Medical Policy Bulletin
Title:
Treatments for Complex Regional Pain Syndrome (CRPS)
Policy #:
MA08.026m

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

MEDICALLY NECESSARY

The following interventions are considered medically necessary, and, therefore, covered, for treatment of CRPS when their respective criteria are met:

- Local anesthetic sympathetic nerve blocks, i.e., stellate ganglion block for upper-extremity pain or lumbar sympathetic block for lower-extremity pain related to CRPS when first-line pain management strategies (e.g., oral medications [e.g, NSAIDS, corticosteroids, opioids, antiepileptics, antidepressants, clonidine, muscle relaxants], physical therapy, or occupational therapy) tried for at least a two-week period have failed to diminish or eliminate the individual's pain.
    - Following a positive response to the initial diagnostic stellate ganglion block, and sustained benefit in pain and function after three (3) sympathetic blocks from baseline (pre block) pain and function; additional regional sympathetic blocks of up to a maximum of six (6) total blocks in a 12-month period, performed at a frequency of no more than two (2) per week, are considered medically necessary, and, therefore, covered when all the following criteria have been met:
        - Benefit has been demonstrated by prior blocks as evidenced by all of the following:
            - Decreased use of pain medication
            - Improved level of function (e.g., increased range of motion, strength, and use of extremity in activities of daily living)
            - Improved tolerance to touch (e.g., decreased allodynia) or other objective measures
        - The intervention is being provided as part of a comprehensive pain management program (physical therapy, patient education, psychosocial support, and oral medication).
- Epidural or Intrathecal opioids: A preliminary trial of opioid drug administration for the treatment of severe, chronic, intractable pain via a temporary intrathecal/epidural catheter is indicated for individuals who are

unresponsive to less-invasive medical therapy such as orally administered systemic opioids and/or nerve blocks with local anesthetics and steroids.
    - If this preliminary trial demonstrates pain relief and a degree of side effects that are adequately acceptable (including effects on activities of daily living) and has the individual's acceptance, a permanent implantable infusion pump may be considered for continuous intrathecal (IT) or epidural administration of opioids.
    - The drug being administered and the purpose of its administration must be consistent with the indicated uses in the pump's US Food and Drug Administration (FDA)--approved labeling.
    - The individual has a life expectancy of at least 3 months.
- Intrathecal ziconotide (Prialt®): The administration of IT ziconotide (Prialt®) is indicated for the management of severe chronic pain in individuals for whom IT therapy is warranted and who are intolerant of, or refractory to, other treatments such as systemic analgesics (e.g., NSAIDS, opioids, antiepileptics, antidepressants) adjunctive therapies (e.g., physical therapy, nerve blocks, spinal cord stimulation), or IT morphine.
- Intrathecal baclofen: A preliminary trial of IT baclofen is indicated when pain is due to spasticity for individuals who are unresponsive to, or intolerant of, at least a six-week trial of non-invasive medical therapy, such as orally administered anti-spasmodic drugs.
    - If this preliminary trial demonstrates pain relief and a degree of side effects that are adequately acceptable (including effects on activities of daily living) and has the individual's acceptance, a permanent implantable infusion pump may be considered for continuous IT or epidural administration of opioids.
    - The drug being administered and the purpose of its administration must be consistent with the indicated uses in the pump's FDA-approved labeling.

EXPERIMENTAL/INVESTIGATIONAL

All other interventions are considered experimental/investigational and, therefore, not covered, for the treatment of CRPS because their safety and/or effectiveness cannot be established by review of the available published peer-reviewed literature (not an all-inclusive list):

- Chemical sympathectomy
- Continuous peripheral nerve block with any drug
- Epidural clonidine
- Intramuscular botulinum toxin
- Intramuscular ketamine
- Intramuscular magnesium sulfate
- Intrathecal clonidine
- Intrathecal glycine
- Intrathecal methylprednisolone
- Intrathecal opioids in combination with bupivacaine or lidocaine
- Intrathoracic administration of analgesics
- Intravenous regional sympathetic nerve block (IVRB) with any drug (e.g., bretylium, guanethidine, ketamine, ketanserin, lidocaine, phenoxybenzamine, reserpine)
- Intravenous (systemic) administration with any of the following agents:
    - Intravenous bisphosphonates
    - Intravenous bupivacaine
    - Intravenous dexmedetomidine
    - Intravenous dimethylsulfoxide (DMSO)
    - Intravenous immunoglobulin G (IVIG)
    - Intravenous ketamine
    - Intravenous lidocaine
    - Intravenous magnesium
    - Intravenous mannitol
    - Intravenous opioids
- Plasma exchange
- Plasmapheresis
- Cervical plexus catheter nerve block with any drug
- Brachial plexus catheter nerve block with any drug
- Lumbar plexus catheter nerve block with any drug

- Sacral plexus catheter nerve block with any drug

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity of the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request Failure to produce the requested information may result in a denial for the drug.

BILLING REQUIREMENTS

Inclusion of a code in this policy does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

If there is no specific HCPCS code available for the drug administered, then the drug must be reported with the most appropriate unlisted code along with the corresponding National Drug Code (NDC).

Guidelines

- Ziconotide (Prialt®); epidural infusions of opioids; intrathecal infusions of opioids and baclofen by implantable pumps:
    - This policy is consistent with Medicare's coverage criteria.
- IV regional sympathetic nerve block and systemic administration via the IV route, and intrathoracic administration of opioids and non-opioids
    - There are no Medicare coverage determinations addressing these services; therefore, the Company policy is applicable.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable Evidence of Coverage, certain parenteral treatments for complex regional pain syndrome are covered under the medical benefits of the Company's Medicare Advantage products when medical necessity criteria in this medical policy are met.

Drugs that are experimental/investigational are excluded for the Company’s Medicare Advantage plans because they are not covered by Medicare. Therefore, they are not eligible for reimbursement consideration.

ADMINISTRATION

Intrathecal (IT) ziconotide (Prialt®) is intended for use only in the Medtronic SynchroMed® II Infusion System, and the CADD-Micro Ambulatory Infusion Pump; it is not intended for intravenous (IV) or epidural administration.

Description

A number of parenterally administered drugs have been promoted for the treatment of complex regional pain syndrome (CRPS), formerly known as reflex sympathetic dystrophy (RSD), and sometimes designated as RSD/CRPS. This disorder has also been called post-traumatic dystrophy, causalgia, minor causalgia, Sudeck’s atrophy, and shoulder-hand syndrome. CRPS is a chronic, regional, post-traumatic pain syndrome with abnormalities in the sensory, motor, and autonomic nervous systems that typically develops some time after an acute injury to a joint or limb. However, CRPS may occur with no obvious precipitating event, or it may emerge in nontraumatized parts of the body.

Considerable confusion and controversy exist regarding the terminology, diagnosis, and treatment of CRPS. This is

due in part to the recent explosion of information on the subject of post-traumatic limb pain in general. Currently, most pain experts adhere to the terminology for CRPS that was developed by the International Consensus Conference (Merskey and Bogduk, 1994; Stanton-Hicks et al, 1995), which deliberately avoids suggesting the etiology or the site.

There are two types of CRPS, each with identical clinical features. Type 1 CRPS follows an illness or injury that has not directly damaged the affected limb. Type 2, once termed causalgia, occurs in patients who have had a major peripheral nerve injury (International Association for the Study of Pain Diagnostic Criteria).

DIAGNOSIS OF CRPS

There are no universally accepted diagnostic criteria for CRPS (Harden, 2001), nor is there a single diagnostic test that identifies it. Moreover, diagnosing CRPS is difficult because the condition is associated with a variety of clinical features, temporal factors, vascular and musculoskeletal phenomena, and underlying causes (Schott, 2001).

Although a variety of diagnostic criteria for CRPS has been proposed, most authorities agree that the diagnosis of CRPS should be based on history of injury, the individual's complaints, and physical signs (Atkins, 2003; Harden, 2001).

Following are the IASP Diagnostic Criteria for Type 1 and Type 2 Complex Regional Pain Syndrome (adapted from Merskey and Bogduk, 1994, Harden 2013):

- **Type 1 CRPS**
    - Continuing pain, allodynia, or hyperalgesia in which the pain is out of proportion to the initiating event;
    - Evidence of edema, changes in skin blood flow, or abnormal sudomotor activity in the painful region (this criterion is satisfied by either a sign or a symptom); and
    - No other condition that would account for the degree of pain and dysfunction.
- **Type 2 CRPS**
    - Type 2 CRPS is diagnosed when, in addition to the above three criteria for CRPS 1, there is also an initiating noxious event or a cause of immobilization.

Following are the Clinical Diagnostic Criteria for Complex Regional Pain Syndrome (adapted from Harden, 2013):

- Continuing pain, which is disproportionate to any inciting event
- At least one symptom in three of the four following categories, AND at least one sign** at time of evaluation in two or more of the following categories:
    - Sensory: Reports/evidence of hyperalgesia and/or allodynia
    - Vasomotor: Reports/evidence of temperature asymmetry and/or skin color changes and/or skin color asymmetry
    - Sudomotor/Edema: Reports/evidence of edema and/or sweating changes and/or sweating asymmetry
- Motor/trophic: Reports/evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
- 3. No other diagnosis that better explains the signs and symptoms

**** A sign is counted only if it is observed at time of diagnosis

TERMS RELATED TO COMPLEX REGIONAL PAIN SYNDROME

- **Allodynia:** perception of pain with an ordinarily nonpainful stimulus (e.g., air or clothing)
- **Hyperalgesia:** increased sensitivity to noxious stimulation
- **Hyperesthesia:** lowered pain threshold that permits increased pain from typically noxious stimulation
- **Neuropathic:** pertaining to injury to the peripheral or central nervous system
- **Nociceptive:** pertaining to damage to tissues due to thermal, chemical, mechanical, or other types of irritants and sensed by nociceptors
- **Sudomotor:** pertaining to stimulation of the sweat glands
- **Vasomotor:** pertaining to nerves supplying muscles in the walls of blood vessels

DISTINCTION BETWEEN CRPS-TYPE PAIN AND NOCICEPTIVE PAIN

CPRS is part of a broader classification of disorders called neuropathic pain disorders, which include postherpetic

neuralgia (PHN), painful diabetic neuropathy (PDN), and central poststroke pain syndrome. The neuropathic pain disorders comprise a complex group of disorders with many signs and symptoms that vary in number and intensity over time. Neuropathic pain disorders are related to dysfunction or disease of the nervous system at a peripheral level, a central level, or both, whereas the more commonly understood nociceptive pain is due to the activation of pain receptors (nociceptors). Thus, neuropathic pain in general, and CRPS pain in particular, differ fundamentally in etiology from the pain in nociceptive pain disorders. Chronic neuropathic pain (including CRPS) develops as a result of injury that somehow leads to abnormalities in transmission within the peripheral and/or central nervous system (Dworkin et al., 2003). More specifically—and for poorly understood reasons—CRPS pain develops as a result of reorganization within the nervous system. One outcome of this reorganization is a lowered threshold to nociceptive processing, as well as distorted pain perceptions. For example, patients with chronic neuropathic pain syndromes such as CRPS may have pain in response to stimuli that are normally not painful (allodynia) or they may have exaggerated pain in response to stimuli that are normally less painful (hyperalgesia). Also, patients with neuropathic pain of the CRPS type may experience pain even in the absence of stimuli. It is believed that many of the symptoms found in CRPS, such as allodynia or hyperalgesia, reflect a more easily excited nervous system that promotes pain sensation (Argoff, 2002).

EPIDEMIOLOGY

The variety of diagnostic criteria that have been used for CRPS has contributed to uncertainty regarding the exact incidence of CRPS. It has been estimated that CRPS occurs in approximately 1 of every 2000 traumatic events (Subbarao and Stillwell, 1981). CRPS affects both genders and all ages (including children). The disorder appears to be more common between the ages of 40 and 60 and may be more frequent in women. Genetic factors may play a role (Kimura and Komatsu, 2000; Devor and Raber, 1990; Mailis and Wade, 2001).

ETIOLOGY

The exact cause or etiology of CRPS is poorly understood. Its development is sometimes preceded by diseases of the peripheral and central nervous system, such as stroke, multiple sclerosis, spinal trauma, and shingles. Systemic diseases associated with CRPS include myocardial infarction, cardiac surgery, and drugs. Although there is no single specific etiology of CRPS, it is agreed that its most common antecedent is trauma. Bonica (1979) and Veldman et al (1993), using the definition of RSD, reported on a study that found that 65% of CRPS cases followed trauma (mostly a fracture); 19% followed an operation; and 2% followed an inflammatory process. In 4% of cases, onset of symptoms followed various other precipitating factors, such as injection, intravenous infusion, or cerebrovascular accident. In 10% of cases, no precipitant could be identified. CRPS type 2 (causalgia) has been reported after automated laser discectomy and cervical epidural injection.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE “STATE OF THE SCIENCE” WORKSHOP SUMMARY

The National Institute of Neurological Disorders and Stroke and the NIH Office of Rare Diseases (NINDS, 2015) reviewed the status of current research on CRPS/RSD and concluded that 1) RSD/CRPS appears to be a disease of the central nervous system, 2) there is little evidence upon which to base a choice of therapy for CRPS, and 3) there is an urgent need for many of these therapies to be tested in appropriately designed prospective clinical trials. This need is most urgent in the following areas: a) diagnostic criteria, b) epidemiology, c) CRPS model systems, d) disease mechanisms, e) integration between basic research and clinical research, and f) therapy (NINDS, 2015).

TREATMENT IN GENERAL

Because of the heterogeneity of neuropathic pain disorders and the lack of knowledge about their underlying causes, progress in developing reliable treatments for neuropathic pain disorders in general has proceeded very slowly. The same can be said of CRPS in particular. Most authorities recommend aggressive treatment in the early stages of CRPS, reasoning that the earlier treatment is instituted, the greater the likelihood that symptom progression will be contained (Schwartzmann 2000). Patients first presenting with moderate pain are more likely to have pain improvement or resolution than those presenting with severe pain. Delay in treatment prolongs rehabilitation. Without treatment, permanent tissue damage, chronic pain, and impairment are likely (Atkins 2003).

Currently, initial treatment of CRPS consists of reassurance, excellent analgesia, and intensive, careful physiotherapy to minimize pain and avoid disuse of the affected limb (Stanton-Hicks 1998). CRPS responds poorly to traditional treatments and to usual doses of analgesics. Nonsteroidal anti-inflammatory drugs may be more effective than opiates. Patients who do not respond rapidly to these agents should be evaluated by a pain specialist for consideration of second-line treatment with drugs. However, drug therapy is often unsuccessful (Harden 2001; Stanton-Hicks 1998). A variety of drugs have been used in CRPS to accomplish sympathetic nerve block—by means

of either intravenous regional block (IVRB) or direct block of ganglia, as occurs in brachial plexus, stellate ganglion (i.e., cervical), and lumbar-blocking procedures. Also, some authorities advocate using permanent sympathectomy when sympathetic nerve blocks no longer prove effective. Other interventions include desensitization of peripheral nerve receptors with capsaicin and nerve root stimulation by either transcutaneous or implanted dorsal column stimulator methods. Again, no treatment method has proved itself to be reliably effective over time, and claims of benefit remain unconfirmed (Kingery 1997; Harden 2001).

A meta-analysis to assess which agent should be prioritized when designing a therapeutic regimen was performed by Wertli, et al (2014). They found bisphosphonates, *N*-Methyl-D-aspartate receptor (NMDA) analogs, and vasodilators showed better long-term pain reduction than placebo. The authors note the lack of available well-designed studies. In their analysis there were insufficient data from which to analyze effect on disability.

Zernikow, et al. 2015, reviewed the literature to assess current evidence on the effectiveness of invasive treatments for CRPS in 173 children and adolescents. The invasive treatments applied most often were singular sympathetic blocks, epidural catheters, and continuous sympathetic blocks. Individual patients frequently received more than one invasive procedure. The authors noted the lack of methodological quality in the studies, and found that outcomes were rarely evaluated using validated measures. Consequently, they concluded the level of evidence for invasive therapies in the treatment of CRPS in children and adolescents is weak.

According to NINDS, parenteral non-opioid treatment options include sympathetic nerve block, botulinum toxin injections, and N-methyl-D-aspartate (NMDA) receptor antagonists (such as dextromethorphan and ketamine). However, the NINDS notes that no single drug or combination of drugs is guaranteed to be effective in every individual, and no drug has been approved by the FDA specifically for CRPS. According to the NINDS, no studies of intrathecal drug pumps with clonidine or baclofen have shown benefit for CRPS. Intravenous immunoglobulin and ketamine are still considered “emerging treatments”. (NINDS 2015).

Noting that there are few clinical guidelines for using IV therapies to treat CRPS, Xu, et al. 2016, conducted a systematic review of the literature that focused specifically on IV therapy. The search strategy yielded 299 articles of which 101 were deemed relevant and 63 were retrieved for analysis. The authors addressed IV bisphosphonates, IV immunoglobulin, IV ketamine, IV magnesium, IV mannitol, IV regional blocks and IV anti-TNF antibodies. They recommended the following: IV bisphosphonates to reduce pain associated with bone loss in patients with CRPS type I, IV immunoglobulin for refractory pain cases, IV ketamine in some refractory patients, IVRB with ketorolac (when used with lidocaine) for short-term pain reduction, and IVRB lidocaine at 5 mg/kg/h for reducing thermal pain. In recommending that bisphosphonates can be used to reduce pain associated with bone loss in patients with CRPS, the authors found evidence level 1B+ (4 references) and 2C+ (2 references). All references have been previously reviewed in this document with the exception of a letter to the editor. The recommendation for IV immunoglobulin (2B+/2C+) was based on work by Goebel, et al., also previously reviewed in this document. The ketamine recommendation (2B+/2C+) was based on studies also previously reviewed in this document. Many of the same ketamine studies were reported multiple times by different authors in different journals. IVRB with ketorolac (when used with lidocaine) was recommended (level of evidence 2B+/2C+) based on studies (other than animal reports and case studies) previously reviewed. While recommending these treatments the authors indicate that most studies of IV therapies for CRPS are not high quality, and further studies of RCT quality are required. It is not known if the recommended drugs are useful for acuity or chronicity. The authors found the following to lack sufficient evidence or were studied in trials that yielded conflicting results: IV magnesium (2B+), IVRB with clonidine, phenoxybenzamine or labetalol (2C+). Not recommended were the following: IV methylprednisolone and parecoxib (2B-/2C+), IV mannitol (2B-), IVRB with guanethidine, reserpine or droperidol (2A-/2B-), IV TNF-a antibodies (2B-).

An article from Vanderbilt University School of Medicine while noting that reviews suggest that physical and occupational therapy, bisphosphonates, calcitonin, sub-anesthetic intravenous ketamine, free radical scavengers, oral corticosteroids and spinal cord stimulation may be effective treatments, also observed the lack of high quality evidence to support the efficacy of the most commonly used interventions for treatment of CRPS (Kim et al 2016).

According to Gatti, et al. 2016, the few studies available regarding CRPS treatments are too small to be conclusive. However, they suggest that on the basis of the results of a few RCTs, high doses of bisphosphonates should be considered the treatment of choice for patients with CRPS I.

A review by authors from Massachusetts General Hospital observed that evidence of efficacy of CRPS treatment is strongest for rehabilitation therapies including graded motor imagery, neuropathic pain medications, and electric stimulation of the spinal cord, injured nerve or mortar cortex. Investigational treatments include ketamine, botulinum toxin, immunoglobulins and transcranial neuromodulation. (Oaklander and Horowitz 2015).

The same conclusion regarding botulinum toxin was reached by Oh and Chung (2015) after a review. Additionally, an

opinion piece from Case Western, the University of Pennsylvania and Yale concluded that botulinum toxin for treatment of CRPS is preliminary and awaits RCT results (Mittal 2016). A low dose IVIG RCT is being conducted in the UK with results expected by the end of July, 2016 (Gobel et al 2014).

An Up-to-date review by Abdi (2016), notes there is some support for bisphosphonates for CRPS including IV alendronate, IV neridronate, IV pamidronate and IV clodronate. Calcitonin is also a drug that has been studied for CRPS. However, of 3 trials, only 1 found benefit. Only low to moderate evidence is available to support using ketamine as a CRPS treatment, and there is a need for further trials to assess the efficacy of IVIG. According to Abdi, the limited evidence base for regional sympathetic nerve block and epidural clonidine suggests no benefit from these procedures.

The role of surgery in CRPS is limited.

PEDIATRIC TREATMENT

A review of treatments for pediatric CRPS noted that when there is a response to ketamine treatment, the duration of its effect can be limited from a few weeks to two months (Weissman, et al 2016). While a few non-controlled reports support use of bisphosphonates in the early stages, the authors concluded that to date, no specific pharmacological treatments are recommended for pediatric CRPS, and no large clinical trials are being conducted. The most commonly used invasive treatments in pediatric CRPS are single sympathetic blocks, epidural catheters and continuous sympathetic blocks. However, the authors also indicate that there is a weak level of evidence for the use of invasive treatments in the pediatric population, and no large prospective blinded controlled trials are available. According to Williams & Howard (2016), while interest in the use of intravenous therapies for CRPS treatment in children has increased (bisphosphonates in the presence of bone loss or demineralization) the evidence of efficacy for intravenous therapies is weak and further evaluation in terms of long-term efficacy, risks and cost effectiveness needs to be explored. The authors note the concern for short-term and long-term neuropsychiatric effects of using ketamine along with studies that suggest long-term pain reduction may not be sustained. Other intravenous agents including magnesium, free radical scavengers (mannitol), anti-inflammatory agents, local anesthetics, drugs acting on the sympathetic nervous system (guanethidine, reserpine, phenoxybenzamine, beta blockers, and anti-tumor necrosis factor (TNF) antibodies (infliximab) have not been tested in RTCs. Efficacy of intravenous regional blockage is not proven. Evidence of interventional modalities including peripheral nerve catheters and epidural blockade in children and adolescents is weak.

After a review of the literature of invasive modalities for pediatric CRPS, Rodriguez, et al. 2015, found no randomized controlled trials that compared conservative and invasive management in children. The paucity of data, lack of randomized trials and lack of quality evidence led the authors to conclude that interventional treatments for CRPS in children should be provided only in clinical research settings that have the experience and ability to report the outcomes.

SYMPATHETIC NERVE BLOCKS (STELLATE GANGLION BLOCK AND LUMBAR SYMPATHETIC BLOCK)

Freedman (2014) reviewed interventional treatments, including sympathetic blockade, and found that they are most beneficial in patients who demonstrate sympathetically medicated symptoms and those whose pain is limiting participation in therapy.

The efficacy of local anesthetic sympathetic blocks is a subject of controversy, and reviewers have noted that the quality of evidence on lumbar and stellate blocks is poor (Nelson 2006; Albazaz 2008; Cepeda 2005;Harden 2013). However, it is also noted that local anesthetic blocks have been used for many years to treat CRPS. Van Eijs (2011) considers sympathetic block to be the interventional treatment of first choice, but O'Connell (2013), in a comprehensive review, found low-quality evidence that sympathetic nerve blocks with anesthetic is not effective. Reviewers find that results may depend on early application before central pain pathways can set in (Nelson 2006; Albazaz 2008). In addition, uncontrolled surveys in the literature note that approximately 70% of patients report full or partial responses (Wheeler 2010).

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."

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”.

In an opinion article, Resmini, et al. 2016, note that sympathetic nerve blocks are commonly indicated in spite of lack of efficacy in current literature. There are no guidelines that define what medications should be administered for CRPS treatment but several drugs have been used, despite lack of scientific evidence supporting their use. This list of drugs include anti-inflammatory drugs, analgesics, anesthetics, anticonvulsants, antidepressants, corticosteroids, calcitonin, bisphosphonates, and calcium channel blockers. While noting the lack of evidence for bisphosphonates, the authors suggest that neridronate is associated with clinically relevant and persistent benefits in CRPS patients. Moreover, the use of bisphosphonates as first-line drug treatment is advocated by these researchers. It should be noted that neither neridronate nor other bisphosphates are FDA approved for treatment of CRPS. A clinical trial is ongoing for neridronate in CRPS-1 (Clinicaltrials.gov).

Chemical sympathectomy is a procedure in which phenol or alcohol is injected to destroy the sympathetic chain. The outcomes of trials are variable, with questionable efficacy. In concluding that there is poor evidence for the long-term effectiveness of this modality, the authors cited a Cochrane review that also concluded that sympathectomy should be used cautiously in selected patients and only after failure of other treatment options (Straube 2013).

PLEXUS CATHETER NERVE BLOCK AND CONTINUOUS PERIPHERAL NERVE BLOCK

According to Harden (2013), preoperative post-trauma, postoperative pain relief, and intractable pain of CRPS I & II are indications for brachial plexus blockade. Van Eijs et al 2011 recommend plexus brachialis blocks for individuals refractory to conventional treatment. Related to plexus catheter nerve blocks are continuous peripheral nerve blocks (CPNBs), also known as perineural local anesthetic infusion. CPNBs are indicated for prolonging intraoperative anesthesia and treating intractable hiccups. Although some have suggested that these blocks may be effective treatment of CRPS, (Aquirre 2012), this indication has, as yet, not been validated through well-designed studies(Ilfeld, 2011).

INTRAVENOUS REGIONAL SYMPATHETIC NERVE BLOCKADE (IVRB) IN GENERAL

Intravenous regional sympathetic nerve blockade (IVRB) in CRPS is intended to confine and concentrate medication at the sympathetic nerve endings in a particular region to produce sympathetic denervation without interrupting motor activity (Brown 1997). Frequent or chronic use of the various agents recommended in IVRB has never been supported in the scientific literature (Stanton-Hicks 1998), although Harden (2001) suggests that a short trial of a limited number of nerve blocks with very clear goals and time limitations may be indicated for ethical reasons, and may be cost-effective if attempts at functional restoration are unsuccessful. In any event, the timing of IVRB should be guided by the need for functional restoration (Stanton-Hicks 1998). For example, failure to progress in 2 to 4 weeks with a combination of reactivation, contrast baths, and desensitization to the next level of flexibility exercises, edema control, peripheral E-stimulation, and isometric strengthening should prompt consideration of introducing the most aggressive therapies, such as intravenous regional sympathetic blocks, psychotherapy, and/or pharmacotherapy (Stanton-Hicks 1998). Few studies support the use of other agents in IVRB (atropine, bretylium, phentolamine, clonidine, guanethidine, parecoxib, reserpine, droperidol with heparin, lidocaine, methylprednisolone with lidocaine, ketorolac, ketanserin), alone or in combination. (Harden 2013; O'Connell 2013; Goebel 2012; Abdi 2014; Freedman et al, 2014).

SPECIFIC AGENTS PROPOSED FOR IVRB

INTRAVENOUS BRETYLIUM TOSYLATE IN IVRB
Bretylium tosylate had been promoted as an IVRB adrenergic blocking agent. However, bretylium has not been approved by the FDA for use in CRPS. Moreover, although it was once available for other indications, injectable bretylium is no longer available in the U.S. Previously, intravenous bretylium in combination with lidocaine in IVRB significantly reduced pain compared with lidocaine alone in one randomized crossover, controlled study involving 12

patients (Hord 1995). No other trials involving bretylium in CRPS were identified in this assessment.

INTRAVENOUS BUPIVACAINE IN IVRB

A search of the medical literature revealed a single low-quality study of bupivacaine in subjects diagnosed with RSD (Bonelli et al 1983). The study found no difference between stellate ganglion block via bupivacaine and regional intravenous block via guanethidine. In 2012, a pilot study by Toshniwal et al randomnized 33 individuals to either continuous stellate ganglion (CSG) block or continuous infraclavicular brachial plexus block (CIPB) for the management of CRPS I of the upper extremity. Bupivacaine 0.125% was infused for 1 week, after which the individuals were followed for 4 weeks. The CIPB group showed significant improvement vs. the CSG group during the first 12 hours after the infusions. After 12 hours, the pain score was similar between the groups. At four weeks, both groups showed significant improvement in edema and ROM scores, which led the authors to recommend a larger well-randomized, well-controlled clinical trial to confirm the findings. Therefore, evidence that intravenous bupivacaine improves the net health outcome is lacking. Furthermore, the FDA has not approved its use in CRPS.

INTRAVENOUS GUANETHIDINE IN IVRB

Guanethidine is a postadrenergic blocking agent that has been promoted for IVRB in CRPS. However, its use in CRPS has not been approved by the FDA. Guanethidine alone, during an attempt to achieve IVRB, produced no benefit over placebo in an RCT involving 16 patients (Jadad et al 1995). In a cross-over RCT, Ramamurthy and Hoffman (1995) found no significant differences from intravenous guanethidine alone or in combination with lidocaine. In a low-quality crossover study (Rocco et al 1989) (12 patients), no difference in pain reduction between intravenously administered guanethidine plus lidocaine, reserpine plus lidocaine, or lidocaine alone was found. An RCT performed by Gschwind et al (1995) in 71 patients undergoing fasciectomy for Dupuytren's disease resulted in preoperative intravenous guanethidine showing no advantage over placebo in the prevention of CRPS. In addition, most guanethidine trials have failed to show improvement in efficacy over lidocaine or saline. O'Connell (2013) found moderate-quality evidence that IVRB using guanethidine is not effective and may be associated with complications. A review by Rockett (2014) observes that intravenous regional anesthesia or intravenous regional block (IVRA or IVRB) with guanethidine is no longer recommended due to significant adverse effects. In summary, for intravenous guanethidine in CRPS, there is limited evidence suggesting that it does not improve the net health outcome. In addition, intravenous guanethidine has not received FDA approval for use in CRPS.

INTRAVENOUS KETAMINE IN IVRB

Ketamine, a drug well known for its ability to induce dissociation during anesthesia, has been proposed in IVRB in the treatment for CRPS. The agent has been reported to reduce continuous and evoked pain when given in prolonged and low doses in patients with injury of the peripheral and central nervous system (Correll et al 2002; Eide 1995). A search of the medical literature produced no RCTs involving the use of intravenous ketamine in CRPS. Existing studies investigating ketamine are of poor quality or address only non-CRPS pain. Therefore, intravenous ketamine in CRPS has not been shown to improve the net health outcome. In addition, intravenous ketamine has not been approved by the FDA for use in CRPS.

INTRAVENOUS KETANSERIN IN IVRB

Two RCT studies investigated intravenous ketanserin (a selective serotonin receptor antagonist with weak adrenergic receptor--blocking properties) against placebo to achieve regional sympathetic blockade. A study by Hanna and Peat (1989) found a significant improvement in pain in patients diagnosed with RSD who were receiving 10 mg of ketanserin in a single bolus. The other study involving ketanserin (Bounameaux et al 1984) showed no difference in pain reduction with ketanserin compared to placebo. For intravenous ketanserin in CRPS, there is inadequate evidence upon which to make conclusions regarding health outcomes. Intravenous ketanserin is not available outside investigational settings, and it has not been approved by the FDA for use in CRPS.

INTRAVENOUS LIDOCAINE IN IVRB

Lidocaine hydrochloride is used during IVRB as a local anesthetic and sometimes with other injectable medications such as a diluent solution providing local anesthesia (Dunn 2000). An RCT involving seven patients diagnosed with CRPS I (Price et al 1998) showed intravenous lidocaine administered to achieve an IVRB resulted in a slight improvement when compared with saline. The improvement was not significant, however. In a low-quality crossover study (Rocco et al 1989) (12 patients), no difference in pain reduction between intravenously administered guanethidine plus lidocaine, reserpine plus lidocaine, or lidocaine alone was found.

A systematic review (Challapalli et al 2005) of the analgesic effect of lidocaine and its oral analogs found that these agents were safe in controlled clinical trials for neuropathic pain, were better than placebo, and were as effective as other analgesics. However, these results are limited by the few trials with adequate information on safety and efficacy, and by the heterogeneity of the model. A retrospective study of IVRB with lidocaine and methylprednisolone for treatment of upper extremity CRPS in 168 individuals was conducted in Greece by Varitimidis et al (2011). According to the authors, after a mean follow-up of 5 years, a complete absence of pain was reported by 92% of

patients. They noted that treatment must start early to expect such good results. As with other non-randomized, uncontrolled studies, the placebo effect cannot be discounted in this report. Eckmann, et al. (2011) reported the results of a randomized, double-blinded, crossover study of lidocaine with ketamine in CRPS of the lower extremity in 10 adults where only one individual achieved significant improvement. In addition, Goebel et al (2012) found evidence to be conflicting for lidocaine sympathetic ganglion blocks. Therefore, for intravenous lidocaine in CRPS, there is limited evidence that suggest that it does not improve the net health outcome. Lidocaine has not been approved by the FDA for use in CRPS.

INTRAVENOUS PARECOXIB IN IVRB
Intravenous parecoxib is the only injectable COX-2-inhibitor. It is widely used in Europe under the brand name Dynastat. In a randomized placebo-controlled double blind trial, neither pressure pain threshold nor quantitative sensory testing was improved with the drug (Breuer et al 2014). The FDA declined to approve parecoxib for use in the United States in 2005. The lack of scientific evidence does not permit conclusions regarding net health outcomes.

INTRAVENOUS PHENOXYBENZAMINE IN IVRB
Because oral phenoxybenzamine and other oral alpha-adrenergic blocking agents have been used with varying degrees of success in CRPS, there has been speculation that phenoxybenzamine could be used as an IVRB agent in CRPS. The agent has not been approved by the FDA for use in CRPS (Malik et al 1998). A search of the medical literature produced no RCTs involving the use of intravenous phenoxybenzamine in CRPS. Therefore, evidence upon which to base conclusions regarding the use of phenoxybenzamine in IVRB is lacking. The use of phenoxybenzamine in CRPS has not been shown to improve the net health outcome.

INTRAVENOUS PHENTOLAMINE IN IVRB
A high-quality study (Verdugo and Ochoa, 1994) (77 patients) showed that 30 minutes of 35 mg of intravenous phentolamine for the treatment of “reflex sympathetic dystrophy” was ineffective. Therefore, for intravenous phentolamine in CRPS, there is limited evidence upon which to base a conclusion (Kosharakyy 2013). That evidence suggests that intravenous phentolamine does not improve the net health outcome. Therefore, intravenous phentolamine in CRPS has not been shown to be as beneficial as any established alternatives. According to Wheeler 2014, controlled clinical trials of IV phentolamine showed mixed results and are hampered by poor methodology. Intravenous phentolamine is available outside investigational settings; however, it has not been approved by the FDA for use in CRPS.

INTRAVENOUS PHENYLEPHRINE IN IVRB
In a randomized controlled trial by Verdugo and Ochoa (1994), phenylephrine given during IVRB for the treatment of “reflex sympathetic dystrophy” was ineffective. Accordingly, for intravenous phenylephrine in CRPS, there is limited evidence suggesting that it does not improve the net health outcome. Therefore, intravenous phenylephrine in CRPS has not been shown to be as beneficial as any established alternatives. Intravenous phenylephrine is available outside investigational settings; however, it has not been approved by the FDA for use in CRPS.

INTRAVENOUS RESERPINE IN IVRB
Intravenous reserpine combined with intravenous guanethidine to achieve regional sympathetic blockade gave no benefit over placebo in one RCT (Blanchard et al 1990). For intravenous reserpine in CRPS, there is limited evidence suggesting that it does not improve the net health outcome. Intravenous reserpine has not been approved for use in CRPS.

SYSTEMIC INTRAVENOUS AGENTS IN GENERAL

Casale, et al. 2015, comprehensively reviewed currently available systemic drug treatments for CRPS. The authors indicate that over the last few decades, a large number of drugs have been proposed for systemic administration. However, due to the lack of randomized, controlled trials this approach to treatment remains empirical. Corticosteroids although often the first agents to be employed, continue to be controversial. According to these authors, good results have been obtained using dexamethasone and mannitol. However, neither of these agents have been FDA approved for CRPS treatment. The NMDA receptor antagonists (ketamine, amantadine, memantine, dextromethorphan {DM} and methadone) need additional clinical trials to establish the most clinically useful cost/benefit regarding side effects and analgesic action. In addition, none of these drugs have FDA approval for CRPS. Alpha-adrenoceptor blockers including phenoxybenzamine, phentolamine, yohimbine, and clonidine have been used in CRPS with equivocal results. The use of propranolol has been abandoned. A calcium channel blocker, ziconotide, administered intrathecally has been used in CRPS. There is little compelling scientific evidence for sodium channel blocker anti-epileptic agents in CRPS. Effective doses of intravenous lidocaine may be difficult to achieve due to development of adverse cardiovascular effects. Anti TNF (ex. infliximab), thalidomide, and lenalidomide need additional double-blind, controlled trials. Other agents are listed below:

SYSTEMIC INTRAVENOUS BISPHOSPHONATES

Alendronate, pamidronate, neridronate, etidronate, risedronate, ibandronate, and clodronate (also known as clodronate disodium, clodronic acid, or dichloromethylene bisphosphonate) are classed as bisphosphonates. These agents may be capable of relieving pain by modulation of nociceptive primary afferents in bone and pain-associated changes in the spinal cord (Schott 1997; Schott 2001). Although bisphosphonates are promoted for systemic intravenous treatment of CRPS, their use in CRPS has not been approved by the FDA. One high-quality RCT (Varenna et al 2000) found a significant improvement in pain reduction in patients receiving intravenous clodronate, compared to placebo. Another RCT (Adami et al 1997) found that intravenous alendronate significantly improved pain, compared to placebo.

More recent studies of the use of bisphosphonates in CRPS have been performed. Verenna et al (2013) performed a randomized, double-blind placebo-controlled clinical trial of IV neridronate in 82 individuals with CRPS I where significant improvements in the Visual Analogue Scale (VAS) vs. placebo were reported. However, this drug is approved only for treatment of osteogenesis imperfecta and only in Italy. O'Connell et al (2013) found low-quality evidence that bisphosphonates may effectively reduce pain when compared with placebo, at least in the short term. They concluded that although the efficacy of bisphosphonates was promising, it has not been proven efficacious with confidence and warrants further investigation. While the UK Guidelines found strong evidence of efficacy of IV alendronate, IV pamidronate, and IV clodronate in CRPS, none of these drugs are approved for use in either the UK or the US (Goebel et al 2012). Trials of bisphosphonates in CRPS I have demonstrated the potential to reduce pain associated with bone loss. Most studies found improvement in pain symptoms and increased functionality. However, because of small sample sizes, more studies are needed to recommend bisphosphonates for CRPS treatment. (Kosharskyy 2013).

In a comprehensive review of CRPS, Borchers and Gershwin (2014) note that there is convincing evidence that bisphosphonates can significantly relieve spontaneous and stimulus-evoked pain and improve function in patients with early disease. According to Wheeler (2014), IV clodronate and alendronate have been shown to significantly improve pain, swelling, and range of motion in individuals with acute CRPS. Varenna, et al. 2014, indicates that studies show that bisphosphonates may be effective in the early stages of CRPS. However, according to Casale 2015, only a few trials are available that would allow definitive conclusions.

A study by Eun Young et al 2016, compared the effectiveness of IV pamidronate and oral prednisolone in 21 patients with CRPS subsequent to hemiplegic strokes. Patients were randomly assigned to pamidronate (n=11) or prednisolone (n=10). Subjective pain and hand edema (circumference of the middle finger and the wrist were measured at baseline and at 1, 2, and 4 weeks following the end of treatment. Both groups showed significant improvement in pain scores that were maintained to the 4 week period. Finger edema reduction was maintained at 4 weeks for those in the steroid group. Wrist edema reduction was maintained for 4 weeks in those on pamidronate. The authors noted the need for larger controlled longer-term studies to validate the findings. An editorial discussing the study indicated that for now pamidronate appears to be the drug of choice in both post-traumatic and post-stroke CRPS type I (Van Daele 2016). Additionally, according to Frediani and Bertoldi (2015), IV clodronate has been used off-label for decades for CRPS type 1 with doses that range from 3-5 grams.

Therefore, for intravenous bisphosphonates in the treatment of CRPS, there is limited evidence that they improve the net health outcome.

SYSTEMIC INTRAVENOUS BUPIVACANE

No data were found for IV bupivacaine treatment of CRPS.

SYSTEMIC INTRAVENOUS DEXMEDETOMIDINE

Clinical investigations of dexmedetomidine for the treatment of CRPS are limited. according to Kosharakyy, et al., 2013, further studies are needed to assess the efficacy of dexmedetomidine for treatment of chronic pain. Dexmedetomidine has not been approved by the FDA for treatment of CRPS.

SYSTEMIC INTRAVENOUS DIMETHYLSULFOXIDE (DMSO)

A number of free radicals have been proposed for use in CRPS including DMSO, but no convincing evidence is available. DMSO has been FDA approved only for interstitial cystitis (Casale 2015).

SYSTEMIC INTRAVENOUS IMMUNOGLOBULIN G

In a double-blind placebo-controlled trial, intravenous immunoglobulin G (IVIG) was provided to a randomly assigned group of 13 patients who had refractory CRPS for 6-30 months. Pain levels were greater than 4 on a 0-10 rating scale. With IVIG treatment, the average pain intensity was 1.55 units lower than with placebo treatment (P= 0.001). In spite of these results, the researchers acknowledge the need for studies to determine best dose, duration of effect, and frequency of treatment (Gobel, Baranowski, Mauer, et al).

In their systematic reviews, both Cossins (2013) and Goebel (2012) found limited evidence for the efficacy of low dose IVIG. An opinion article suggested that immune mechanisms may be involved in long-standing pain, and IVIG may moderate pain by reducing immune activation (Gonzales 2012). However, no data were presented to support the theory.

Like ketamine, the NINDS considers IVIG to be an emerging treatment for CRPS (NINDS 2013). The authors cited a small study (Gobel, 2010, previously reported) and note that a larger study involving individuals with acute phase CRPS is planned. IVIG has not been FDA approved for treatment of CRPS.

In a review of data, Abdi (2015) continues to classify IVIG as an experimental approach to the treatment of CRPS. Gierthmuhlen, et al, in 2014, noted two aspects of IVIG in the treatment of CRPS: 1. CRPS may have an autoimmunity component and 2. There have been observations of pain relief with IVIG in CRPS. Despite these points, the relevance of these findings remain unclear. Furthermore, per Gierthmuhlen (2014) and Freedman (2014), there is a scarcity of data, thus, further research is necessary.

In addition, IVIG has not received FDA approval for use in CRPS.

SYSTEMIC INTRAVENOUS KETAMINE
In a small observational study, ketamine was titrated from 10 mg/hr to a maximum dose of 40 mg/hr to achieve comfort without evidence of significant side effects. Infusions were provided to 6 CRPS patients over a 5-day period. Patients were admitted to a monitored telemetry unit and maintained on their usual medication during the infusion period. Daily pain assessments and ketamine blood levels were collected. Minimal pain relief was observed on day 1, but significant pain relief ($P < 0.05$) was observed by day 3, compared to baseline, and continued throughout the 5-day period. However, uniformity of relief was not achieved. On day 5, there was little or no change in the pain measure assessed as the worst pain experienced over the last 24 hours in 6 of the 16 patients. In this study, there was no follow-up after the 5-day period (Goldberg, Torjman, Schwartzman, et al).

Twenty patients were infused with ketamine in anesthetic doses over 5 days. Significant pain relief was observed at 1, 3, and 6 months following treatment. Complete remission from CRPS was observed at 1 month in all patients, at 3 months in 17 patients, and at 6 months in 16 patients. In spite of suggested benefit in relief of CRPS symptoms, the authors state that randomized controlled trials are needed to prove efficacy (Kiefer, Rohr, Ploppa, et al).

Sigtermans et al enrolled 60 patients in a double-blind randomized placebo-controlled trial. Patients were admitted to a short-stay inpatient facility where they received either ketamine or saline infused over 4 days. Ketamine was titrated at regular intervals to a maximum of 30 mg/hr for a 70 kg patient. The infusion rate was increased when pain relief was insufficient. Liver function (daily) and blood pressure (TID) were measured. Pain scores over the 12-week monitoring period were significantly lower than those in patients receiving placebo ($P < 0.001$); however, the significance was lost between the groups at week 12 ($P = 0.07$). Patients receiving the drug experienced more psychomimetic side effects than controls (93% vs. 17%, $P < 0.001$). In fact, patient and investigator guesses of administered treatment were correct in 74% and 88%, respectively, most likely due to psychomimetic side effects. Functional improvement did not occur in either group. The authors suggested that 4-day treatment with low-dose ketamine is safe, with psychomimetic side effects that were acceptable to most patients (Sigtermans, Van HIlten, Bauer, et al).

Schwartzman et al described a double-blind placebo-controlled outpatient trial that randomized 19 patients with refractory CRPS into a ketamine group ($n = 9$) or a placebo group ($n = 10$). All subjects were infused with 100 mL of normal saline with or without ketamine for 4 hours (25 mL/h) daily for 10 days (5 days on, 2 days off, 5 days on). The maximum ketamine rate was 0.35 mg/kg/h not to exceed 25 mg/h. Subjects in both arms received clonidine and versed. Patients were seen at 2 weeks and then monthly for the following 3 months. Following treatment the ketamine group showed a 21.4% reduction in pain scores ($P< 0.01$), while the placebo group demonstrated a non-significant 3.1% reduction ($P> 0.05$). There was no change in patient activity in either the pre- or post-treatment phase. Side effects were described as nausea, headache, tiredness, or dysphoria in 4 out of 9 patients in the ketamine group and in 2 out of 10 patients in the placebo group. The authors suggest that the lack of any psychomimetic side effects may be due to the addition of midazolam and clonidine. This trial was conducted with multiday subanesthetic doses of ketamine, although the authors note (citing the study by Kiefer) that in their experience only the 5-day intravenous ketamine regimen at anesthetic doses with midazolam and clonidine provide complete remission of CRPS symptoms lasting over 5 years. In fact, this trial was prematurely terminated because during the 2-year trial period the researchers found that doses of 50 mg/h (200 mg over a 4-hour period) provided much greater pain relief lasting for a longer period of time without complications. Therefore, they did not want to continue treating patients at the low ketamine dose (Schwartzman, Alexander, Grothusen, et al).

In a commentary on the previous two studies involving ketamine, Bell and Moore question the safety of repeated infusions of ketamine should pain return. Furthermore, they note that not only do safety questions remain, but optimal ketamine treatment regimens for chronic pain have yet to be established (Bell, Moore).

A retrospective study (without a control group) of ketamine infusions for refractory chronic pain was conducted at the University of Chicago Medical Center (Patil et al 2013). Forty nine patients underwent 369 infusions. Of these patients, 18 (37%) had a diagnosis of CRPS, 8 had refractory headaches and 7 severe back pain. All patients reported significant reduction in Visual Analogue Scale (VAS) scores and reportedly, up to half of the patients experienced pain relief for up to 3 weeks.

Cossins et al (2013) found moderate evidence for low-dose ketamine, but, according to the author, this evidence becomes compromised by the findings by Noppers et al (2011), of liver failure after prolonged or repeated treatment. O'Connell et al (2013) found low-quality evidence that IV ketamine may effectively reduce pain. Moreover, it is associated with many side effects, and, in the studies cited, the effect was not sustained beyond 4-11 weeks post-treatment.

The National Institute of Neurological Disorders and Stroke (NINDS) considers ketamine an emerging treatment for CRPS. The authors noted that investigators are using low doses of ketamine to either reduce substantially, or eliminate, the chronic pain of CRPS. "In certain clinical settings, ketamine has been shown to be useful in treating pain that does not respond well to other treatments." It should be noted that the information on its website does not represent endorsement of the treatments or an official position by the NINDS.

According to Kosharakyy et al (2013) in a literature review, there are obstacles to the use of ketamine for chronic pain, including low oral bioavailability, a lack of an easily available formulation for chronic delivery, concerns over psychomimetic side effects, and mixed efficacy in clinical trials. The authors concluded that the use of ketamine infusions for the treatment of CRPS shows promise, but further prospective, randomized, double-blind placebo-controlled studies of anesthetic and sub-anesthetic doses of ketamine are needed.

In a systematic literature review specific to ketamine treatment for CRPS, Azari, et al (2012), concluded that the drug, while promising, needs well-designed clinical trials to determine the optimum dose, route and timing of administration. The efficacy, safety and long-term benefit also need to be demonstrated.

Wheeler (2014) indicates that while the rationale for ketamine for CRPS seems reasonable, no studies have shown benefit using objective outcome measures with double-blind randomized controlled methodology. In addition, several research questions remain to be settled. While Birklein et al (2015), opines that currently the only medical treatment that is effective against chronic CRPS pain is ketamine infusions, the patient's function is not improved and the infusions have side effects.

An UpToDate review (Abdi 2015) continues to classify ketamine as an experimental approach to treatment of CRPS. Additionally, researchers indicate that overall evidence for intravenous ketamine treatment in CRPS is limited and adverse effects restrict its usage. Further studies are necessary to assess efficacy and risk-benefit ratio (Casale 2015, Gierthmuhlen 2014). Ketamine has not been FDA approved for treatment of CRPS.

An additional study from Drexel University College of Medicine noted that poor responders to ketamine treatment had a lower body mass index (BMI) than responders. The researchers investigated the mechanisms underlying lower BMI that characterizes CRPS patients who respond poorly to IV ketamine therapy. They also sought to identify potential biomarkers for predicting response. Regulation of proopiomelanocortin (POMC) expression is crucial in normal body weight homeostasis. The authors found that although ketamine treatment did not alter POMC expression, poor responders had higher levels of POMC mRNA than responders. There was a positive correlation between the pretreatment levels of miR-34a to BMI and response to therapy. Larger studies are required to confirm the findings (Shenoda et al, 2016).

The above authors also investigated treatment-induced circulating microRNA as potential biomarkers. According to the authors, differences in miRNA signature in responders and poor responders before and after therapy indicate the prognostic value of miRNA response to intravenous ketamine (Douglas et al, 2015).

An observational longitudinal cohort study was conducted to assess the efficacy of sub-anesthetic ketamine infusions on children with chronic pain. Sixty-three individuals who received infusions were included. Of these, 23 had CRPS (37%). Ketamine infusions at doses of 0.1-0.3 mg/kg/h lasted for 4-8 hours per day up to a maximum of 16 hours over a maximum of 3 consecutive days. Pain scores after each infusion were significantly reduced from pretreatment scores ($p<0.001$). Greater reductions occurred in CRPS patients than in other chronic pain syndromes. Ketamine infusions did not change oral morphine intake compared to baseline doses. No follow-up except after treatment days

was reported. Effect on function was not reported. The authors note the need for further studies to assess the optimum dose and long-term effect of ketamine on CRPS in children and adolescents (Sheehy et al, 2015).

A study to assess the effects of long-term ketamine treatment on cognitive function was reported by Kim, et al 2016. Thirty CRPS patients were divided into a long-term frequent ketamine treatment group (n=14) and a non-long-term group (n=16). The participants completed questionnaires including demographic and clinical characteristics and variables affecting cognitive function. They also performed neuropsychological tests. Patients who received long-term ketamine treatment showed impairment in cognitive function – specifically in executive function compared with the non-long-term individuals.

Ketamine in anesthetic dosage was administered to 5 patients with CRPS of a mean of 8 years duration. The drug was administered over a 10 day period and patients received 1-5 doses. Pain reduction began on the 4-5th day of treatment. No improvement was noted in function. Pain reduction lasted 1.5-2.5 months following treatment then relapsed to baseline level. The authors observed the short-term analgesic effect of the therapy but also noted the lack of effect on movement or function of the affected limbs (Puchalski, Zyluk 2016).

Wheeler (2015), observes that the optimal dosing and duration of infusions of ketamine is unknown. These and other questions have yet to be answered. In addition, studies to date have not validated the benefit of ketamine using objective outcome parameters with double-blind randomized controlled methodology.

SYSTEMIC INTRAVENOUS LIDOCAINE
A study of lidocaine in CRPS, used as a continuous intravenous infusion in escalating doses, was reported. The treatments were administered to 49 CRPS patients over 5 days. Pain parameters were assessed at 1, 3, and 6 months following therapy. The researchers reported significant reduction in pain that lasted an average of 3 months (Schwartzman et al 2009).

When intravenous lidocaine was compared with lidocaine used in a lumbar sympathetic block, IV lidocaine failed to produce significant changes in spontaneous and evoked pain intensity measurement compared to pretreatment values (Meier et al 2009).

There are some uncontrolled studies of lidocaine in neuropathic pain, but few address IV lidocaine in CRPS (Mackey S 2007; Carroll and Younger 2010; Challapalli et al 2005). One recent small study found benefit from lidocaine infusions for CRPS (Schwartzmann et al 2009), while another found no significant changes in pain resulting from IV lidocaine use (Meier et al 2009). Additionally, there is no consensus for this treatment, and long-term response is unknown.

According to Harden et al (2013), lidocaine infusions have fallen out of favor and are lacking evidence of efficacy. Kosharakyy et al (2013) performed a comprehensive review and noted that the best results were reported in Schwartzman et al (2009), but this study was small and non-randomized. They therefore concluded that additional studies were needed to confirm the results. O'Connell et al (2013) and Gierthmuhlen, et al. (2014) found low-quality evidence (based on one study) that high-dose IV lidocaine may have a small effect on pain when compared with diphenhydramine. Casale (2015) notes that systemic lidocaine is only therapeutic in cases of cold-induced allodynia. However, its channel blocking activity is unspecific and effective doses may be difficult to achieve due to adverse cardiovascular effects.

Lidocaine is not FDA approved for intravenous infusion for treatment of CRPS.

SYSTEMIC INTRAVENOUS MAGNESIUM
In a pilot study, intravenous magnesium was provided to 8 patients, while 2 patients received normal saline as placebo. The placebo results were not analyzed or reported. At follow-up of 12 weeks, pain was significantly reduced from baseline. Impairment level and quality of life also improved, while there was no difference in skin sensitivity or functional limitations (Collins, Suurmond, de Lange, et al). This is a small study whose results need to be confirmed in a large, well-designed trial. In a review, Casale, Atzeni, Sarzi-Puttini 2015, indicates that intravenous magnesium can be considered a potential non-pharmacological supplement because it has fewer side effects than other treatments; however, further studies are necessary to identify the best route of administration. No additional studies of magnesium for treatment of CRPS have been performed. The drug is not FDA approved for CRPS.

SYSTEMIC INTRAVENOUS MANNITOL
It has been proposed that free radical scavengers may have a role in curtailing the CRPS disease process. Perez et al conducted a randomized, placebo-controlled, double-blind trial involving 41 patients that compared intravenous mannitol in normal saline, infused in 4 hours over 5 days, with equal volumes of normal saline as placebo. Both groups received physical therapy. Pain was monitored using the Visual Analogue Scale (VAS) during the trial.

Impairment and disability levels and quality of life were assessed up to 9 weeks. At the end of the study, no significant differences were found between mannitol and placebo treatment (Perez, Pragat, Geurts, et al).

A small study compared treatment strategies in four groups of CRPS type I individuals (Lee 2012). Group A was administered a NSAID (n=10), group B oral gabapentin (n=12), group C IV mannitol 10% and a steroid (n=11), group D IV mannitol, steroid and oral gabapentin (n=26). The best results occurred in group D which showed recovery of grip strength and improvement in pain level, finger range of motion. This is a small study that needs replication. Moderate evidence of non-efficacy was found in the UK review (Goebel 2012). O'Connell, et al. 2013, found very low quality evidence that IV mannitol is not effective.

Intravenous mannitol has not been FDA approved for treatment of CRPS.

SYSTEMIC INTRAVENOUS OPIOIDS
According to Freeman (2014), opioids for chronic benign pain syndromes remain controversial secondary to potential for abuse, diversion, and overdoses leading to death. Recent reviews found in Casale 2015 reported that opioids are not recommended as systemic treatment for CRPS. Although it is generally recognized that opioids have little or no effect on chronic nerve pain, there have been some reports of pain reduction and improved quality of life in individuals with chronic nerve pain. However, there has been no controlled studies performed to demonstrate this finding.

INTRATHECAL AGENTS

INTRATHECAL BACLOFEN
A search of the literature for studies of intrathecal baclofen in CRPS revealed one small randomized crossover trial (van Hilten et al 2000) (7 patients) suggesting that either continuous therapy or bolus injections of the agent might be effective in the treatment of dystonia in reflex sympathetic dystrophy. Therefore, there is limited evidence suggesting that intrathecal baclofen in CRPS improves the net health outcome. However, intrathecal baclofen has not been approved by the FDA for use in CRPS.

Intrathecal baclofen (ITB) was evaluated for treatment of dystonia in CRPS. Thirty-eight patients met the responder criteria, and 36 of those received a pump for continuous ITB administration in a dose-escalation study. Dose effect of baclofen on dystonia severity was shown in 31 patients with doses up to 450 mcg/day. One patient did not respond, and 3 patients dropped out. Thirty-six patients entered an open-label study. Intention-to-treat analysis at 12 months found improvement in dystonia, pain, disability and quality of life. Eighty-nine adverse events occurred in 26 patients. Of these, 19 were directly related to baclofen, 52 to pump defects, and 18 to unspecified problems. The pump was explanted in 6 patients during the follow-up phase. Although CRPS symptoms improved and ITB remained efficacious over a period of 1 year, the authors noted the problems with high complication rate and suggested that methods to improve patient selection and pump integrity are warranted (Van Rijn, Munts, Marinus et al).

A study to assess the effect of varying the infusion rate on the efficacy and safety of intrathecal baclofen delivery was reported. (van der Plas 2011). Individuals with CRPS-related dystonia who had no beneficial response to a minimum dose of baclofen, or who were intolerant of dose escalation because of side effects, were randomized to slower infusion rate delivery (SIRD) or four times faster infusion rate delivery (FIRD). There were no significant differences between the FIRD and the SIRD groups for the primary outcomes of dystonia and pain. The same researchers in a later open study found significant improvement in global intense pain, sharp pain, dull pain and deep pain during the first six months in a study of individuals with CRPS-related dystonia receiving titrated doses of intrathecal baclofen. After this period pain scores leveled off despite further improvement of dystonia and continued ITB titration (van der Plas 2013).

Intrathecal baclofen is advised for individuals who display a dystonic component to CRPS. Harden et al (2013) reports level 3 evidence for intrathecal baclofen in dystonic CRPS. According to Harden et (2013), if oral baclofen is effective but poorly tolerated, administration by intrathecal pump is a treatment option. Although O'Connell et al 2013 concludes that intrathecal baclofen infusion needs further study, Goebel et al. (2012) recommends using intrathecal baclofen if other options have failed.

INTRATHECAL CLONIDINE
Like epidural clonidine, intrathecal clonidine infusion requires additional investigation (Tran, Duong, Bertini et al, 2010). A small study showed a 30% or greater reduction in pain 2 hours after injection in 10 out of 22 individuls. However, the change in pain report did not correlate with the percentage change in areas of hyperalgesia (P= 0.09) or allodynia (P=0.24). The authors note that analgesia does not parallel antihyperalgesia with these treatments. (Rauck, North, Eisenach 2015.) No other recent studies were found.

INTRATHECAL GLYCINE
Intrathecal glycine was investigated as a potential therapy for pain and movement disorders in a randomized double-blind placebo-controlled trial in 19 patients. Over a 4-week period, no significant differences were found between the treatment and control groups (Munts, van der Plas, Voormolen, et al).

INTRATHECAL METHYLPREDNISONE
A double-blind, randomized placebo-controlled parallel-group trial was reported using a single intrathecal administration of methylprednisolone. The trial was stopped prematurely at 6 weeks when no difference was found between the treatment and control group (Munts, van der Plas, Ferrari, et al; Gierthmuhlen J, Binder A, Baron R, 2014). A 2014 review article (Rijsdijk, van Wijck, Kalkman, et al 2014) comments that the reports of the efficacy of intrathecal methylprednisolone are contradictory and that its safety is debated.

INTRATHECAL OPIOIDS
Patients with intractable malignant and non-malignant pain were treated with intrathecal opioid infusion with an implantable pump. At follow-up of 3 years, reduction of non-malignant pain on the Visual Analogue Scale (VAS) was reduced by more than 50% in 71.3% of patients. According to the authors, the treatment should be provided only in specialized centers (Koulousakis, Kuchta, Bayarassout, et al 2007). According to Singh, Patel, Grouthsen et al, a morphine pump should be carefully considered for chronic pain of non-malignant origin. Other studies recommend intrathecal opioid administration as an option for non-malignant pain, including CRPS, which can significantly improve quality of life in selected patients (Koulousakis 2007, Singh, Nelson 2006). A Consensus Guideline (Deer 2010) published an algorithm for intrathecal therapies which advised opioids and/or ziconotide be first-line treatments for CRPS. According to the NINDS, intrathecal infusion requires lower doses than that is required for oral administration, therefore decreasing side effects and increasing effectiveness.

INTRATHECAL OPIOIDS IN COMBINATION WITH BUPIVACAINE
In small retrospective studies, bupivacaine was found to be stable in an implantable infusion system (Hildebrand 2001, Goucke 2010). However, clinical outcomes were mixed. In retrospective studies to assess the efficacy of bupivacaine when added to IT opioids for treatment of nonmalignant pain, a significant improvement in paid reduction, disability and quality of life scores was reported (Kumar 2009). In a larger retrospective study, (n=126) a significant reduction in opioid dose escalation was demonstrated when bupivacaine combined with opioids was compared with opioids alone (Veizi 2011). It should be noted that of the 143 subjects enrolled in these trials, only 12 were treated for CRPS. The only randomized trial of opioids alone or opioids with bupivacaine found the addition of bupivacaine to IT opioids failed to produce improvement in pain control, and the researchers concluded that IT mixtures of opioids and bupivacaine are not efficacious in the treatment of chronic nonmalignant pain. There is a need for additional large randomized trials to define the use of IT bupivacaine, including long-term toxicity and neuropathology, particularly when used with other agents. Also unknown is the type of pain for which IT bupivacaine is most efficacious (Deer 2002, Kumar 2009, Veizi 2011, Mironer 2002). Bupivacaine is not approved by the FDA for IT administration.

INTRATHECAL OPIOIDS IN COMBINATION WITH LIDOCAINE
There is a lack of scientific evidence of positive impact on health outcomes with IT lidocaine/opioid treatment in CRPS. Lidocaine is not FDA approved for IT infusion.

INTRATHECAL ZICONOTIDE (PRIALT®)
A randomized, placebo-controlled trial with gradually increasing dosage over a 3-week period showed a statistically significant improvement in the Visual Analogue Scale of Pain Intensity (VASPI) with ziconotide (Prialt®) versus placebo. In addition, an open-label, multicenter study enrolled 644 patients with chronic pain in an evaluation of ziconotide (Prialt®) long-term use. Of patients with VASPI scores of 50 mm or greater at baseline who completed 1 month of therapy, 32.7% had greater than 30% improvement in VASPI scores. Also recorded was the pain impact on daily life which significantly differed between baseline and month two.

INTRAMUSCULAR AGENTS

INTRAMUSCULAR BOTULINUM
A search of the literature for randomized controlled trials related to intramuscular botulinum in CRPS produced one record: a small observational study of 11 patients with CRPS type 1 affecting one upper extremity. The study suggests that botulinum A toxin may provide analgesic effects for several neuropathic pain states, including CRPS type 1, spinal cord injury pain, post-herpetic neuralgia, and pain associated with brachial plexopathies (Argoff 2002). A retrospective study of intramuscular botulinum toxin in 37 CRPS patients with spasm/dystonia in the neck and/ or upper limb girdle muscles was reported (Kharkar 2011). Ninety-seven percent of patients had significant pain relief with mean pain score decreases of 43%. These results were reported only in the short-term, up to 4 weeks. As noted by the authors, this is a study that lacks a control group, so the placebo effect cannot be discounted. Also, according

to the UK Guidelines, evidence for regional botulinum toxin for CRPS-related dystonia is poor (Goebel 2012). A comprehensive review (O'Connell, et al 2013), reported very low-quality evidence that sympathetic block using botulinum toxin A with a local anesthetic may effectively increase the duration of analgesia compared to local anesthetic alone by approximately 2 months. However the authors were unclear regarding the level of pain relief that might be achieved by this intervention. Brown, et al, 2014, conducted a review to summarize the highest quality literature pertaining to application of botulinum toxin in neuropathic pain conditions, including CRPS. They found level U (insufficient) evidence in CRPS.

Therefore, for intramuscular botulinum toxin A in CRPS, there is limited evidence that it improves the net health outcome. Intramuscular botulinum has not been approved by the FDA for use in CRPS.

INTRAMUSCULAR KETAMINE
In a review of topical and peripheral ketamine, Sawynok (2014) notes that peripheral administration of ketamine by localized injection produced some alterations in sensory thresholds in experimental trials in CRPS subjects, but many variables remained unchanged. Intramuscular ketamine is not FDA approved for CRPS treatment. The lack of scientific evidence does not permit conclusions regarding net health outcomes.

INTRAMUSCULAR MAGNESIUM SULFATE
A double-blind, randomized placebo-controlled crossover study was performed to assess the effect and safety of intramuscular magnesium sulphate (IMMG) vs. placebo in CRPS patients with dystonia (Van der Plas 2013). Thirty patients were administered IMMG or placebo over 3 weeks. The primary outcome was the difference in change in the Burke-Fahn-Marsden dystonia scores between both interventions. Only 22 patients were available for analysis which revealed no differences between IMMG and placebo. According to the investigators, there is insufficient support for new studies evaluating the efficacy of other routes of MG administration in CRPS related dystonia. IMMG has not been approved by the FDA for use in CRPS.

EPIDURAL AGENTS

EPIDURAL CLONIDINE
Epidural infusion with an alpha 2-adrenergic agonist such as clonidine has been proposed for the relief of purportedly "sympathetically maintained pain," such as reflex sympathetic dystrophy (Rauck et al 1993). This method of treatment was classified as a sympathetic blockade in the review by Forouzanfar et al (2002). A single high-quality RCT (Rauck et al 1993) in 27 patients found that epidural clonidine in patients diagnosed with reflex sympathetic dystrophy reduced pain significantly more than placebo. According to Harden, the effectiveness of epidural analgesia for treatment of CRPS has been demonstrated in several studies. The value of the treatment is to allow a more rigorous PT program (Harden 2013). van Elijs suggests that epidural infusions "can be tried" for individuals refractory to other conventional treatment (van Elijs 2011). The main limitation to continuous infusions is the high infection rate of indwelling lines which, according to Harden, needs to be defined by further prospective study on infusion techniques in CRPS patients (Harden 2013). O'Connell, et al., found very low quality evidence that clonidine provides relief of pain that is refractory to sympathetic blockade (one study), and recommends further study (O'Connell 2013). According to Freedman et al. 2014, there is no convincing evidence for epidural clonidine to treat sympathetic pain in CRPS. Therefore, for epidural clonidine in CRPS, there is limited evidence that it improves the net health outcome. However, epidural clonidine has not been approved by the FDA for use in CRPS.

INTRATHORACIC MEDICATIONS

Intrathoracic (i.e., intrapleural or intrapulmonary) administration of non-opioid medication for CRPS that does not have as its goal direct chemical ablation of sympathetic ganglia or fibers does not appear to be used.

In summary, despite optimism for the use of various parenterally administered non-opioid drugs for CRPS, there are no completed clinical trials on the efficacy of these treatments with consistently applied evidence-based-medicine criteria. Most reports of trials in CRPS represent small anecdotal clinical studies with few experimental findings. Unquestionably, a consensus definition of CRPS, with standardized diagnostic criteria, is needed. Practical agreement about the minimal clinical criteria (signs and symptoms) that define CRPS does exist among neurologists, anesthesiologists, and others. Without a universally accepted definition and diagnostic criteria for CRPS, it is difficult to accurately identify CRPS patients, to select patients for clinical trials, to validate experimental human and animal model systems for research, and to formulate testable hypotheses (NINDS 2001). Finally, none of the non-opioid agents proposed for the treatment of CRPS, and in particular none of the parenterally administered agents, has been approved by the FDA.

PLASMAPHERESIS

Plasmapheresis is a method of withdrawing blood and separating it into plasma and cells, and transfusing the cells back into the bloodstream. It is used to remove antibodies when treating autoimmune conditions. Although it is hypothesized that there is an autoimmune component to CRPS, no outcome data were found specific to CRPS treatment with plasmapheresis. The lack of scientific evidence does not permit conclusions regarding net health outcomes.

PLASMA EXCHANGE

Plasma exchange is an extra-corporeal therapy that extracts the patient's whole blood which is then separated into plasma and blood cells. The plasma is removed and replaced with another solution such as human albumin in saline or a specifically prepared donor plasma. The reconstituted plasma substitute along with the blood cells is then returned to the patient.

A study from Drexel University College of Medicine described a retrospective case series of patients with CRPS and a clinical presentation suggestive of a small fiber neuropathy (SFN) who were treated with plasma exchange (PE). The use of PE was based on a hypotheses proposing an autoimmune etiology for CRPS. Thirty-three patients who had not responded, or responded poorly, to their current treatment received a series of PEs (mean 7.2 treatments) over a 2-3 week period. Three patients showed no improvement in pain with the treatment, and 1 patient reported short-term relief that returned to pre-treatment level within 3 days. The remaining patients reported significant pain reduction that was either maintained with immune modulating therapies of weekly PE (n=15), or oral immune modulating therapy (n=8) or they slowly returned to pre-treatment pain levels with no further therapy (n=6). The authors conceded that the study, because of its retrospective, non-randomized, and uncontrolled nature, is limited. Moreover, since the patients described were only those with SFN, the results cannot be extrapolated to the entire CRPS population. They concluded that randomized, placebo controlled studies may be required to confirm the results. (Aradillas, et al. 2015.)

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)

MEDICALLY NECESSARY

POSTEPIDURAL CONTINUOUS PAIN MANAGEMENT CARE

01996

STELLATE GANGLION BLOCK (SGB)

64510

LUMBAR SYMPATHETIC BLOCK/IVRB

64520

EPIDURAL INFUSION

62324, 62325, 62326, 62327

CATHETER IMPLANTATION/REMOVAL (EPIDURAL OR INTRATHECAL)

62350, 62351, 62355

EPIDURAL RESERVOIR/PUMP IMPLANTATION (EPIDURAL OR INTRATHECAL) AND ELECTRONIC ANALYSIS

62360, 62361, 62362, 62365, 62367, 62368, 62369, 62370, 95990, 95991

EXPERIMENTAL/INVESTIGATIONAL FOR CRPS

36514, 36516, 64415, 64416, 64450, 64520

THE FOLLOWING CODE IS USED TO REPRESENT INJECTION, ANESTHETIC AGENT; CERVICAL, LUMBAR AND/OR SACRAL PLEXUS.

64999

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)

G56.40 Causalgia of unspecified upper limb

G56.41 Causalgia of right upper limb

G56.42 Causalgia of left upper limb

G56.43 Causalgia of bilateral upper limbs

G57.70 Causalgia of unspecified lower limb

G57.71 Causalgia of right lower limb

G57.72 Causalgia of left lower limb

G57.73 Causalgia of bilateral lower limbs

G90.50 Complex regional pain syndrome I, unspecified

G90.511 Complex regional pain syndrome I of right upper limb

G90.512 Complex regional pain syndrome I of left upper limb

G90.513 Complex regional pain syndrome I of upper limb, bilateral

G90.519 Complex regional pain syndrome I of unspecified upper limb

G90.521 Complex regional pain syndrome I of right lower limb

G90.522 Complex regional pain syndrome I of left lower limb

G90.523 Complex regional pain syndrome I of lower limb, bilateral

G90.529 Complex regional pain syndrome I of unspecified lower limb

G90.59 Complex regional pain syndrome I of other specified site

M89.00 Algoneurodystrophy, unspecified site

M89.011 Algoneurodystrophy, right shoulder

M89.012 Algoneurodystrophy, left shoulder

M89.019 Algoneurodystrophy, unspecified shoulder

M89.021 Algoneurodystrophy, right upper arm

M89.022 Algoneurodystrophy, left upper arm

M89.029 Algoneurodystrophy, unspecified upper arm

M89.031 Algoneurodystrophy, right forearm

M89.032 Algoneurodystrophy, left forearm

M89.039 Algoneurodystrophy, unspecified forearm

M89.041 Algoneurodystrophy, right hand

M89.042 Algoneurodystrophy, left hand

M89.049 Algoneurodystrophy, unspecified hand

M89.051 Algoneurodystrophy, right thigh

M89.052 Algoneurodystrophy, left thigh

M89.059 Algoneurodystrophy, unspecified thigh

M89.061 Algoneurodystrophy, right lower leg

M89.062 Algoneurodystrophy, left lower leg

M89.069 Algoneurodystrophy, unspecified lower leg

M89.071 Algoneurodystrophy, right ankle and foot

M89.072 Algoneurodystrophy, left ankle and foot

M89.079 Algoneurodystrophy, unspecified ankle and foot

M89.08 Algoneurodystrophy, other site

M89.09 Algoneurodystrophy, multiple sites

HCPCS Level II Code Number(s)

THIS IS NOT AN ALL-INCLUSIVE LIST

C9812 Echogenic nerve block needles (e.g. sonoplex, sonoblock, sonotap), non-opioid medical device (must be a qualifying medicare non-opioid medical device for post-surgical pain relief in accordance with section 4135 of the caa, 2023)

J0475 Injection, baclofen, 10 mg

J0476 Injection, baclofen, 50 mcg for intrathecal trial

J2278 Injection, ziconotide, 1 mcg

J2270 Injection, morphine sulfate, up to 10 mg

J2274 Injection, morphine sulfate, preservative-free for epidural or intrathecal use, 10mg

S0093 Injection, morphine sulfate, 500 mg (loading dose for infusion pump)

EXPERIMENTAL/INVESTIGATIONAL FOR CRPS

J0585 Injection, onabotulinumtoxinA, 1 unit

J0586 Injection, abobotulinumtoxinA, 5 units

J0587 Injection, rimabotulinumtoxinB, 100 units

J0588 Injection, incobotulinumtoxinA, 1 unit

J0665 Injection, bupivicaine, not otherwise specified, 0.5 mg

J0735 Injection, clonidine HCl, 1 mg

J1010 Injection, methylprednisolone acetate, 1 mg

J1212 Injection, DMSO, dimethyl sulfoxide, 50%, 50 ml

J1459 Injection, immune globulin (Privigen), intravenous, nonlyophilized (e.g., liquid), 500 mg

J1556 Injection, immune globulin (bivigam), 500 mg

J1557 Injection, immune globulin, (Gammaplex), 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, (Octagam), intravenous, nonlyophilized (e.g., liquid), 500 mg

J1569 Injection, immune globulin, (Gammagard liquid), nonlyophilized, (e.g., liquid), 500 mg

J1572 Injection, immune globulin, (flebogamma/flebogamma dif), intravenous, non-lyophilized (e.g., liquid), 500 mg

J1599 Injection, immune globulin, intravenous, nonlyophilized (e.g., liquid), not otherwise specified, 500 mg

J2002 Injection, lidocaine hcl in 5% dextrose, 1 mg

J2003 Injection, lidocaine hydrochloride, 1 mg

J2004 Injection, lidocaine hcl with epinephrine, 1 mg

J2151 Injection, mannitol, 250 mg

J2272 Injection, morphine sulfate (fresenius kabi) not therapeutically equivalent to j2270, up to 10 mg

J2760 Injection, phentolamine mesylate, up to 5 mg

J2919 Injection, methylprednisolone sodium succinate, 5 mg

J3475 Injection, magnesium sulfate, per 500 mg

THE FOLLOWING CODE REPRESENTS BISPHOSPHONATES, BRETYLIUM, DEXMEDETOMIDINE, GLYCINE, GUANETHIDINE, KETAMINE, KETANSERIN, PHENOXYBENZAMINE, AND RESERPINE:

J3490 Unclassified drugs

Revenue Code Number(s)
N/A

Coding And Billing Requirements

BILLING REQUIREMENTS

Inclusion of a code in this policy does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

If there is no specific HCPCS code available for the drug administered, then the drug must be reported with the most appropriate unlisted code along with the corresponding National Drug Code (NDC).

Policy History

Revisions From MA08.026m:

03/20/2026	Inclusion of a policy in a Code Update memo does not imply that a full review of the policy was completed at this time. This policy has been identified for the CPT code update, effective 03/20/2026. The following HCPCS code has been added to this policy: C9812 Echogenic nerve block needles (e.g. sonoplex, sonoblock, sonotap), non-opioid medical device (must be a qualifying medicare non-opioid medical device for post-surgical pain relief in accordance with section 4135 of the caa, 2023) The following HCPCS code has been deleted from this policy: J1572 Injection, immune globulin, (flebogamma/flebogamma dif), intravenous, non-lyophilized (e.g., liquid), 500 mg _____ Note: In accordance with the CMS - Revised 2026 HCPCS Code Update - January Edition - Correct Coding publication posted on their site on 12/31/2025 to communicate that the below HCPCS code remains effective, on 03/20/2026, the following code was added back to this policy: J1572 Injection, immune globulin, (flebogamma/flebogamma dif), intravenous, non-lyophilized (e.g., liquid), 500 mg

Revisions From MA08.026l:

12/15/2025	This policy has been identified for the HCPCS code update, effective 12/15/2025. The following HCPCS code has been deleted from this policy: J2150 Injection, mannitol, 25% in 50 ml The following HCPCS codes have been added to this policy: J2151 Injection, mannitol, 250 mg

Revisions From MA08.026k:

12/16/2024	This policy has been identified for the HCPCS code update, effective 12/16/2024. The following CPT code has been **removed** from this policy: J2001 Injection, lidocaine HCl for intravenous infusion, 10 mg The following CPT codes have been **added** to this policy: J2002 Injection, lidocaine hcl in 5% dextrose, 1 mg J2003 Injection, lidocaine hydrochloride, 1 mg J2004 Injection, lidocaine hcl with epinephrine, 1 mg

Revisions From MA08.026j:

05/07/2024	This policy has been identified and updated for the HCPCS code update effective 05/07/2024. The following HCPCS codes have been **added** to the policy: Experimental/Investigational: • J1010 Injection, methylprednisolone acetate, 1 mg • J2919 Injection, methylprednisolone sodium succinate, 5 mg The following HCPCS codes have been **removeed** from this policy: • J1020 Injection, methylprednisolone acetate, 20 mg • J1030 Injection, methylprednisolone acetate, 40 mg • J1040 Injection, methylprednisolone acetate, 80 mg

Revisions From MA08.026i:

07/01/2023	This policy has been identified for the CPT code update, effective on 07/01/2023. The following CPT code S0020 has been deleted from this policy. The following CPT code J0665 has been added to this policy.

Revisions from MA08.026g

09/28/2020	This version of the policy will become effective on 09/28/2020. This policy has been updated to communicate the Company's experimental/investigational position on treatment of complex regional pain syndrome (CRPS) with plexus catheter nerve block and continuous peripheral nerve block. This policy has been identified for the following code update: 64450 Injection, anesthetic agent; other peripheral nerve or branch 64520 Injection, anesthetic agent; lumbar or thoracic (paravertebral sympathetic) THE FOLLOWING CODES ARE USED TO REPRESENT INJECTION, ANESTHETIC AGENT; CERVICAL, LUMBAR AND/OR SACRAL PLEXUS. 64999 Unlisted procedure, nervous system.

Revisions from MA08.026f

05/20/2020	The policy has been reviewed and reissued to communicate the Company’s continuing position on Treatments for Complex Regional Pain Syndrome (CRPS).

01/01/2020	This policy has been identified for the CPT code update, effective 01/01/2020. The following CPT code has been **removed** from this policy: 64413 The following CPT code has been **added** to this policy: 64450

MA08.026e

09/25/2019	This policy has been reissued in accordance with the Company's annual review process.
03/01/2018	This version of the policy will become effective on 03/01/2018. The title of this policy was changed from:Complex Regional Pain Syndrome (CRPS) Parenteral Treatments To: Treatments for Complex Regional Pain Syndrome (CRPS) Additional changes include: • Up to a maximum of six (6) total local anesthetic sympathetic nerve blocks, i.e., stellate ganglion block for upper-extremity pain or lumbar sympathetic block for lower-extremity pain related to CRPS are considered medically necessary, and, therefore covered in a 12-month period when other criteria detailed in the policy are met.

MA08.026d

01/01/2018	CPT code update for this policy, effective 01/01/2018: The following CPT code has been **removed** from this policy: 36515 Therapeutic apheresis; with extracorporeal immunoadsorption and plasma reinfusion The following CPT narrative has been **revised** in this policy: 36516: **FROM:** Therapeutic apheresis; with extracorporeal selective adsorption or selective filtration and plasma reinfusion **TO:** Therapeutic apheresis; with extracorporeal immunoadsorption, selective adsorption or selective filtration and plasma reinfusion

MA08.026c

05/17/2017	This policy was updated to communicate the coverage position of plasma exchange for the treatment of CRPS. The coverage criteria was clarified for epidural opioids and for intrathecal baclofen.

MA08.026b

01/01/2017	This policy has been identified for the CPT code update, effective 01/01/2017. The following CPT codes have been **deleted** from this policy: 62318, 62319 The following CPT codes have been **added** to this policy: 62324, 62325, 62326, 62327

MA08.026a

10/28/2016	This policy has been reissued in accordance with the Company's annual review process.
03/29/2016	This policy was updated to clarify new criteria for the Medical Necessity of intrathecal opioids and intrathecal baclofen.

	This policy was also updated to convey new coverage determinations as Experimental/Investigational for the following drugs/nerve blocks/procedures for the treatment of CRPS: chemical sympathectomy, continuous peripheral nerve block with any drug, intramuscular ketamine, intrathecal opioids in combination with bupivacaine or lidocaine, intravenous dexmedetomidine, intravenous dimethylsulfoxide (DMSO), intravenous opioids, plasmapheresis, plexus catheter nerve block with any drug. The experimental/investigational statement was revised from an all-inclusive list to a not all-inclusive list. Information regarding epidural infusions of opioids, intrathecal infusions of opioids and baclofen by implantable pumps is consistent with Medicare's coverage criteria.

MA08.026

01/01/2015	This is a new policy. 12/03/2014: While the policy was in notification, this policy was identified for the HCPCS code update, effective 01/01/2015. Inclusion of a policy in a Code Update memo does not imply that a full review of the policy was completed at this time. On 12/04/2014, this Notification was revised to include HCPCS coding updates, effective 01/01/2015. This policy has been identified for the HCPCS code update, effective 01/01/2015. The following HCPCS codes have been **termed** from this policy: J2271 Injection, morphine sulfate, 100 mg J2275 Injection, morphine sulfate (preservative-free sterile solution), per 10 mg Q9974 Injection, Morphine Sulfate, Preservation-Free For Epidural Or Intrathecal Use, 10 mg The following HCPCS code has been **added** to this policy: J2274 Injection, morphine sulfate, preservative-free for epidural or intrathecal use, 10mg

Version Effective Date:
03/20/2026
Version Issued Date:
03/20/2026
Version Reissued Date:
N/A