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Clinical Policy Bulletin:
Complex Regional Pain Syndrome (CRPS) / Reflex Sympathetic Dystrophy (RSD): Treatments

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Policy

I. Aetna considers continuous epidural analgesia medically necessary for the treatment of members with intractable complex regional pain syndrome (CRPS), also known as reflex sympathetic dystrophy (RSD), when all of the following selection criteria are met:

- Members have experienced pain for more than 3 months despite conservative therapy (e.g., exercises, physical modalities and medications); *and*
- Members have failed a trial of physical therapy; *and*
- Members have failed a trial of nerve blocks with local anesthetics and steroids.

Aetna considers continuous epidural analgesia experimental and investigational for the treatment of CRPS when criteria are not met.

II. Aetna considers sympathetic blocks (e.g., stellate ganglion block [cervical sympathetic block] and lumbar sympathetic block) medically necessary for the treatment of CRPS when conservative treatments, including analgesia and physical therapy, have failed. Up to three sympathetic blocks are considered medically necessary to diagnose a member's pain and achieve a therapeutic effect; if the member experiences no pain relief after three injections, additional injections are not considered medically necessary. Repeat sympathetic blocks for complex regional pain syndrome beyond the first three injections are considered medically necessary when provided as part of a comprehensive pain management program, which includes physical therapy, patient education, psychosocial support, and oral medications, where appropriate. It is not considered medically necessary to repeat sympathetic blocks more frequently than once every 7 days.

III. Aetna considers dorsal column stimulators medically necessary durable medical equipment for the management of CRPS if the member meets all of the criteria listed in CPB 0194 - Dorsal Column Stimulation.

IV. Aetna considers intravenous administration of guanethidine, ketamine (including "ketamine coma" -- extended use of ketamine at anesthetic dosages), lidocaine or midazolam experimental and investigational for the treatment of CRPS, other types of chronic pain, and depression because their effectiveness for these indications has not been established.

V. Aetna considers intrapleural analgesia experimental and investigational for the treatment of CRPS with chronic pain involving the thoracic dermatomes since there is a lack of scientific evidence to support its effectiveness for this indication.

VI. Aetna considers neurolysis of the spinal accessory nerve experimental and investigational in the treatment of CRPS and post traumatic chronic pain syndrome because there is inadequate evidence in the peer-reviewed published clinical literature regarding its effectiveness.

VII. Aetna consider the following approaches experimental and investigational for the treatment of CRPS because their effectiveness for this indication has not been established:

> Bisphosphonates Botulinum
> toxin Electroconvulsive
> therapy Intrathecal baclofen
> Intrathecal corticosteroid
> Intravenous immunoglobulin
> Intravenous magnesium
> Mirror visual feedback/mirror therapy
> Multi-site continuous peripheral nerve catheters
> Neuroplasty
> Occlusal splint
> Pulsed light therapy
> Radiofrequency sympathetic neurotomy
> Tadalafil
> Thalidomide
> Tumor necrosis factor-α antagonists (e.g., adalimumab, certolizumab, etanercept, golimumab, and infliximab).

See also CPB 0113 - Botulinum Toxin, CPB 0135 - Acupuncture, CPB 0147 - Reflex Sympathetic Dystrophy Diagnosis, CPB 0206 - Parenteral Immunoglobulins, CPB 0310 - Thoracoscopic Sympathectomy, CPB 0445 - Electroconvulsive Therapy, and CPB 0755 - Motor Cortex Stimulation.

Background

Spinal administration of opioids has been demonstrated to be effective in the management of patients with chronic malignant pain. It has also been used in the treatment of chronic non-malignant pain such as reflex sympathetic dystrophy (RSD), also known as complex regional pain syndrome (CRPS). In some patients who have failed physical therapy and medical treatment, hospitalization (4 to 6 days) for continuous epidural narcotic analgesia,

with or without local anesthetics, may be necessary to break the pain cycle and prevent worsening of RSD symptoms. This route of administration allows maximum narcotic effect in the dorsal horn with very low blood levels, thus minimizing toxicity.

On the other hand, there is a lack of scientific evidence on the effectiveness of intrapleural analgesia for treatment of CRPS with chronic pain involving the thoracic dermatomes.

Ketamine hydrochloride, an agent used for general anesthesia, has local anesthetic effects as well as N-methyl-D-aspartate (NMDA) receptor antagonist action. During the last decade it has been shown that low, sub-anesthetic doses of ketamine may produce effective analgesia, especially when combined with opioids (Bell et al, 2002). Moreover, it has been suggested that ketamine may have potential in treating CRPS as co-analgesics when used in combination with opioids (Hewitt, 2000; Singh and Patel, 2001). However, there is insufficient evidence to support the use of intravenous ketamine in the treatment of CRPS/RSD. Hord and Oaklander (2003) noted that some common treatments (e.g., local anesthetic blockade of sympathetic ganglia) are not supported by the aggregate of published studies.

In an evidence-based review on the use of ketamine in the management of chronic pain, Hocking and Cousins (2003) concluded that the evidence for efficacy of ketamine for treatment of chronic pain is moderate to weak and that further controlled studies are needed. Additionally, Kingery (1997) noted that intravenous ketamine is not a realistic option for treatment of chronic neuropathic pain due to intolerable side-effects associated with long-term infusion.

The effectiveness of systemic lidocaine in the treatment of chronic pain (e.g., intractable neuropathic pain) has not been established. In a randomized controlled study (n = 22), Taskaynatan and colleagues (2004) examined the effect of intravenous regional anesthesia (Bier block) with methylprednisolone and lidocaine in CRPS type I. These investigators concluded that Bier block with methylprednisolone and lidocaine in CRPS type I does not provide long-term benefit in CRPS, and its short-term benefit is not superior to placebo. Furthermore, in a review on chronic neuropathic pain (Harden 2005), intravenous lidocaine is not listed as a treatment option. In addition, guidelines from the International Research Foundation for RSD/CRPS (2003) do not state that intravenous lidocaine is indicated for CRPS.

In a Cochrane systematic review, Cepeda et al (2005) reviewed the evidence supporting the use of intravenous regional anesthesia (Bier blocks) for CRPS. The investigators identified 2 small randomized double-blind cross-over studies that evaluated 23 subjects. The combined effect of the 2 trials produced a relative risk (RR) to achieve at least 50 % of pain relief 30 mins to 2 hrs after the sympathetic blockade of 1.17 (95 % confidence interval [CI]: 0.80 to1.72). The investigators stated that it was not possible to determine the effect of sympathetic blockade on long-term pain relief because the 2 randomized controlled trials (RCTs) evaluated different outcomes. Cepeda et al (2005) concluded that this systematic review revealed the scarcity of published evidence to support the use of local anesthetic sympathetic blockade as the "gold standard" treatment for CRPS. The 2 randomized studies that met inclusion criteria had very small sample sizes; therefore, no conclusion concerning the effectiveness of this procedure could be drawn. The investigators concluded that there is a need to conduct RCTs to address the value of sympathetic blockade with local anesthetic for the treatment of CRPS.

In a review on the management of patients with RSD/CRPS type I, Berthelot (2006) stated that mirror visual feedback was introduced recently for the rehabilitation of these patients. This approach entails the use of visual input from a moving, unaffected limb to re-establish the pain-free relationship between sensory feedback and motor execution. However, the

author concluded that the effectiveness of mirror visual feedback in treating RSD/CRPS type I needs to be assessed in RCTs.

Rothgangel and associates (2011) evaluated the clinical aspects of mirror therapy (MT) interventions after stroke, phantom limb pain and CRPS. A systematic literature search of the Cochrane Database of controlled trials, PubMed/MEDLINE, CINAHL, EMBASE, PsycINFO, PEDro, RehabTrials and Rehadat, was made by 2 investigators independently. No restrictions were made regarding study design and type or localization of stroke, CRPS and amputation. Only studies that had MT given as a long-term treatment were included. Two authors independently assessed studies for eligibility and risk of bias by using the Amsterdam-Maastricht Consensus List. A total of 10 randomized trials, 7 patient series and 4 single-case studies were included. The studies were heterogeneous regarding design, size, conditions studied and outcome measures. Methodological quality varied; only a few studies were of high quality. Important clinical aspects, such as assessment of possible side effects, were only insufficiently addressed. For stroke, there is a moderate quality of evidence that MT as an additional intervention improves recovery of arm function, and a low quality of evidence regarding lower limb function and pain after stroke. The authors stated that the quality of evidence in patients with CRPS and phantom limb pain is also low. Firm conclusions could not be drawn. Little is known about which patients are likely to benefit most from MT, and how MT should preferably be applied. Future studies with clear descriptions of intervention protocols should focus on standardized outcome measures and systematically register adverse effects.

In a pilot study, Kiefer and colleagues (2008a) investigated the effectiveness of subanesthetic isomeric S(+)-ketamine in refractory CRPS patients. Four refractory CRPS patients received continuous S(+)-ketamine-infusions, gradually titrated (50 mg/day to 500 mg/day) over a 10-day period. Pain intensities (average, peak, and least pain) and side effects were rated on visual analog scale (VAS), during a 4-day baseline, over 10 treatment days, and 2 days following treatment. Quantitative sensory testing (QST: thermo-, mechanical detection, and pain thresholds) was analyzed at baseline and following treatment. Subanesthetic S(+)-ketamine showed no reduction of pain and effected no change in thermo- and mechanical detection or pain thresholds. This procedure caused no relevant side effects. The lack of therapeutic response in the first 4 patients led to termination of this pilot study. The authors concluded that S(+)-ketamine can be gradually titrated to large doses (500 mg/day) without clinically relevant side effects. There was no pain relief or change in QST measurements in this series of long-standing severe CRPS patients.

In an open label phase II study, Kiefer et al (2008b) examined the effectiveness of ketamine in anesthetic dosage in refractory CRPS patients who had failed available standard therapies. A total of 20 American Society of Anesthesiologists (ASA) I-III patients suffering from refractory CRPS received ketamine in anesthetic dosage over 5 days. Outcome criteria were 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 observed at 1, 3, and 6 months following treatment (93.5 +/- 11.1 %, 89.4 +/- 17.0 %, 79.3 +/- 25.3 %; p < 0.001). Complete remission from CRPS was observed at 1 month in all patients, at 3 months in 17, and at 6 months in 16 patients. If relapse occurred, significant pain relief was still attained at 3 and 6 months (59.0 +/- 14.7 %, p < 0.004; 50.2 +/- 10.6 %, p < 0.002). Quality of life, the associated movement disorder, and the ability to work significantly improved in the majority of patients at 3 and 6 months. The authors concluded that these findings suggest benefit in pain reduction, associated CRPS symptoms, improved quality of life and ability to work following anesthetic ketamine in previously refractory CRPS patients. However, they stated that a RCT will be needed to prove its effectiveness.

Goldberg et al (2005) reported on the effectiveness of low-dose outpatient ketamine infusion for the treatment of CRPS diagnosed by International Association for the Study of Pain criteria in patients who have failed conservative treatment. Patients diagnosed with CRPS by a single neurologist were assigned to receive a 10-day outpatient infusion of ketamine supervised by an anesthesiologist/pain management specialist. The infusion was administered in a short procedure unit after each patient had been instructed on how to complete a pain questionnaire. Monitoring consisted of continuous ECG, pulse oximetry, and non-invasive blood pressure every 15 mins. Patients made journal entries each day prior to the infusion of 40 to 80 mg of ketamine. Subjects were also asked to rate their pain intensity using a verbal analog scale of 0 to 10 and the affective component using a verbal scale of 0 to 4. There was a significant reduction in pain intensity from initiation of infusion (day 1) to the 10th day, with a significant reduction in the percentage of patients experiencing pain by day 10 as well as a reduction in the level of their "worst" pain. The nadirs of pain were lower by day 10 with a significant reduction in the incidence of "punishing pain". Moreover, there was a significant improvement in the ability to initiate movement by the 10th day. The authors concluded that a 4-hr ketamine infusion escalated from 40 to 80 mg over a 10-day period can result in a significant reduction of pain with increased mobility and a tendency to decreased autonomic dysregulation. They also stated that although pain data showed some variability, the results are encouraging and point to the need for additional studies.

Webster and Walker (2006) examined the safety and effectiveness of prolonged low-dose, continuous intravenous (IV) or subcutaneous ketamine infusions in non-cancer outpatients. A total of 13 outpatients with neuropathic pain were administered low-dose IV or subcutaneous ketamine infusions for up to 8 weeks under close supervision by home health care personnel. Using the 10-point VAS, 11 of 13 patients (85 %) reported a decrease in pain from the start of infusion treatment to the end. Side effects were minimal and not severe enough to deter treatment. Prolonged analgesic doses of ketamine infusions were safe for the small sample studied. The authors concluded that these findings demonstrate that ketamine may provide a reasonable alternative treatment for non-responsive neuropathic pain in ambulatory outpatients. Moreover, the authors stated that additional studies should follow to ascertain optimal dose and duration for specific pain disorders and to minimize side effects. They also noted that questions regarding which patients would be most susceptible to this type of therapy and when treatment should be instituted remain unanswered.

Kiefer and associates (2007) described the treatment of an intractable CRPS-I patient with anesthetic doses of ketamine supplemented with midazolam. The patient presented with a rapidly progressing contiguous spread of CRPS from a severe ligamentous wrist injury. Standard pharmacological and interventional therapy successively failed to halt the spread of CRPS from the wrist to the entire right arm. Her pain was unmanageable with all standard therapy. As a last treatment option, the patient was transferred to the intensive care unit and treated on a compassionate care basis with anesthetic doses of ketamine in gradually increasing (3 to 5 mg/kg/h) doses in conjunction with midazolam over a period of 5 days. On the 2nd day of the ketamine and midazolam infusion, edema, and discoloration began to resolve and increased spontaneous movement was noted. On day 6, symptoms completely resolved and infusions were tapered. The patient emerged from anesthesia completely free of pain and associated CRPS signs and symptoms. The patient has maintained this complete remission from CRPS for 8 years now. The authors concluded that in a patient with severe spreading and refractory CRPS, a complete and long-term remission from CRPS has been obtained utilizing ketamine and midazolam in anesthetic doses. This intensive care procedure has very serious risks but no severe complications occurred. The psychiatric side effects of ketamine were successfully managed with the

concomitant use of midazolam and resolved within 1 month of treatment. The authors stated that large RCTs are needed to confirm the finding of this single case.

In a case report, Shirani et al (2008) described the effect of ketamine infusion in the treatment of severe refractory CRPS I. The patient was initially diagnosed with CRPS I in her right upper extremity. Over the next 6 years, CRPS was consecutively diagnosed in her thoracic region, left upper extremity, and both lower extremities. The severity of her pain, combined with the extensive areas afflicted by CRPS, caused traumatic emotional problems for this patient. Conventional treatments failed to provide long-term relief from pain. The patient was then given several infusions of IV ketamine. After the 3rd infusion, the edema, discoloration, and temperature of the affected areas normalized. The patient became completely pain-free. At 1-year follow-up, the patient reported that she has not experienced any pain since the last ketamine infusion. The authors concluded that treatment with IV ketamine appeared to be effective in completely resolving intractable pain caused by severe refractory CRPS I. Moreover, they stated that more research on this treatment is needed to better define its effectiveness in CRPS.

Sigtermans et al (2009) evaluated if ketamine improves pain in CRPS-1 patients. A total of 60 patients (48 females) with severe pain participated in a double-blind randomized placebo-controlled parallel-group trial. Patients were given a 4.2-day intravenous infusion of low-dose ketamine (n = 30) or placebo (n = 30) using an individualized step-wise tailoring of dosage based on effect (pain relief) and side effects (nausea/vomiting/psychomimetic effects). The primary outcome of the study was the pain score (numerical rating score: 0 to 10) during the 12-week study period. The median (range) disease duration of the patients was 7.4 (0.1 to 31.9) years. At the end of infusion, the ketamine dose was 22.2 +/- 2.0 mg/hr/70 kg body weight. 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. Patients receiving ketamine more often experienced mild-to-moderate psychomimetic side effects during drug infusion (76 % versus 18 %, p < 0.001). The authors concluded 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. However, it is important to note that the significance in pain relief between groups was lost in week 12.

Henson and Bruehl (2010) stated that although the pathophysiology of CRPS is unclear, it appears to reflect multiple interacting mechanisms. In addition to altered autonomic function, a role for inflammatory mechanisms and altered somatosensory and motor function in the brain is increasingly suggested. Several possible risk factors for development of CRPS, including genetic factors, have been identified. Few treatments have been proven effective for CRPS in well-designed clinical trials. However, recent work suggests that bisphosphonates may be useful in CRPS management and that the NMDA receptor antagonist ketamine significantly reduces CRPS pain when administered topically or intravenously at subanesthetic dosages. Extended use of ketamine at anesthetic dosages ("ketamine coma") remains a controversial and unproven treatment for CRPS. Spinal cord stimulation may be effective for reducing pain in approximately 2/3 of CRPS patients not responding to other treatments, but its efficacy appears to diminish over time.

Collins and colleagues (2010) performed a meta-analysis evaluating the effects of (individual) NMDA receptor antagonists on neuropathic pain, and the response (sensitivity) of individual neuropathic pain disorders to NMDA receptor antagonist therapy. PubMed (including MEDLINE), EMBASE and CENTRAL were searched up to October 26, 2009 for RCTs on neuropathic pain. The methodological quality of the included trials was

independently assessed by 2 authors using the Delphi list. Fixed or random effects model were used to calculate the summary effect size using Hedges' "g" (unbiased estimator). The outcome of measurements was the reduction of spontaneous pain. A total of 28 studies were included, meeting the inclusion criteria. Summary effect sizes were calculated for subgroups of studies evaluating ketamine IV in CRPS, oral memantine in post-herpetic neuralgia and, respectively, ketamine IV, and oral memantine in post-amputation pain. Treatment with ketamine significantly reduced pain in post-amputation pain (pooled summary effect size: -1.18 (95 % CI: -1.98 to 0.37, p = 0.004). No significant effect on pain reduction could be established for ketamine IV in CRPS (-0.65 [95 % CI: -1.47 to 0.16], p = 0.11) oral memantine in post-herpetic neuralgia (0.03 [95 % CI: -0.51 to 0.56], p = 0.92) and for oral memantine in post-amputation pain (0.38 [95 % CI: -0.21 to 0.98], p = 0.21). The authors concluded that based on this systematic review, no conclusions can yet be made about the efficacy of NMDA receptor antagonists on neuropathic pain. They stated that additional RCTs in homogenous groups of pain patients are needed to explore the therapeutic potential of NMDA receptor antagonists in neuropathic pain.

Sabia et al (2011) noted that historically, CRPS was poorly defined, which meant that scientists and clinicians faced much uncertainty in the study, diagnosis, and treatment of the syndrome. The problem could be attributed to a non-specific diagnostic criteria, unknown pathophysiologic causes, and limited treatment options. The 2 forms of CRPS still are painful, debilitating disorders whose sufferers carry heavy emotional burdens. Current research has shown that CRPS-1 and CRPS-2 are distinctive processes, and the presence or absence of a partial nerve lesion distinguishes them apart. Ketamine has been the focus of various studies involving the treatment of CRPS; however, currently, there is incomplete data from evidence-based studies. The question as to why ketamine is effective in controlling the symptoms of a subset of patients with CRPS and not others remains to be answered. A possible explanation to this phenomenon is pharmacogenetic differences that may exist in different patient populations.

Azari and colleagues (2012) reviewed published literature for evidence of the safety and effectiveness of ketamine in the treatment of CRPS. PubMed and the Cochrane Controlled Trials Register were searched (final search May 26, 2011) using the MeSH terms "ketamine", "complex regional pain syndrome", "analgesia" and "pain" in the English literature. The manuscript bibliographies were then reviewed to identify additional relevant papers. Observational trials were evaluated using the Agency for Healthcare Research and Quality criteria; randomized trials were evaluated using the methodological assessment of RCTs. The search methodology yielded 3 randomized, placebo-controlled trials, 7 observational studies and 9 case studies/reports. In aggregate, the data available reveal ketamine as a promising treatment for CRPS. The optimum dose, route and timing of administration remain to be determined. The authors concluded that RCTs are needed to establish the safety and effectiveness of ketamine and to determine its long-term benefit in CRPS.

MacDaniel (2003) reported 3 cases in which electroconvulsive therapy (ECT) for depression led to the relief of co-morbid CRPS as well as depression. In one of the cases, concomitant fibromyalgia was not relieved during 2 separate series of ECT. Wolanin et al (2007) reported a case of CRPS in a patient who also suffered from medically refractory depression. She was treated with ECT for her depression and subsequently was relieved of all her CRPS symptoms. The subject, a 42-year old female, underwent a series of 12 standard bi-temporal ECT for medically refractory depression. Physical examination and QST were performed before and after the patient's treatment with ECT. This standard treatment procedure for refractory depression completely resolved the patient's depressive symptoms. In addition, the patient's CRPS symptoms were also reversed. Physical examination as well as QST carried out before and after the ECT treatment correlated with her CRPS symptom improvement. The authors concluded that ECT was effective in the

treatment of severe refractory CRPS in this patient. The findings of these studies need to be validated by well-designed studies.

Kemler and associates (2008) assessed the effectiveness of spinal cord stimulation (SCS) in reducing pain due to CRPS-I at the 5-year follow-up. The authors performed a randomized trial in a 2:1 ratio in which 36 patients with CRPS-I were allocated to receive SCS and physical therapy (PT) and 18 patients to receive PT alone. Twenty-four patients who received SCS pluse PT also underwent placement of a permanent spinal cord stimulator after successful test stimulation; the remaining 12 patients did not receive a permanent stimulator. These researchers evaluated pain intensity, global perceived effect, treatment satisfaction, and health-related quality of life. Patients were examined before randomization, before implantation, and every year until 5 years thereafter. A total of 10 patients were excluded from the final analysis. At 5 years post-treatment, SCS plus PT produced results similar to those following PT for pain relief and all other measured variables. In a sub-group analysis, the results with regard to global perceived effect (p = 0.02) and pain relief (p = 0.06) in 20 patients with an implant exceeded those in 13 patients who received PT.

Manjunath et al (2008) compared the safety and effectiveness of 2 therapeutic options: (i) percutaneous radiofrequency (RF) thermal lumbar sympathectomy and (ii) lumbar sympathetic neurolysis. These researchers randomized 20 patients to receive percutaneous RF lumbar sympathectomy or lumbar sympathetic neurolysis with phenol 7 % in lower limb CRPS type 1. The study end points were pain relief and side effects. Within each group, there were statistically significant reductions from baseline in various pain scores after the procedure. However, there was no statistically significant difference in mean pain scores between the groups. The authors concluded that based on this pilot study, RF lumbar sympathectomy may be comparable to phenol lumbar sympathectomy. They stated that a larger trial is needed to confirm these findings.

In a prospective, RCT, Fischer et al (2008) evaluated the effectiveness of occlusal splint (OS) therapy on self-reported measures of pain in patients with chronic CRPS as compared with a non-treatment group. A total of 20 patients with CRPS were randomly assigned to either the OS or control group. Patients in the OS group were asked to use the OS at night-time and for 3 hrs during day-time for a total of 7 weeks; the control group had no stomatognathic intervention. The primary outcome was self-reported assessment of CRPS-related pain on numerical rating scales. Secondary outcome measures were the temporomandibular index (TMI), and the Short Form 36 Health Survey (SF-36). All patients had TMD signs and symptoms, but OS had no effect on CRPS-related pain on the numerical rating scale (p > 0.100). The changes in the TMI scores over time were 16.6 % +/- 24.6 % (improvement) in the OS group and -21.3 % +/- 25.9 % (impairment) in the control group that was significant (p = 0.004). There were no differences in the changes of SF-36 scores between groups (p = 0.636). The authors concluded that the use of OS for 7 weeks has no impact on CRPS-related pain, but improved signs and symptoms of TMD pain. They stated that future studies should include an active control group and evaluate if long-term changes in measures of oral health impact general health in CRPS-related pain.

van Rijn and colleagues (2009) stated that dystonia in CRPS responds poorly to treatment. Intrathecal baclofen (ITB) may improve this type of dystonia, but information on its efficacy and safety is limited. A single-blind, placebo-run-in, dose-escalation study was carried out in 42 CRPS patients to evaluate whether dystonia responds to IT. Thirty-six of the 38 patients, who met the responder criteria received a pump for continuous ITB administration, and were followed-up for 12 months to assess long-term efficacy and safety (open-label study). Primary outcome measures were global dystonia severity (both studies) and dystonia-related functional limitations (open-label study). The dose-escalation study showed a dose-effect of baclofen on dystonia severity in 31 patients in doses up to 450

microg/day. One patient did not respond to treatment in the dose-escalation study and 3 patients dropped out. Thirty-six patients entered the open-label study. Intention-to-treat analysis revealed a substantial improvement in patient and assessor-rated dystonia scores, pain, disability and quality-of-life (QoI) at 12 months. The response in the dose-escalation study did not predict the response to ITB in the open-label study. Eighty-nine adverse events occurred in 26 patients and were related to baclofen (n = 19), pump/catheter system defects (n = 52), or could not be specified (n = 18). The pump was explanted in 6 patients during the follow-up phase. Dystonia, pain, disability and QoI all improved on ITB and remained efficacious over a period of 1 year. However, ITB is associated with a high complication rate in this patient group, and methods to improve patient selection and catheter-pump integrity are warranted.

Tran et al (2010) summarized the evidence derived from RCTs pertaining to the treatment of CRPS. Using the Medline (January 1950 to April 2009) and Embase (January 1980 to April 2009) databases, the following medical subject headings (MeSH) were searched: "complex regional pain syndrome", "reflex sympathetic dystrophy", and "causalgia" as well as the key words "algodystrophy", "Sudeck's atrophy", "shoulder hand syndrome", "neurodystrophy", "neuroalgodystrophy", "reflex neuromuscular dystrophy", and "posttraumatic dystrophy". Results were limited to RCTs conducted on human subjects, written in English, published in peer-reviewed journals, and pertinent to treatment. The search criteria yielded 41 RCTs with a mean of 31.7 subjects per study. Blinded assessment and sample size justification were provided in 70.7 % and 19.5 % of RCTs, respectively. Only bisphosphonates appear to offer clear benefits for patients with CRPS. Improvement has been reported with dimethyl sulfoxide, epidural clonidine, ITB, motor imagery programs, spinal cord stimulation, and steroids, but further trials are required. The
available evidence does not support the use of calcitonin, vasodilators, or sympatholytic and neuromodulative intravenous regional blockade. Clear benefits have not been reported with stellate/lumbar sympathetic blocks, mannitol, gabapentin, and physical/occupational therapy. The authors concluded that published RCTs can only provide limited evidence to formulate recommendations for treatment of CRPS. In this review, no study was excluded based on factors such as sample size justification, statistical power, blinding, definition of intervention allocation, or clinical outcomes. Thus, evidence derived from "weaker" trials may be over-emphasized. These researchers stated that further well-designed RCTs are warranted.

In a randomized, double-blind, placebo-controlled cross-over study, Goebel et al (2010) assessed the effectiveness of intravenous immunoglobulin (IVIG) in patients with longstanding CRPS. Persons who had pain intensity greater than 4 on an 11-point (0 to 10) numerical rating scale and had CRPS for 6 to 30 months that was refractory to standard treatment were enrolled in this trial. Subjects received IVIG, 0.5 g/kg, and normal saline in separate treatments, divided by a washout period of at least 28 days. The primary outcome was pain intensity 6 to 19 days after the initial treatment and the cross-over treatment. A total of 13 eligible participants were randomly assigned; 12 completed the trial. The average pain intensity was 1.55 units lower after IVIG treatment than after saline (95 % CI: 1.29 to 1.82; p < 0.001). In 3 patients, pain intensity after IVIG was less than after saline by 50 % or more. No serious adverse reactions were reported. The authors concluded that low-dose IVIG can reduce pain in refractory CRPS. The drawbacks of this trial were small sample size, recruitment bias, and chance variation could have influenced results and their interpretation. The authors stated that more studies are needed to determine the best immunoglobulin dose, the duration of effect, and when repeated treatments are needed.

In an editorial that accompanied the afore-mentioned study, Birklein and Sommer (2010) noted that "a less obvious but critical limitation is the missing placebo response, which raises doubts about the adequacy of blinding. The observed response to IVIG (20 % to 30 % pain reduction from baseline) is in the range that one would expect for the placebo

response. Another concern relates to the definition of "refractory to standard treatment" as a criterion for patient eligibility. Study participants had not tried certain treatments that have been shown to have some effectiveness in randomized, controlled trials, such as motor or sensory learning, steroids, bisphosphonates, and sympathetic blocks .... A closer look at the individual treatment responses in Goebel and colleagues' study shows another reason that future trials should use "enriched" designs. Although 3 of 13 patients had very positive responses, the remaining 10 patients had no or only a transient response. If one could identify patients likely to respond, the efficacy of treatment and the cost-effectiveness ratio might be greatly improved. Only then might IVIG offer what we have long looked for: a safe, effective, easy-to-adhere-to, and scientifically validated treatment for CRPS".

In a pilot study, Breuer and colleagues (2008) examined the safety and effectiveness of ibandronate (a highly potent bisphosphonate) for the treatment of CRPS. A total of 10 patients received 6-mg ibandronate infusions on each of 3 days. The infusions were preceded by a 2-week baseline period, and followed by a 4-week follow-up period. One subject dropped out after the first infusion because of a decreased glomerular filtration rate. Aside from transitory flu-like symptoms characteristic of bisphosphonate treatments, the drug was well-tolerated. Significant post-intervention improvements were observed in average and worst pain ratings; the neuropathic pain qualities of "unpleasant", "sensitive", "deep", "intense", "surface", "hot","cold", "sharp", and "dull"; and hyperalgesia and allodynia. Subjects with hand CRPS improved significantly more than those with foot CRPS in average and worst pain, as well as in the following neuropathic pain qualities: "dull", "intense", "deep" and "time". The authors concluded that these findings justify a randomized, double-blind, placebo-controlled trial of ibandronate that should perhaps be limited to patients with hand CRPS.

Brunner et al (2009) performed a systematic review of all RCTs to evaluate the benefit of biphosphonates in the treatment of CRPS-1 patients with bone loss. These investigators selected RCTs comparing biphosphonates with placebo, with the goal of improving pain, function and quality of life in patients with CRPS-1. Two reviewers independently assessed trial eligibility and quality, and extracted data. Where data were incomplete or unclear, conflicts were resolved with discussion and/or trial authors were contacted for further details. They calculated the study size weighted pooled mean reduction of pain intensity (measured with a VAS). Four trials of moderate quality fulfilled the inclusion criteria. In respect to function and quality of life there was a trend in favor of biphosphonates but differences in outcome assessment impeded pooling of results. Two trials provided sufficient data to pool pain outcomes. Biphosphonates reduced pain intensity by 22.4 and 21.6 mm on a VAS after 4 and 12 weeks of follow-up. Data on adverse effects were scarce. The authors concluded that the very limited data reviewed showed that bisphosphonates have the potential to reduce pain associated with bone loss in patients with CRPS -1. However, at present there is insufficient evidence to recommend their use in practice.

In a randomized, double-blind, placebo-controlled, parallel-group trial, Munts et al (2010) examined the safety and effectiveness of a single intrathecal administration of 60 mg methylprednisolone (ITM) in chronic patients with CRPS. The primary outcome measure was change in pain (pain intensity numeric rating scale; range of 0 to 10) after 6 weeks. With 21 subjects per group, the study had a 90 % power to detect a clinically relevant difference (greater than or equal to 2 points). After 21 patients (10 on ITM) were included, the trial was stopped prematurely after the interim analysis had shown that ITM had no effect on pain (difference in mean pain intensity numeric rating scale at 6 weeks 0.3, 95 % CI: -0.7 to 1.3) or any other outcome measure. These researchers did not find any difference in treatment-emergent adverse events between the ITM and placebo group. The authors concluded that a single bolus administration of ITM is not effective in chronic CRPS

patients, which may indicate that spinal immune activation does not play an important role in this phase of the syndrome.

In a pilot study, Safarpour et al (2010) investigated the effectiveness and tolerability of botulinum toxin A (BoNT-A) in allodynia of patients with CRPS. A total of 14 patients were studied -- 8 patients were participants of a randomized, prospective, double-blind, placebo-controlled protocol; 6 patients were studied prospectively in an open-label protocol. Patients were rated at baseline and at 3 weeks and 2 months after BoNT-A administration. Ratings included brief pain inventory, McGill pain questionnaire, clinical pain impact questionnaire, quantitative skin sensory test, sleep satisfaction scale, and patient global satisfaction scale. BoNT-A was injected intradermally and subcutaneously, 5 units/site into the allodynic area (total dose 40 to 200 units). None of the patients with allodynia showed a significant response after treatment. The treatment was painful and poorly-tolerated. The authors concluded that intradermal and subcutaneous administration of BoNT-A into the allodynic skin of the patients with CRPS failed to improve pain and was poorly-tolerated.

Basford et al (2003) assessed the physiological effects of linearly polarized red and near-infrared (IR) light and quantitated its benefits in people with upper extremity pain due to CRPS I (RSD). This was a 2-part study. In the 1st phase, 6 adults (aged 18 to 60 years) with normal neurological examinations underwent transcutaneous irradiation of their right stellate ganglion with linearly polarized 0.6 to 1.6 microm light (0.92 W, 88.3 J); 2nd phase consisted of a double-blinded evaluation of active and placebo radiation in 12 subjects (aged 18 to 72 years) of which 6 had upper extremity CRPS I and 6 served as "normal" controls. Skin temperature, heart rate (HR), sudomotor function, and vasomotor tone were monitored before, during, and for 30 mins following irradiation. Analgesic and sensory effects were assessed over the same period as well as 1 and 2 weeks later. Three of 6 subjects with CRPS I and no control subjects experienced a sensation of warmth following active irradiation (p = 0.025). Two of the CRPS I subjects reported a greater than 50 % pain reduction. However, 4 noted minimal or no change and improvement did not reach statistical significance for the group as a whole. No statistically significant changes in autonomic function were noted. There were no adverse consequences. The authors concluded that irradiation was well-tolerated. There is a suggestion in this small study that treatment is beneficial and that its benefits are not dependent on changes in sympathetic tone. They stated that further evaluation is warranted.

In a systematic review, Dirckx and colleagues (2012) described the current empirical evidence for the effectiveness of administering the most commonly used immunomodulating medication (i.e., bisphosphonates, glucocorticoids, immunoglobulins, thalidomide, and tumor necrosis factor-α antagonists) in CRPS patients. PubMed was searched for original articles that investigated CRPS and the use of one of the afore-mentioned immunomodulating agents. The search yielded 39 relevant articles: from these, information on study design, sample size, duration of disease, type and route of medication, primary outcome measures, and results was examined. The authors concluded that theoretically, the use of immunomodulating medication could counteract the ongoing inflammation and might be an important step in improving a disabled hand or foot, leading to further recovery. However, they stated that more high-quality intervention studies are needed.

Chronic pain generally refers to persistent, non-acute, sometimes disabling pain in the extremities or other areas of the body. The pain can be associated with a known cause such as a major or minor injury, or it can be a symptom of a painful chronic condition or be of unknown etiology. Chronic pain syndrome is a diagnosis of exclusion. It is usually considered ongoing pain lasting longer than 6 months, with some using three months as a minimum criteria. It is associated with diffuse arthralgia and myalgia without signs of joint swelling, muscle weakness, weight loss or fever. Post traumatic pain syndrome is one of the historical terms used to describe excess pain with or without sympathetic dysfunction.

The spinal accessory nerve is the eleventh cranial nerve. It emerges from the skull and receives an extra root (or accessory) from the upper part of the spinal cord. This nerve supplies the sternocleidomastoid and trapezius muscles. The sternocleidomastoid muscle is in the front of the neck and turns the head while the trapezius muscle moves the scapula, turns the head to the opposite side, and helps pull the head back. Neurolysis is the destruction of nerves to promote analgesia or pain relief.

Diazgranados et al (2010) conducted a randomized, placebo-controlled, double-blind, cross-over, add-on study to determine whether an N-methyl-D-aspartate-receptor antagonist produces rapid antidepressant effects in subjects with bipolar depression. The main outcome variable was measured using the Montgomery-Asberg Depression Rating Scale primary efficacy measure scores. The results illustrated that within 40 minutes depressive symptoms significantly improved in subjects receiving ketamine compared with placebo, with a drug difference effect size being largest at day 2; 71 % of subjects responded to ketamine and 6 % responded to placebo.

Aan et al (2012) conducted a systematic review of all available published data on the antidepressant effects of ketamine, including all recently completed, ongoing, and planned studies. They reported that as of the publication of their report, 163 patients, primarily with treatment-resistant depression, had participated in case studies, open-label investigations, or controlled trials. All reported trials used a within-subject, cross-over design with inactive placebo controls. Response rates for the clinical trials and open-label investigations ranged from 25 % to 85 % 24 hours post-treatment. Seventy-two hours post-treatment response rates in the afore-mentioned studies was 14 % to 70 %. The authors concluded that further research of ketamine for individuals with severe mood disorders is warranted, but they did not recommend administration outside of the hospital setting due to the paucity of randomized controlled trials, lack of an active placebo, limited data on long-term outcomes, and potential risks.

Martin et al (2013) described, for the first time, the use of multiple peripheral nerve catheters to treat CRPS type I in a 10-year old girl who had failed multi-modal pharmacologic regimens. At separate times, a peripheral nerve catheter was placed to treat CRPS of the distal left lower extremity as well as the right upper extremity. The goal of this therapy was to relieve pain and thereby allow the re-initiation of intensive PT. A continuous infusion of 0.1 % ropivacaine was infused via the catheters for approximately 60 hours. The patient was subsequently able to participate in PT as well as activities of daily living with improved eating, sleeping, and mood. The authors concluded that although many therapeutic modalities have been tried in CRPS type I, given the debilitating nature of the disorder and the variable response to therapy, new and alternative therapeutic interventions, such as continuous peripheral nerve catheters, are needed. The findings of this single case study need to be validated by well-designed studies.

An UpToDate review on "Prevention and management of complex regional pain syndrome in adults" (Abdi, 2014) states that "Experimental approaches -- Several different approaches have been of interest for the treatment of longstanding or refractory CRPS, including intravenous ketamine, intravenous magnesium, tadalafil, mirror therapy, and intravenous immunoglobulin".

The Colorado Division of Workers' Compensation's medical treatment guidelines on "Complex regional pain syndrome/reflex sympathetic dystrophy" (2011) noted that "Sympathetic injections are generally accepted, well-established procedures. They include stellate ganglion blocks and lumbar sympathetic blocks. Unfortunately, there are no high quality randomized controlled trials in this area."

The Washington State Department of Labor and Industries' guidelines on "Work-related complex regional pain syndrome (CRPS): Diagnosis and treatment" (2011) stated that "Sympathetic blocks have long been a standard treatment for CRPS and can be useful for a subset of cases. Stellate ganglion blocks (cervical sympathetic blocks) and lumbar sympathetic blocks are widely used in the management of upper and lower extremity CRPS. There is limited evidence to confirm effectiveness. An initial trial of up to three sympathetic blocks should be considered when the condition fails to improve with conservative treatment, including analgesia and physical therapy."

Hey et al (2014) identified through case study the presentation and possible pathophysiological cause of complex regional pain syndrome and its preferential response to stellate ganglion blockade. Complex regional pain syndrome can occur in an extremity after minor injury, fracture, surgery, peripheral nerve insult or spontaneously and is characterized by spontaneous pain, changes in skin temperature and color, edema, and motor disturbances. Pathophysiology is likely to involve peripheral and central components and neurological and inflammatory elements. There is no consistent approach to treatment with a wide variety of specialists involved. Diagnosis can be difficult, with over-diagnosis resulting from undue emphasis placed upon pain disproportionate to an inciting event despite the absence of other symptoms or under-diagnosed when subtle symptoms are not recognized. The International Association for the Study of Pain supports the use of sympathetic blocks to reduce sympathetic nervous system over-activity and relieve complex regional pain symptoms. Educational reviews promote stellate ganglion blockade as beneficial. Three blocks were given at 8, 10 and 13 months after the initial injury under local anesthesia and sterile conditions. Physiotherapeutic input was delivered under block conditions to maximize joint and tissue mobility and facilitate restoration of function. The authors concluded that this case demonstrated the need for practitioners from all disciplines to be able to identify the clinical characteristics of complex regional pain syndrome to instigate immediate treatment and supports the notion that stellate ganglion blockade is preferable to upper limb intravenous regional anesthetic block for refractory index finger pain associated with complex regional pain syndrome.

An UpToDate review on "Prevention and management of complex regional pain syndrome in adults" (Abdi, 2014) states that "Local sympathetic blocks (e.g., stellate ganglion block) with local anesthetic, while of unproven benefit in terms of the long-term outcome, nevertheless may provide a short-term decrease in pain that can be diagnostically useful and that can help with mobilization of the affected limb. The author has experience in using clonidine in combination with local anesthetics for stellate ganglion and lumbar sympathetic nerve blocks successfully, but its value needs to be systematically studied. Stellate ganglion blocks may be performed at one week intervals and may be repeated several times. This treatment is abandoned if an immediate response (e.g., improved temperature and decreased pain) does not occur following the first or second nerve block".

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:

01996	Daily hospital management of epidural or subarachnoid continuous drug administration
62318	Injection, including indwelling catheter placement, continuous infusion or intermittent bolus, of diagnostic or therapeutic substance(s) (including anesthetic, antispasmodic, opioid, steroid, other solution),

	not including neurolytic substances, includes contrast for localization when performed, epidural or subarachnoid; cervical or thoracic
62319	lumbar or sacral (caudal)
63650	Percutaneous implantation of neurostimulator electrode array, epidural
63655	Laminectomy for implantation of neurostimulator electrodes, plate/paddle, epidural
63661	Removal of spinal neurostimulator electrode percutaneous array(s), including fluoroscopy, when performed
63662	Removal of spinal neurostimulator electrode plate/paddle(s), placed via laminotomy or laminectomy, including fluoroscopy, when performed
63663	Revision including replacement, when performed, of spinal neurostimulator electrode percutaneous array(s), including fluoroscopy, when performed
63664	Revision including replacement, when performed, of spinal neurostimulator electrode plate/paddle(s), placed via laminotomy or laminectomy, including fluoroscopy, when performed
63685	Insertion or replacement of spinal neurostimulator pulse generator or receiver, direct or inductive coupling
63688	Revision or removal of implanted spinal neurostimulator pulse generator or receiver
64479 - 64484	Injection(s), anesthetic agent and/or steroid, transforaminal epidural, with imaging guidance (fluoroscopy or CT)

CPT codes not covered for indications listed in the CPB:

32554	Thoracentesis, needle or catheter, aspiration of the pleural space; without imaging guidance
32555	Thoracentesis, needle or catheter, aspiration of the pleural space; with imaging guidance
32422	Thoracentesis with insertion of tube, includes water seal (e.g., for pneumothorax), when performed (separate procedure)
64702 - 64727	Neuroplasty (Exploration, Neurolysis or Nerve Decompression)
90281	Immune globulin (Ig), human, for intramuscular use
90283	Immune globulin (IgIV), human, for intravenous use
90284	Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg
90870	Electroconvulsive therapy (includes necessary monitoring)

Other CPT codes related to the CPB:

64400 - 64455, 64490 - 64530	Introduction/injection of anesthetic agent (nerve block), diagnostic or therapeutic [not covered for local anesthetic blockade of sympathetic ganglia]
96360	Intravenous infusion, hydration; initial, 31 minutes to 1 hour
+ 96361	each additional hour (List separately in addition to code for primary procedure)
96365 - 96368	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug)
96369 - 96371	Subcutaneous infusion for therapy or prophylaxis (specify substance or drug)
97001 - 97039	Physical medicine and rehabilitation evaluations and modalities

HCPCS codes covered if selection criteria are met:

A4290	Sacral nerve stimulation test lead, each
C1816	Receiver and/or transmitter, neurostimulator (implantable)
L8680	Implantable neurostimulator electrode, each
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator
L8682	Implantable neurostimulator radiofrequency receiver
L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
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
L8689	External recharging system for battery (internal) for use with implantable neurostimulator

HCPCS codes not covered for indications listed in the CPB:

J0135	Injection, adalimumab, 20 mg
J0475	Injection, baclofen, 10 mg
J0476	Injection, baclofen, 50 mcg for intrathecal trial
J0585	OnabotulinumtoxinA, 1 unit
J0586	OnabotulinumtoxinA, 5 units

J0587	RimabotulinumtoxinB, 100 units
J0717	Injection, certolizumab pegol, 1 mg (code may be used for medicare when drug administered under the direct supervision of a physician, not for use when drug is self administered)
J1438	Injection, etanercept, 25 mg
J1459	Injection, immune globulin (Privigen), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1561	Injection, immune globulin, (Gamunex/Gamunex-C/Gammaked), nonlyophilized (e.g., liquid), 500 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg
J1568	Injection, immune globulin, (Octogam), intravenous, nonlyophilized (e.g., liquid) 500 mg
J1569	Injection, immune globulin, (Gammagard liquid), nonlyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (Flebogamma Dif), intravenous, nonlyophilized (e.g., liquid) 500 mg
J1740	Injection, ibandronate sodium, 1 mg
J1745	Injection, infliximab, 10 mg
J2920	Injection, methylpredisone sodium succinate, up to 40 mg
J2930	Injection, methylpredisone sodium succinate, up to 125 mg
J3475	Injection, magnesium sulfate, per 500 mg
J3487	Injection, zoledronic acid (Zometa) 1 mg
J3489	Injection, zoledronic acid, 1 mg

Other HCPCS codes related to the CPB:

J2760	Injection, phentolamine mesylate, up to 5 mg

ICD-9 codes covered if selection criteria are met:

337.20 - 337.29	Reflex sympathetic dystrophy

ICD-9 codes not covered for indications listed in the CPB:

338.21 - 338.29	Chronic pain
338.3	Neoplasm related pain (acute) (chronic)
338.4	Chronic pain syndrome

Gluanethidine, Ketamine, Lidocaine or Midazolam for the treatment of depression:

Gluanethidine, Ketamine:

No specific

HCPCS codes not covered for indications listed in the CPB:

J2001   Injection, lidocaine HCL for intravenous infusion, 10 mg

J2250   Injection, midazolam HCl, per 1 mg

ICD-9 codes not covered for indications listed in the CPB:

296.20 - 296.36   Major depressive disorder

311   Depressive disorder, not elsewhere classified

The above policy is based on the following references:

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