	Description
	Multiple/varied

*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	2/15/2008	0438	Reflex Sympathetic Dystrophy/Complex Regional Pain Syndrome Treatment

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