Epidemiology, Pathophysiology, and Management of Complex Regional Pain Syndrome

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Abstract: Complex regional pain syndromes (CRPS) are challenging neuropathic pain states quite difficult to comprehend and treat. Although not yet fully understood, advances are being made in the knowledge of the mechanisms involved with CRPS. Patients often present with incapacitating pain and loss of function. Patients suffering from these disorders need to have treatment plans tailored to their individual problems. A comprehensive diagnostic evaluation and early and aggressive therapeutic interventions are imperative. The therapeutic approach often calls for a combination of treatments. Medications such as antiepileptics, opioids, antidepressants, and topical agents along with a rehabilitation medicine program can help a major portion of patients suffering from these disorders. Implantable devices can aid those patients with CRPS. While progress is being made in treating patients with CRPS, it is important to remember that the goals of care are always to: 1) perform a comprehensive diagnostic evaluation, 2) be prompt and aggressive in treatment interventions, 3) assess and reassess the patient's clinical and psychological status, 4) be consistently supportive, and 5) strive for the maximal amount of pain relief and functional improvement. In this review article, the current knowledge of the epidemiology, pathophysiology, diagnostic, and treatment methodologies of CRPS are discussed to provide the pain practitioner with essential and up-to-date guidelines for the management of CRPS.

Key Words: CRPS, comprehensive evaluation, aggressive therapeutic regimen, psychological support, prolonged rehabilitation

In order to further the understanding of the 2 clinical entities known as reflex sympathetic dystrophy (RSD) and causalgia, the International Association for the Study of Pain (IASP) decided to reclassify their terminology. Thus, in 1994 the IASP renamed the 2 disorders respectively CRPS type 1 (formerly referred to as RSD) and CRPS type 2 (the disorder previously known as causalgia, associated with a definable nerve lesion). As described by Stanton-Hicks, the term CRPS implies the presence of regional pain and sensory findings after a noxious event with additional abnormalities including edema and changes in skin color, temperature, and sudomotor activity. These changes all appear to be out of proportion with the physical damage from the noxious event. It must be noted that the IASP diagnostic criteria for CRPS type 1 and type 2 still await full clinical and scientific validation. Moreover, numerous practitioners have questioned the usefulness of these new terms. One major problem is that the diagnostic criteria for CRPS type 1 and type 2 remain too vague. This might result in overdiagnosing the 2 entities and in causing difficulties with analyzing treatment outcome data.

Undoubtedly, these disorders are complex and difficult to understand. Pain medicine experts continue to struggle for the development of satisfactory treatment...
algorithms. CRPS is a formidable challenge for pain medicine specialists as well as for affected patients. This remains true despite all the recent scientific advances in the fields of pain neurophysiology and pharmacology.

In this review, we will present the most updated and relevant information on the epidemiology and pathophysiology of CRPS. We will also discuss the assessment of patients with CRPS, and the use of diagnostic techniques as well as propose new treatment options in its management.

THE ROLE OF SYMPTOMATICALLY MAINTAINED PAIN IN CRPS

In contradistinction to CRPS, sympathetically maintained pain (SMP) is a pathogenetic mechanism and not a clinical entity. In the past, it was often misunderstood that all patients with RSD had abnormal sympathetic nervous system involvement. On the contrary, it is now understood that the majority of patients with CRPS do not have SMP. A neuropathic pain state can be maintained by several peripheral and central nervous system (PNS, CNS) mechanisms. SMP appears to represent 1 of the PNS mechanisms (see below, Pathogenesis). SMP may be present, perhaps only temporarily, and complicate CRPS as well as other painful disorders including shingles, neuralgia, and metabolic or autoimmune neuropathies. Pain not responsive to sympathetic blockade is referred to as sympathetically independent pain (SIP). It is possible that over time a patient may present to the same physician with SMP, then SMP and SIP, and thereafter SIP alone. Therefore, it should be reasserted that the diagnosis of CRPS no longer rests on the response to a sympathetic block alone.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF CRPS

Knowledge of the epidemiology of CRPS suffers from a lack of adequate prospective studies. Retrospective study on the subject by Allen, Galer, and Schwartz that includes 134 patients indicates an average age of onset at 38 years. In their study, patients with CRPS type 1 presented to a multidisciplinary center with an average disease duration of 2.5 years. Females are affected more commonly than males (2:1). A small percentage (5%) of patients could not recall any traumatic insult precipitating their symptoms. It appears that there may be a genetic predisposition to the development of CRPS type 1, with a higher incidence in certain HLA types. Kelmer demonstrated an increased incidence of CRPS type 1 in patients with HLA DQ 1. Mailis and Wade noted an increased incidence of HLA A3, B7, and DR2 in patients with CRPS. A poor response to standard treatments was noted in the DR2 group.

A clear understanding of the pathophysiology of CRPS remains to be elucidated. It is unclear as to what ignites the disease process after the traumatic event and how an injury causes the PNS and CNS to react in an abnormal, exaggerated manner. Hypotheses include the development of ectopic nociceptive activity (occasionally driven by an SMP mechanism), an abnormal response to the local release of neurotrophic factors, and the occurrence of a local neuro-immunological inflammatory process. These peripheral events can be complicated by temporary or long-term CNS changes such as central sensitization and then reorganization of the pain pathways at the dorsal horn level. Pathological studies in 8 patients affected by intractable CRPS type 1 demonstrated a microangiopathic process and on electron microscopy the presence of C fiber axonal sprouts in at least four of the affected patients. These findings suggested the occurrence of a small fiber neuropathy CRPS, however, is likely the expression of neurophysiological abnormalities affecting both the peripheral and central nervous system. A trauma may result in ectopic repetitive discharges from the nociceptors innervating the injured area. Damaged A-delta and C-nociceptors can produce such ectopic discharges. The axons of the injured fibers develop an abnormal mechanosensitivity, and, at times, an alpha-adrenoreceptor excitability. If a component of SMP is present it probably has its origin at this point as injured nociceptors acquire alpha-adrenoreceptor excitability. Of interest, not only abnormal changes are noted in the dorsal root ganglion (DRG) cells of the injured afferent axons, but also in the cell bodies of uninjured axons within the same DRG. A state of CNS hyperexcitability occurs as affected afferent C-fibers release large amounts of glutamate, substance P, and other neuropeptides. This results in a central sensitization state with its clinical correlates of alldynia and hyperalgesia.

The release of neurotrophic factors from damaged tissue may play a role in CRPS. Neurotrophic factors, including nerve growth factor, induce the development of miniature axon sprouts from the endings of small nerve afferent fibers as well as from the sympathetic efferent nerves, and this may favor a coupling between the 2 types of nerve fibers. If the affected nociceptors have begun to express alpha-adrenoreceptor excitability, the coupling may indeed favor the SMP state. Bennett has proposed that CRPS may also be asso-
associated with an abnormal neuro-immunological inflammatory process. If an abnormal immune response occurs after an injury, inflammatory cytokines such as tumor necrosis factor alpha, interleukin 1-beta, IL-6, and IL-8 are released locally. These cytokines are known to induce significant changes in nociceptors, including sensitization, activation, and even axonal damage. An outgrowth of the concept that immunological changes may result in the occurrence of CRPS is the number of observations addressing the role of macrophages and macrophage-released cytokines in contributing to hyperalgesia and Wallerian degeneration, as well as the role of biphosphonates as a nerve treatment option for CRPS (see below).20–23

In summary, while the multiple pathogeneses of CRPS have not been defined, it appears that a traumatic injury to the distal extremity of genetically predisposed individuals may initiate a process that results in a neuropathic “stalemate” state in the affected limb. Of interest is that in several instances CRPS appear to be maintained by “plastic” mechanisms that can be switched off by early and aggressive therapeutic interventions. It is conceivable that these mechanisms are centered on a complex interplay of both physiological (e.g., PNS and CNS sensitization of pain pathways, tissue-released neurotrophic factors) and pathological states (e.g., neuro-immunological inflammation, expression of abnormal receptors and channels in the nociceptors membrane of the affected limbs) that can be more easily and likely rectified by therapeutic interventions employed early in the course of these painful states.

EVALUATION OF THE PATIENT WITH CRPS

Patients suffering from CRPS need to undergo a thorough and comprehensive evaluation so that an individualized treatment plan can be initiated. Treatment usually involves a long-term patient-physician relationship, requiring initiating a medical plan, reevaluation, and likely repeated adjustments of the treatment plan. It is important to keep the referring physician in the “loop” of medical management decision-making so that a continuity of care can be guaranteed. Treatment goals include satisfactory pain relief and improvement in psychological and physical well being.

In obtaining the patient’s history, the pain medicine specialist has to determine the nature of the initiating event, and the onset and features of symptoms. While CRPS usually involves a single distal extremity, there are reports of spread to other extremities. The physician has to assess the degree and qualities of spontaneous pain and bring forth the features of allodynia and hyperalgesia, necessary to the diagnosis of CRPS. At the time of the evaluation, the affected limb may or may not show classic CRPS changes. However, at some point in time from the disease onset, abnormalities such as skin color and temperature changes, edema, and sweating should be elicited. Patients with SMP typically present with cold hyperalgesia in the affected limb.

CRPS is likely dependent on a variety of pathogenetic mechanisms (as discussed under the section Epidemiology and Pathophysiology), and the clinical experience suggests that multiple treatment modalities are often necessary for the majority of cases. Although there is a paucity of controlled trials in the field of CRPS management, established clinical experience indicates that a few treatment modalities have some usefulness. However, in the majority of the affected patients, combinations of treatments are often needed to achieve a satisfactory treatment outcome, such as a sympatholytic procedure for SMP, a combination of pharmacological agents, physical therapy and rehabilitation medicine, and for intractable cases, utilization of implantable devices.

THE DIAGNOSIS OF SMP

Useful diagnostic tests include regional sympathetic blocks, such as the stellate ganglion block for the arm and the lumbar sympathetic block for the leg, and intravenous sympatholytic blocks, such as the phentolamine or the bretylium blocks. Hereafter, we will describe the techniques for blocking the stellate ganglion and the lumbar sympathetic chain.

Stellate Ganglion Block

The stellate ganglion carries the sympathetic fibers to the upper extremity. It is formed from the inferior cervical and the first thoracic sympathetic ganglia. The stellate ganglion is located behind the carotid artery and internal jugular vein, anterior to the longus colli muscle and approximately 2.5 cm × 1 cm × 0.5 cm in size.

Technique. The patient is placed on the stretcher in the supine position. A folded sheet or towel is placed behind the shoulders, and the neck is extended. This maneuver places the esophagus in a direct line posterior to the trachea. The neck is prepped and draped, and the middle and index fingers are placed on the neck above the sternoclavicular junction in the immediate paratracheal area. This can be done at the C7 level. Some physicians like to perform this maneuver at C6. Pulsations of the carotid artery can be appreciated. While using enough pressure
to feel the deep structures of the neck, the carotid sheath and the sternocleidomastoid muscle are retracted laterally, away from the midline. The fingers are then separated and a skin wheal is raised between the fingers. A 22-gauge 3.5 needle is advanced perpendicular to the neck until the advancing needle meets the transverse process of C7. The needle is then withdrawn by 1 mm to bring it proximal to the longus coli fascia, stabilized, and then aspirated for any blood or cerebrospinal fluid (CSF). If aspiration is negative for blood or CSF, a short acting local anesthetic, eg, lidocaine, 5 mL of 1%, and a long acting anesthetic, eg, bupivacaine 10 mL of 0.25% are administered with intermittent aspiration. After finishing the injection of local anesthetic, the needle is removed and the head of the bed is raised. See Figure 1.24

With blockade of the stellate ganglion, ipsilateral Horner’s signs occur. However, the ipsilateral upper extremity should be examined for an increase in temperature of at least 2°C when compared to the temperature of the contralateral limb, the presence of cutaneous vasodilatation, and the absence of any signs of sensory somatic blockade (in particular along the C6, C7, and C8 dermatomes) before a stellate ganglion procedure can be called specific and adequate for the diagnosis of upper limb SMP. When performing this block appropriate resuscitation equipment must be available. The patient may complain of some hoarseness and the sensation of a lump in the throat. Complications can include injection into the vertebral artery, subarachnoid injection, pneumothorax, or brachial plexus lesion.25

Lumbar Sympathetic Block

The sympathetic chain lies on the anterolateral aspect of the L2 vertebra. Therefore, an anesthetic injection at this level is sufficient to obtain a sympathetic blockade of the ipsilateral lower extremity of the patient. Usually, the sympathetic trunk is located 1.5–2 inches deep to the transverse process. The major variable in performing this block is the distance from the skin to the transverse process and this depends on the body habitus of the patient.25

Technique. In performing this block, the patient is placed on the stretcher in the prone position with a pillow placed under the abdomen. Counting cephalad from the L4-5 interspace the L2 spinous process is identified. Alternatively, this site can be verified by fluoroscopy. The back is prepped and draped. A skin wheal is raised 4 cm lateral to the L2 spinous process. A needle is passed perpendicular to the skin until it encounters the transverse process of L2. The needle is then withdrawn and passed caudal to the transverse process of L2 in a slightly medial direction. The needle can be felt to pass the vertebrae. At this point the needle tip is close to the anterolateral aspect of the L2 vertebrae. A syringe is attached to the needle and 5 mL of 1% lidocaine and 10 mL of 0.25% bupivacaine are injected after aspiration is negative for blood or CSF. Aspiration is performed intermittently.25 Another method of performing the block requires the physician to start more laterally, approximately 7–8 cm laterally, and advance the needle to encounter the anterolateral aspect of the L2 vertebrae. The procedure is performed under fluoroscopic guidance.26 If the patient has SMP, relief should be obtained shortly after the procedure has been performed. An increase in skin temperature of at least 2°C, increased cutaneous vasodilatation, and no signs of somatic blockade should be noted in the ipsilateral lower limb before calling the sympatholytic procedure adequate for the diagnosis of SMP (Figure 2).
Therapeutic blocks as a treatment for CRPS/SMP, it is important to employ physical therapy while the patient is benefiting from the sympatholytic effects of the block. In fashioning an individual treatment plan, the combination of relaxation techniques, biofeedback, and cognitive behavioral therapy may be considered as adjuvant therapy for some patients.

Pharmacological Therapies

Antiepileptic drugs (AEDs). Some AEDs have been used successfully in the treatment of neuropathic pain, and, as such, they have also been frequently used as a treatment modality for CRPS. Controlled clinical trials have shown efficacy of gabapentin in the treatment of post-herpetic neuralgia and painful diabetic neuropathy. Overall clinical experience with gabapentin in the management of CRPS has also been encouraging. Of note, gabapentin acts on neither GABA receptors nor sodium channels, and its analgesic mechanism of action is unclear. Trigeminal neuralgia responds well to carbamazepine, while another AED, lamotrigine, has shown some efficacy for carbamazepine-resistant trigeminal neuralgia. Carbamazepine and lamotrigine are known to block voltage-gated neuronal membrane sodium channels. An overexpression of these channels at the site of nerve injury (ie, neuroma) or an up-regulation of a nociceptor-specific sodium channel subtype of the affected limb may play a pathological role in the case of CRPS, in particular perhaps, in CRPS type 2. Lastly, topiramate has been anecdotally used with benefit in the treatment of CRPS type 1.

Opioids, NMDA antagonists, and cannabinoids. Opioids are currently the most potent and effective analgesics utilized to treat acute and chronic pain states, and as such they have been prescribed to patients suffering from intractable CRPS. Efficacy of opioid analgesics for neuropathic pain of noncancer origin has recently been established. Unlike anti-inflammatory drugs, opioid agonists have no analgesic "ceiling dose" and do not cause direct organ damage. Except for constipation, tolerance occurs for most of the opioid related side effects (eg, nausea, vomiting, respiratory depression, and drowsiness). Of note, studies indicate that patients on a stable opioid analgesic regimen do not report significant impairment in their driving ability, attention, mood, and general cognitive functioning. Addiction (ie, a pattern of abnormal drug-seeking and drug-taking behaviors for nontherapeutic purposes) and clinically relevant analgesic tolerance are rarely seen in patients who

TREATMENTS

Physical Therapy and Rehabilitation Medicine

Immobilization appears to be an important predisposing factor to the development of CRPS. Therefore, once this diagnosis is entertained, the patient should be started on an aggressive program of physical and occupational therapy. Early treatment seems to be very advantageous. The goal is to make the extremity as functional as possible. If the patient is receiving a series of sympa-
receive these medications for pain control. Among the available opioid agents, methadone has unique properties. It is a potent long-acting mu opioid agonist with an intrinsic NMDA antagonistic effect. There is evidence gleaned from animal experiments and clinical observations that NMDA receptors play an important role in the central mechanisms of hyperalgesia and chronic pain. Ketamine and the oral agent dextromethorphan are NMDA antagonists that may be used in conjunction with opioids in the management of severe neuropathic states characterized by allodynia and hyperalgesia. However, these agents, in particular ketamine, have a very narrow therapeutic window. Ketamine can easily cause intolerable side effects, such as hallucinations and memory impairment. Also of interest is the possibility that NMDA antagonists may prevent or counteract tolerance to opioid analgesia. These agents may be used at subclinical, and therefore safe, dosages in order to block the progression of opioid tolerance.

Several lines of evidence from experimental animal studies and clinical observations indicate that cannabinoids, including the currently available antiemetic dronabinol, have analgesic properties. Interestingly, the coadministration of inactive doses of cannabinoids in combination with inactive doses of mu opioid agonists can produce antinociception. Moreover, cannabinoids appear to have a predominant antiallodynic/antihyperalgesic effect. This may be quite advantageous in the treatment of some in-capacitating neuropathic pain states.

**Antidepressants.** Tricyclic antidepressants (TCAs) and selective serotonin uptake inhibitors (SSRIs) have often been utilized in the management of chronic pain. Post-herpetic neuralgia and painful diabetic neuropathy may respond to TCAs, such as amitriptyline, nortriptyline, or desipramine. Despite the fact that TCAs have been frequently used for more than 30 years in the management of chronic painful states, their role as primary analgesics in the treatment of CRPS has been quite limited and unsatisfactory. Side effects of the TCAs, such as orthostatic hypotension, confusion, cardiotoxicity, urinary retention, weight gain, dry mouth, and nightmares may be common and persistent, causing serious difficulties to patients taking these medications. A new antidepressant, venlafaxine, seems to possess the analgesic properties of TCAs with the advantage of having fewer side effects. While being also used for neuropathic pain, SSRIs, such as paroxetine and fluoxetine, are not as efficacious as the TCAs. Antidepressants have an important role as adjuvants in the treatment of chronic pain. While not the mainstay medications for CRPS, these agents may be very useful in the management of several comorbidities frequently affecting the CRPS patient population such as anxiety, depression, and insomnia.

**Local anesthetics.** Local anesthetics, eg, intravenous lidocaine or oral mexiletine, have been utilized in patients with neuropathic pain. Mexiletine is a local anesthetic with antiarrhythmic properties. The putative mechanism of its analgesic action relies on the blockade of the neuronal membrane sodium channels and in this, mexiletine is similar to some AEDs, such as carbamazepine or lamotrigine. If a cardiac conduction defect such as a 2nd or 3rd degree heart block is present, mexiletine may not be administered. In addition, if the patient is taking any antiarrhythmic medications, a cardiology consultation should be obtained.

**Topical analgesics.** Capsaicin, lidocaine, and clonidine are 3 agents that can be administered topically to provide pain relief in patients suffering from CRPS and neuropathic pain. Capsaicin, the pungent substance found in the hot chili peppers is a C-fiber/nociceptor specific neurotoxin. Indeed, after prolonged use of topical capsaicin, a significant decrease in cutaneous density of C-fibers occurs. Capsaicin is known to activate the vanilloid receptor, which allows calcium and sodium to enter the nerve fiber. Following a brief period of depolarization (corresponding to the initial burning pain elicited by capsaicin application), desensitization of the nociceptor fibers occurs. The duration and the degree of the desensitizing effect on the nociceptors are dose-dependent. Unfortunately, poor patient compliance is common with the use of capsaicin creams at low concentrations (ie, over-the-counter preparations) since application is painful and a few weeks of multiple daily applications are needed to obtain some benefit. The clinical experience with low-dose capsaicin creams has given overall unimpressive results. However, the administration of a large dose of capsaicin (compounded at >1%), when given at the appropriate site (ie, at the presumed location of the pain generator) and under regional anesthesia, does appear to be efficacious. This novel method of capsaicin administration may provide a long-lasting benefit after a single application and may facilitate physical therapy and functional recovery of the affected limb. In patients suffering from SMP, transdermal clonidine has been shown to relieve allodynia in the area of patch application. Lidocaine patches have also been used in patients suffering from CRPS, with some reports of benefit.
efficacy of transdermal lidocaine has been demonstrated for postherpetic neuralgia.  

**Biphosphonates.** It has been hypothesized that in CRPS type 1 regional osteoporosis (which has been observed to develop over time in the affected limb) as well as sensitization of nociceptors may be related, to some extent, to the pathological activation of osteoclasts and macrophages with consequent release of proinflammatory cytokines, eg, tumor necrosis factor alpha, interleukin (IL) 1-beta, IL-6, and IL-8. Biphosphonates are commonly used in the treatment of osteoporosis. Some of these agents when given intravenously and at a relatively high dose can also relieve bone pain secondary to metastatic disease. Biphosphonates such as clodronate, alendronate, and pamidronate may not only inhibit osteoclastic and macrophagic activity, but also block or interfere with the macrophagic and osteoclastic release of proinflammatory cytokinins. Of note, in the neuropathic pain model of sciatic nerve ligation, thermal hyperalgesia was significantly decreased by a biphosphonate. While the mechanism of action has not been totally elucidated, it has been suggested that the analgesic effect of intravenous biphosphonates may be mediated through the depletion of macrophages in the area of injury and the decreased release of proinflammatory cytokines.

More recently intravenous biphosphonates have been noted to be efficacious in the treatment of CRPS. Intravenous pamidronate was used in 10 women and 13 men with recalcitrant CRPS. A significant decrease in pain was observed. In a recently conducted randomized trial, Varenna et al. utilized clodronate as a 10-day intravenous treatment for CRPS type 1. Significant pain relief was obtained when compared to placebo controls. The following case report reflects a very recent anecdotal experience from our institution, the Hospital for Joint Diseases (HJD) in New York City. It points out not only the potential useful role of intravenous biphosphonate therapy in the management of CRPS type 1, but also the importance of performing combinations of pharmacological trials according to our current understanding of CRPS pathophysiology.

**Case Study**

A 38-year-old female sustained a traumatic injury to her right arm after a fall, which resulted in significant wrist and arm pain. The patient underwent carpal tunnel release after the diagnosis of posttraumatic carpal tunnel syndrome was made by electrodiagnostic studies; the arm was immobilized after the procedure. A few days later, the patient began to experience a new type of pain, which she described as a severe throbbing, burning pain associated with marked skin sensitivity to light touch and air movement. Swelling of the arm and skin color changes were noted. The cast was removed and the patient was diagnosed as having CRPS type 1. She underwent multiple stellate ganglion blocks (>10 blocks) which provided a few hours of pain relief with a decrease in allodynia after each block. An MRI of the right shoulder was unremarkable, while a MRI of the cervical spine showed a narrow left C3-C4 foramen.

At the time of her presentation to the Comprehensive Pain Treatment Center at HJD (1 year after the onset of her symptoms), she was taking tramadol 100 mg PO QID, propoxyphene 60 mg PO TID PRN, amitriptyline 50 mg PO QHS, gabapentin 900 mg PO TID, Lidoderm patch QD, and ibuprofen 400-800 mg PO TID PRN. She was also applying 0.1 mg clenidine patch to the right deltoid region Q3-4 days. The patient rated her overall pain at 8 on the numerical scale 0–10 (where 0 = no pain and 10 = the worst pain imaginable). Her neurological examination revealed normal cranial nerves I-XII, full strength in the nonsymptomatic limbs (strength in the right arm was formally untestable due to excruciating pain elicited by minimal movements and tactile stimuli), normal coordination on finger to nose and heel/knee/shin testing bilaterally, 1+ DTRs in the asymptomatic limbs with downgoing plantar responses (DTRs of the right arm were untestable because of pain), normal gait, and a sensory examination remarkable for mechanical allodynia (primarily along the radial aspect of her right hand and along the lateral aspect of her forearm).

Three days after her initial consultation, the patient was hospitalized for more advanced pharmacological trials and diagnostic work-up. On day #1, propoxyphene, tramadol, amitriptyline and ibuprofen were discontinued. The patient was maintained on gabapentin at the dose of 600 mg QID. She was also started on a patient controlled analgesia (PCA) titration trial of intravenous (IV) fentanyl, intravenous pamidronate 90 mg infusion QD, tizanidine 2 mg BID PRN and dextromethorphan 30 mg PO TID.

On hospital day #2, the patient was still symptomatic of her allodynia. She rated her ongoing arm pain at 7 out of 10. She continued to use the IV PCA fentanyl. A transdermal fentanyl patch of 25 mcg/hour was added to her medication regimen. She complained of moderate drowsiness and moderate to severe nausea. For nausea and as analgesic adjuvant, the patient was started on dronabinol 10 mg PO BID, while for drowsiness the pa-
tient was given methylphenidate 5 mg PO Q6am and 5 mg PO Qnoon. The clonidine patch was moved from the patient's shoulder to her right wrist. Tizanidine was withheld due to drowsiness. An MRI of the brachial plexus was unremarkable. On the morning of day #2, the patient underwent an EMG-NCV study. Because of pain, the patient was unable to tolerate the completion of the study. The preliminary report, however, indicated no evidence of entrapment neuropathy, brachial plexopathy, or cervical radiculopathy. Of note, the patient reported a worsening of her pain following the EMG study. On the evening of day #2, the patient was in severe distress with worsening of her allodynia and was complaining of severe nausea. She received her second intravenous dose of pamidronate. The patient was noted to use the IV PCA fentanyl extensively. The dose of the fentanyl patch was increased to 50 mcg/h. A consultation was also called for a spinal cord stimulation trial.

In the late morning of her hospital day #3, the patient began to experience pain relief, reporting a significant improvement in allodynia. The intensity of her ongoing pain decreased to 3 out of 10. The use of the IV PCA fentanyl decreased progressively throughout the day. The patient also reported a substantial improvement in drowsiness and nausea. She received her third infusion of pamidronate. By the evening of day #3, the patient rated her pain at 1 out of 10. Her mood was much improved. On hospital day #4, the patient reported resolution of her allodynia and no ongoing pain except for brief and intermittent sharp mild pains in her right arm. The patient rated her pain at 0–1 out of 10. No allodynia or hyperalgesia was present in her right arm. The patient was discharged from the hospital in excellent conditions on the evening of day #4. She was given prescriptions for gabapentin 600 mg PO QID, dronabinol 10 mg PO BID, dextromethorphan 30 mg PO TID, fentanyl patch 25 mcg/hour Q 3 days, clonidine patch 0.2 mg Q 3 days. The patient was discharged with remarkable pain relief. Ten days later, the patient returned to the HJD Comprehensive Pain Treatment Center for follow-up evaluation (follow-up visit #1). She stated that when she left the hospital she could not fill out her hospital prescriptions. She could not afford paying in advance for the fentanyl patches, dronabinol, and dextromethorphan, since the overall cost amounted to more than $1000.00. However, the patient felt so great that she thought she had been cured. According to the patient, her right hand had regained its normal shape and size after being shiny, swollen, and darker. At that point the patient's medications included only gabapentin and the clonidine patch. At her follow-up visit, the patient was reporting 80% improvement in her condition when compared to her prehospitalization state. The swelling of her arm and the allodynia had vanished. Her baseline pain intensity level was 1 out of 10. She was still complaining of brief attacks of sharp pains. However, the patient reported that the frequency of the brief pains was at least 50% less when compared to the frequency of the attacks she had prior to the hospitalization.

At the time of her most recent follow-up (follow-up visit #2), 4 weeks following her hospital discharge, the patient was taking gabapentin 900 mg TID, clonidine 0.2 mg patches applied to the right wrist Q 3 days, and tizanidine 2 mg PO BID PRN. She continued to experience good to excellent pain relief. The patient wrote a thank you letter:

"...I'd like to take this time to express my sincere gratitude for being able to participate in your treatment for my RSD. I have had surgery, been on countless medications, and have endured at least 12 stellate ganglion blocks, which were painful...with results that almost ended me up on a respirator due to complications. Being a woman and a registered nurse, this disease has taken tolls on me that have been unimaginable. I am right-handed and it has affected the extremity that is involved. My hand has been black and swollen for over a year. No other treatment that I have ever received has done what you have accomplished in three days. I cried all weekend staring at my normal-sized hand... This disease is so complicated, misunderstood, and unknown (even to the medical profession)... There are so many people affected by this condition that could benefit from these new therapies that you have to get the word out in any way. Thank you." Signed by the patient.

Invasive Treatment Interventions

Implantable devices have become more popular in treating patients with intractable pain. Implantable devices include spinal cord stimulators and pumps. Spinal cord stimulators have been successfully used in patients with intractable pain that is not treatable by conventional methods. A recent randomized trial showed efficacy of spinal cord stimulation for CRPS. Thirty-six patients were randomly assigned to receive spinal cord stimulation. After trial test stimulation, only 24 patients received permanent spinal cord stimulators. Patients who received spinal cord stimulation (SCS) and physical ther-
any demonstrated a significant decrease in pain intensity
when compared to those receiving physical therapy alone.
However, while significant pain relief was obtained

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