Abstract: The goal of treatment in patients with complex regional pain syndrome (CRPS) is to improve function, relieve pain, and achieve remission. Current guidelines recommend interdisciplinary management, emphasizing 3 core treatment elements: pain management, rehabilitation, and psychological therapy. Although the best therapeutic regimen or the ideal progression through these modalities has not yet been established, increasing evidence suggests that some cases are refractory to conservative measures and require flexible application of the various treatments as well as earlier consideration of interventions such as spinal cord stimulation (SCS). While existing treatment guidelines have attempted to address the comprehensive management of CRPS, all fail to provide guidance for contingent management in response to a sudden change in the patient's medical status. This paper reviews the current pathophysiology as it is known, reviews the purported treatments, and provides a modified clinical pathway (guideline) that attempts to expand the scope of previous guidelines.

Key Words: guidelines, clinical pathway, treatments, complex regional pain syndromes, RSD, causalgia, neurostimulation, psychological therapy, pain management, pharmacology, regional anesthesia, rehabilitation

PROLOGUE

“We have some doubt as to whether this form of pain ever originates at the moment of the wounding . . . . Of the special cause, which provokes it, we know nothing, except that it has sometimes followed the transfer of pathological changes from a wounded nerve to unwounded nerves, and has then been felt in their distribution, so that we do not need a direct wound to bring it about. The seat of the burning pain is very various; but it never attacks the trunk, rarely the arm or thigh, and not often the forearm or leg. Its favorite site is the foot or hand . . . . Its intensity varies from the most trivial burning to a state of torture, which can hardly be credited, but reacts on the whole economy, until the general health is seriously affected.

Spinal Cord Stimulation is indicated for intractable pain of the trunk and limbs. Information regarding other uses is included with this article.
The part itself is not alone subject to an intense burning sensation, but becomes exquisitely hyperesthetic, so that a touch or tap of the finger increases the pain.”—Silas Weir Mitchell, 1872

INTRODUCTION

The International Association for the Study of Pain (IASP) introduced the taxonomy of complex regional pain syndromes (CRPS) in 1994 to more accurately describe the pain syndromes reflex sympathetic dystrophy (CRPS-I) and causalgia (CRPS-II). CRPS is a regional pain syndrome of unclear pathophysiology typically affecting the hand or foot (but may either occur or spread to other parts of the body or to different areas). Excruciating pain is the hallmark of the disease. A diagnosis of CRPS-I may include regional pain, sensory changes (allodynia, hyperalgesia), edema, and abnormalities of temperature, sudomotor activity, and skin color that occur (usually) after an identified precipitating event or trauma. CRPS-II is differentiated from CRPS-I by the presence of a definable nerve lesion; otherwise, the signs and symptoms are the same. Refer to Table 1 for the IASP Diagnostic Criteria for CRPS-I and CRPS-II.

In considering a differential diagnosis based on the IASP diagnostic criteria, underlying pathology including local pathology, neuropathic pain syndromes, peripheral neuropathies, and infectious, inflammatory, and vascular disorders should be identified as primary factors causing pain. It may be difficult to distinguish the clinical symptoms of acute trauma or postsurgery from acute CRPS. A recent study demonstrated that motor signs, trophic changes, and increased sweating are the most obvious clinical symptoms to recognize early CRPS. The diagnosis should be established as soon as possible since interdisciplinary treatment is thought to be most effective early in the disease process. However, an excellent response can be achieved in a patient whose diagnosis for whatever reason has been delayed.

The principles outlined in the interdisciplinary clinical pathway are designed to promote optimal circumstances for the treatment of all CRPS patients. Just as was the intent of its authors, modification of the IASP diagnostic criteria has been proposed as a result of validation studies. Therefore, the current treatment guidelines are vulnerable to change when it is suggested by new research and field experience. Multicenter studies designed to validate the IASP criteria by Harden et al. and Bruehl et al. indicate that the IASP criteria may be too nonspecific and, therefore, result in overdiagnosis. In particular, separation of criteria for vasomotor signs/symptoms from those reflecting sudomotor dysfunction may improve the validity of the criteria. Furthermore, their data suggests that adding motor and trophic changes to the criteria may be appropriate.

The management of CRPS continues to improve as scientific understanding of the syndrome as a neurological disease has evolved. Consensus treatment guidelines for CRPS developed in 1998, focused on functional restoration that is facilitated by psychological and medical interventions (see Figure 1). Because of inherent deficiencies in their application, these guidelines and relevant literature were reexamined by an expert panel in August 2001. Clinical evidence suggests that timing and sequencing of the treatment guidelines should be refined, and that under certain circumstances, concurrent rather than linear, utilization of interdisciplinary interventions should be emphasized. In fact, for example, recent literature includes some studies that support the use of pharmacotherapy, particularly gabapentin, and intrathecal baclofen for reducing pain and/or improving quality of life (QOL) in CRPS patients. The updated guidelines are presented in Figure 2.

CLINICAL PRESENTATION AND NATURAL HISTORY

The epidemiology and natural history of CRPS are poorly understood, complicated by the diversity of patients, ret

Table 1. International Association for the Study of Pain (IASP) Diagnostic Criteria for CRPS-I and CRPS-II

<table>
<thead>
<tr>
<th>CRPS-I (Reflex Sympathetic Dystrophy)</th>
<th>CRPS-II (Causalgia)</th>
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<tbody>
<tr>
<td>1. The presence of an initiating noxious event, or a cause of immobilization.</td>
<td>1. The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve.</td>
</tr>
<tr>
<td>2. Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event.</td>
<td>2. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.</td>
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<tr>
<td>3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.</td>
<td>3. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.</td>
</tr>
<tr>
<td>4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.</td>
<td>Note: All three criteria must be satisfied.</td>
</tr>
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Note: Criteria 2-4 must be satisfied.
rospective data collection, and anecdotal reports. The principal trends are summarized below.

Demographic and Background Information
The mean age of CRPS patients ranges from 36 to 42 years with women predominating (60% to 81%).\(^6\)\(^{10}\)\(^{13}\)\(^{14}\) The upper extremity is involved in 44% to 61% of cases, and the lower extremity in 39% to 51%\(^6\)\(^{10}\)\(^{13}\) The etiology of CRPS is typically an injury (often minor): 16% after a fracture,\(^6\)\(^{13}\) 10% to 29% after a strain or sprain,\(^6\)\(^{13}\) 3% to 24% post-surgery,\(^6\)\(^{9}\)\(^{13}\)\(^{15}\)\(^{18}\) 8% after contusion or crush injury,\(^6\)\(^{13}\) and 6% are spontaneous,\(^13\) 2% to 17% other causes, or of unknown etiology.\(^6\)\(^{13}\) Allen et al demonstrated that it is common to have multiple failed or partially successful treatments prior to referral (physical therapy in 88%, nerve blocks in 82%, multiple pharmacologic agents in >60%, immobilization in 47%, psychological treatment in 50%, and spinal cord stimulation in 6%).\(^13\)

Sensory Signs and Symptoms
Intense pain and hyperesthesia are predominant sensory symptoms.\(^6\)\(^{19}\) In most patients the pain, characterized as aching, burning, pricking, or shooting is localized deep in the somatic tissue.\(^20\) Evoked abnormal sensations of hyperalgesia, predominantly to mechanical stimuli or upon joint movement, and allodynia are frequently present.\(^6\)\(^{20}\) Sensory deficits are common in CRPS patients.\(^21\)\(^{22}\) Rommel and colleagues observed 33% of patients had hemisensory impairment with decreased temperature and pinprick sensation ipsilateral to the affected limb.\(^21\) Trigeminal hypoesthesia was found in 49% of CRPS patients with upper extremity disease versus <10% in patients with other pain and normal individuals.\(^22\)

Autonomic Signs and Symptoms
Autonomic signs and symptoms are swelling, color and temperature changes, and sweating abnormalities. The majority of patients describe swelling of the affected
limb, which can be aggravated by physical load, painful stimuli, environmental and local temperature changes, and hydrostatic pressure.\textsuperscript{3,6} Temperature asymmetry between the affected and unaffected side measured with infrared thermography exceeds 1°C.\textsuperscript{23} Such asymmetry is dynamic and can be warmer or colder.\textsuperscript{24} Sweating abnormalities were observed in 59% of patients (increased production in 94% of these patients).\textsuperscript{21}

Motor and Dystrophic Signs and Symptoms
Motor dysfunction in CRPS includes weakness, decreased range of motion, tremor, dystonia, and myoclonus. Muscular strength is often decreased, especially grip strength. Zyluk observed 78% of patients had significantly reduced grip strength.\textsuperscript{25} Range of motion is decreased by joint effusion early in the disease and by contraction and fibrosis later in the disease.\textsuperscript{20} Tremor has been reported in 24% to 60% of patients.\textsuperscript{6,23,26} Dystonic posturing and myoclonic jerks can also be present in CRPS.\textsuperscript{27} Dystrophic manifestations include increased or decreased nail and hair growth in the affected extremity. Typical skin changes are palmar or plantar fibrosis, hyperkeratosis, and thin glossy skin.\textsuperscript{5}

Myofascial Dysfunction
The majority of cases (56% to 61%) have a myofascial component associated with CRPS.\textsuperscript{13,28} Myofascial dysfunction is more prevalent in the affected upper extremity (69% to 70%) than the lower extremity (42% to 47%).\textsuperscript{13,28} Also, a longer duration of CRPS symptoms increases the likelihood of myofascial dysfunction.\textsuperscript{13}
Recurrence or Spread

Recurrence or spread to involve another extremity or region is reported to be 10% with the incidence of recurrence projected at 1.8% per year. Maleki et al prospectively reported the mean onset of contiguous spread (usually proximal progression) was 78 days; independent and mirror image spread was longer; 2.6 and 2.5 years, respectively.14

Natural History

The natural history of CRPS treatment suggests that reported outcomes of pain relief, functional capacity, and disease remission are suboptimal. A retrospective study of 146 patients found that although 64% of patients had a “good” outcome, only 29% were pain free and only 15% had grip strength >50% of normal.23 In 1 series of patients with CRPS, 64% of the patients with severe pain >12 months had severe impairment and rated their pain a “7” on the 10-point Visual Analog Scale.30 CRPS was present in 10% of patients 1 year after tibial plateau fracture and in 9% of patients 10 years after Colles fracture.31,32 A prospective study of 93 patients with CRPS found that activities of daily living were significantly impaired in 62% of patients.33 Kemler and de Vet found that QOL was negatively impacted by mobility/control issues in patients with lower extremity CRPS, while self-care issues negatively affected QOL in patients with upper extremity CRPS.34 Results from the self-report questionnaires of 31 patients showed CRPS significantly interfered with many activities including general activity, normal work, mood, and recreational and social activities.19

PATHOPHYSIOLOGY

The underlying pathophysiologic mechanisms of CRPS have not yet been delineated. Multiple components most likely play roles in the generation and maintenance of CRPS,35,36 including those of a neuropathic nature (ie, sympathetically maintained and independent pain),36 and immunologically mediated mechanisms,37-39 such as inflammation and altered expression of human leukocyte antigens (HLA). Moreover, the site of dysfunction is unclear, and hypotheses exist for both peripheral40 and central mechanisms.21,26,41-43

A retrospective analysis by van der Laan in 1,006 patients demonstrated that immunologically-mediated (ie, infection, edema) factors were associated with severe complications.37 Also, Mails and Wade, who examined a correlation of class I and II HLA expression in 15 patients with poor treatment outcome, found elevated levels of both types of HLA antigens in 80% of treatment-resistant patients.38 The authors postulated that strictly defined CRPS might constitute a neuroimmune disorder. Consistently high (or low) expression of heritable antigens has also been reported in a murine model of neuropathic pain.39

Cline and colleagues proposed a peripheral mechanism based on observations from a single patient.40 Diagnostic stellate ganglion blocks were unsuccessful, and sympathetic efferent neural activity and vasomotor effector responses were normal (ie, absence of vasoconstrictor deficit). Based on psychosocial assessments, nerve fiber blocks, skin graft measurements, and microangiographic recordings, Aδ fibers were not the primary carriers of pain input; C polymodal nociceptors from sensitized skin were identified as the culprits.

There are also data supporting a central mechanism. Rommel et al prospectively studied 24 patients with CRPS-I, and reported sensory deficits extending beyond the painful area of the affected limb.21 They noted a significantly increased frequency of mechanical allodynia and movement disorders in patients with hemisensory impairment or sensory deficits in the upper quadrant compared to those with impairment limited to the affected limb (92% vs. 17%; P < 0.005). Similar significant increases were also reported for motor impairment (83% vs. 42%; P < 0.05), and correlated with allodynia/hyperalgesia (P < 0.005). They concluded that functional alterations in central processing might result in motor/sensory impairment in CRPS patients. This is supported by data obtained from positron emission tomography (PET) in patients (n = 5) with chronic post-traumatic neuropathic pain or neuralgia. Compared to normal controls, there was a significantly decreased level of thalamic activity contralateral to the symptomatic side.41

Two prospective studies (n = 145 and 50, respectively) from Germany also support the central hypothesis but failed to detect any significant correlations between abnormalities of sympathetic function or clinical symptoms.3,42,43 To examine the role of inflammation in the disease process, investigators measured skin temperature/perfusion,42 they did not find a role for inflammation. In another approach, the anti-inflammatory agent acetylsalicylic acid was studied prospectively in 40 patients to assess the role of inflammation.26 It also examined mechanical hyperalgesia to test a central hypothesis. While hyperalgesia to heat was insignificant (similar to static stimulation), there was significant hyperalgesia to phasic impact stimuli
(P < 0.003), and "wind-up" related pain was also significantly increased in the affected limb (P < 0.02). The authors concluded that pathogenesis in CRPS had a non-inflammatory central origin. Birklein et al postulated that the symptomatology of CRPS could not be explained by a single pathophysiologic process, but distinct multiple pathways (ie, pain and hyperalgesia might have unique mechanisms in CRPS-I and CRPS-II). Hypothetical mechanisms for the conditions that account for pain and dysfunction are reviewed elsewhere in considerable detail. A working hypothesis that presumes CRPS is a neurologic disease may incorporate the following elements. According to experimental data, small-diameter polymodal C and Aδ afferent neurons are sensitized after noxious stimuli, this could suggest a rationale for hyperalgesia to heat and algesic agents. Central spinal mechanisms may also play a role, including the sensitization of central neurons following either intense mechanical stimuli or continuous nociceptive input. Alterations in non-nociceptive neurons may also be a source of noxious stimuli. Experimental evidence in humans or non-human primates tends to implicate alpha 1-adrenoceptors in sympathetic efferent, afferent aberrant coupling, whereas data from the majority of animal studies have identified the alpha2-adrenoceptor as being responsible for excitation, sensitization of nociceptive afferents, in some cases via prostaglandin E2. Drummond et al have provided evidence that alpha 1-adrenoceptors are not only present in the epidermis, but their density is increased in the hyperalgesic skin of CRPS compared with their numbers in nonpainful skin. Thus, the sympathetic outflow, discharge pattern, and manner in which sympathetic terminals interact with peripheral tissues may result in the initiation and/or maintenance of neurogenic symptoms.

CURRENT GUIDELINES

The primary goal of the current guidelines, published in 1998, is to facilitate functional restoration; and they emphasize the concept of time contingency, i.e., the failure to achieve a favorable response with any treatment modality should not persist beyond 2 weeks. The guidelines also include a physiotherapeutic algorithm, the underlying principles of which include motivation, desensitization, and mobilization facilitated by pain relief using pharmacologic and/or interventional procedures to treat specific signs and symptoms (see Figure 1). Although these guidelines list a number of specific interventions to be applied (physical, medical, psychological), they fail to provide guidance in respect to the optimal sequence or application of these various modalities.

UPDATED CLINICAL PATHWAY (GUIDELINE)

The proposed CRPS clinical pathway, illustrated in Figure 2, centers around the same 3 domains as in the original: rehabilitation, pain management, and psychological treatment. However, it has been updated to encourage an interdisciplinary, time-contingent guidance that incorporates more recently published treatment options. These should be addressed simultaneously, with advanced approaches in each area applied according to the patient’s response to the treatment. The reader is cautioned not to attribute any particular emphasis with respect to the relative size of the different "boxes." The relative contribution of each modality will be determined by the patient’s response and progress.

Rehabilitation

Rehabilitation is the mainstay of CRPS treatment. The concurrent implementation of physiotherapy with pain management and psychological therapies is meant to facilitate a sequential progression through the steps of the rehabilitation pathway. If the patient fails to progress in a timely manner, it is imperative to utilize those pain management and psychological modalities in an incremental fashion that will ensure his or her progress through the physiotherapeutic algorithm. At which point a patient enters the treatment algorithm and the speed with which the patient progresses will depend on factors such as their clinical presentation and their response to therapy.

In the early stages of CRPS treatment, occupational and physical therapy are crucial to a patient’s progression through specific areas of the clinical pathway and hinge on the development of an effective therapeutic alliance. In this manner, the therapist can assess a patient’s motivation and help set goals that are pivotal to early success. Adequate analgesia, encouragement, and education of the disease process are essential to ensure the successful application of physical modalities; desensitization, isometric exercises, resisted range of motion (ROM), and stress loading. It should be reinforced, however, that physical therapy, if not applied in the manner discussed here, cannot only be detrimental to progress through the algorithm, but may in fact adversely impact the disease.

The next step in the clinical pathway is to increase the patients’ flexibility, beginning with gentle active ROM. The almost inevitable myofascial pain syndrome (MFPS), associated with the affected region, requires the use of
stretching, strengthening and postural correction and may require trigger point injections (TPIs), electrical stimulation, and muscle relaxants. These measures are supported by anecdotal data, and have not been validated by randomized prospective trials. Edema control may require elevation, retrograde massage, Jobst compression pump, sympathetic blocks, diuretics, and in some cases with sympathetically maintained pain (SMP), the use of adrenergic receptor blockers. Introduction of the foregoing modalities should be incorporated on an individual basis and in response to manifestation of particular signs and symptoms.

Successive steps in the pathway as stated above involve gentle active ROM, stress loading, scrubbing techniques, isometric strengthening, general aerobic conditioning, and postural normalization.\textsuperscript{31,32} Coordinated team intervention will usually be required to keep a patient motivated and engaged.\textsuperscript{53} The final steps of the pathway involve normalization of use, assessment of ergonomics, posture, and required modifications at home and the workplace. Complementary recreation therapy and vocational rehabilitation will encourage ongoing and normalized use of the affected limb. In this and successive stages of the guidelines, it is important to reiterate that failure to progress will require stronger drugs for pain relief, more intensive psychotherapy, or the use of more aggressive pain management techniques, such as regional anesthesia or SCS.

Psychological Therapy
The focus of psychological treatment for CRPS is on improving QOL, developing pain coping skills, cognitive-behavioral psychotherapy (CBT) and facilitating progress in the other treatment modalities. For early CRPS patients (eg, within 4 to 6 weeks of onset), the degree of psychological response is usually minimal. A diagnosis of CRPS may be confusing and have extremely negative connotations (regardless of symptom duration), thus most patients would benefit from an understanding of the syndrome and its management. In particular, education should: 1) emphasize that CRPS related pain sensations do not necessarily indicate tissue damage, and 2) highlight the importance of re-activation of the affected extremity to prevent increased dysfunction and to facilitate improvement.

As the disease progresses, psychological factors play an even greater role as the patient struggles to adapt to their disease.\textsuperscript{54} It is, therefore, recommended that patients experiencing significant CRPS symptoms for more than 6 to 8 weeks should undergo clinical psychological assessment. This assessment should focus in part on the identification of significant ongoing life stressors or any comorbid Axis I psychiatric disorders; particularly depression, generalized anxiety, panic, and posttraumatic stress disorder. The last factor is important given the sometimes traumatic nature of the inciting injury. Psychological arousal associated with these psychological factors has the potential to impact the severity of pain and other CRPS symptoms.\textsuperscript{54-57} If Axis I disorders (clinical disorders such as somatiform and mood disorders and schizophrenia) are present, these should be treated with appropriate pharmacotherapy, eg, tricyclics and/or cognitive-behavioral therapy (CBT).

Even in the absence of distinct Axis I disorders, CBT designed to enhance patients' skills for coping with stress and pain is likely to enhance the patient's QOL and to facilitate progression during physical therapy.\textsuperscript{53} Training in relaxation skills for pain control is also an important component of the overall CBT package. If possible, it should be supplemented with thermal and surface EMG biofeedback in the affected region.\textsuperscript{57-59} In particular, EMG biofeedback may help minimize problems with secondary myofascial pain that can occur with CRPS.\textsuperscript{28}

Another component in psychological treatment is the involvement of individuals that may otherwise interfere with the patients' treatment progress.\textsuperscript{60} For example, family members may interfere with efforts at re-activation due to unrealistic concerns about pain and tissue damage. Also, close interdisciplinary collaboration between the psychologist, physical and occupational therapists, and physician is crucial, as it can result in synergistic treatment effects.

Pain Management
It is well known that pain is the fundamental symptom of CRPS. Management of this pain must be dynamic and flexible, corresponding to the disease progression, to provide the patient pain relief and enhance their ability to optimize function. Less invasive techniques are pharmacologic management and regional anesthesia techniques. When these prove less efficacious, then it becomes important to consider more invasive techniques such as neurostimulation.

Pharmacologic Management. Pharmacologic selection should be focused on symptom management and pathological mechanisms. For symptomatic treatment, tricyclic antidepressants,\textsuperscript{61} particularly amitriptyline, which has effectively measured efficacy in the treatment of neuropathic pain and antiepileptic compounds, particu-
larly gabapentin, should be considered for neuropathic pain symptoms. Steroids, should be used for the anti-inflammatory treatment of CRPS. Additionally, dimethyl sulfoxide is effective to reduce free oxygen-derived radicals. Other agents for consideration in the pharmacological armamentarium include nonsteroidal anti-inflammatory drugs (NSAIDS), heterocyclic antidepressants, opioids, calcitonin, alpha adrenoceptor antagonists, eg, terazosin or phenoxybenzamine that can be very effective for the treatment of demonstrated SMP by regional anesthetic block. The alpha 2 adrenoceptor agonist clonidine has proven efficacy by both transdermal or epidural administration. NMDA-receptor antagonists, and ketamine and dextromethorphan have been suggested as candidates.

Minimally Invasive Interventions. Sympathetic, intravenous (IV) regional, and somatic nerve blocks should be incorporated into the overall rehabilitation program. The type of block and technique, including injection site and concentration of local anesthetic, depends on the degree of SMP, stage in the rehabilitation pathway (ie, passive vs. active movement), and response to blocks. Patients with SMP should receive a sympathetic block. The response to this may determine the course of treatment. If a patient responds to the block (ie, SMP), a series of 3 to 6 blocks in combination with physical therapy might be all that is required to achieve remission. In nonresponders (ie, no SMP), a somatic block or epidural infusion may be indicated to optimize analgesia for physical therapy.

More Invasive Interventions. If a patient fails to progress in the rehabilitative pathway, or has inadequate or partial pain relief, more invasive procedures should be used. Tunneled epidural catheters for prolonged somatic and/or sympathetic blockade may be considered if the patient has had a partial response to sympathetic or somatic nerve blocks. The next step in the pain management pathway is neuroaugmentation. New evidence supports the efficacy of neurostimulation, one of many techniques of neuroaugmentation, in the treatment of CRPS. Spinal cord stimulation is employed in CRPS-I and CRPS-II. In CRPS-II, peripheral nerve stimulation (PNS) may be used if the signs and symptoms are limited to the distribution of a major peripheral nerve. Intrathecal drug delivery is used in patients who have a significant component of dystonia, failed neurostimulation, long-standing disease, multi-limb involvement, or need palliative care. A recent study demonstrated the effectiveness of intrathecal baclofen in the treatment of CRPS associated dystonia.

Surgical and Experimental Therapies and Palliative Care. CRPS patients refractory to conventional measures may be considered for surgical and experimental therapies. Sympathectomy, although very controversial (see discussion in the Literature Review), may be considered in patients with SMP that respond to sympathetic blockade via regional anesthetic procedures. Radiofrequency and neurolytic techniques should be employed and outcomes assessed prior to consideration of surgical sympathectomy. Motor cortex stimulation may be considered as an experimental option.

While pain relief is usually geared toward facilitating rehabilitation, in a few cases the clinical management may require a palliative approach using the aforementioned interventions.

Timing/Sequence of the Clinical Pathway. CRPS patients generally respond positively to conservative treatment measures. However, due to the unpredictable temporal nature of CRPS, it cannot be over stressed that frequent assessment and response to a patient’s progression in therapy (ie, rehabilitative, pain management, psychological) is obligatory if unwanted disease progression is to be avoided. This is especially true of the small number of cases which by their fulminant nature any positive treatment response comes to a standstill early in the course of their disease despite all conservative measures and nerve blocks; spinal cord stimulation should be considered to facilitate the restoration of function. The proposed inter-disciplinary clinical pathway allows flexibility in interdisciplinary treatment strategies that are based on each patient’s clinical progress. The patient who improves clinically with an educational session about CRPS, a short course of physiotherapy, the use of analgesics and a sympathetic block is well served. Likewise, the patient who is resistant to more conservative treatment modalities and shows neither a worsening of symptoms nor improvement within a reasonable time should progress through the pathway in a time-contingent manner, making use of the physical modalities, supported by successive pain management and psychological treatments. Although, the timing for more invasive pain management interventions should be made on a case-by-case basis, it is reasonable and may be expedient to consider epidural infusions and/or spinal cord stimulation at 12 to 16 weeks when the patient has failed all conservative pain management techniques and is at a standstill in the rehabilitation pathway. While this time frame may seem to the reader empiric, some evidence-based data lend support for this number.
Outcome Measures and Objective Responses. The patient and physician, with cooperation from the psychologist and physical therapist, must assess the response together. Although the level of pain intensity is an important outcome measure, it alone is insufficient to gauge the response to therapy. The patient's functional status, vocational status, family relationships, psychological status, medication consumption, and pain intensity must all be taken into consideration when assessing the overall health-related QOL. Therefore, such objective measures as function, psychometric measures of daily pain intensity and emotional distress most appropriately gauge treatment efficacy. These may be measured by tools such as the McGill Pain Questionnaire-Short Form,75 the Pain Disability Index,76 the Beck Depression Inventory,77 Treatment Outcomes in Pain Survey,78 and the State Trait Anxiety Inventory.79 In addition to measuring QOL and pain relief, objective measures of response to physiotherapy are needed to evaluate progress through the proposed clinical pathway. Assuming that a close patient-physician relationship is established and a careful history is provided,80,81 the panel believes that it is reasonable to categorize responses to therapy as: inadequate response, partial response, or excellent response respectively, without the need for extensive testing. While the clinician's judgment is paramount to evaluate progress through the clinical pathway, there is a pressing need to acknowledge "evidence-based" outcomes. However, unless these principles are followed progressively, the management of this disease will continue to languish.

For patients who fail to progress in rehabilitation, the concurrent use of progressive pain management and psychological treatments will be dictated by selection of their respective pathways (see Figure 2). Likewise, an inadequate or partial response to pain management and psychological treatments mandates progression in the respective side pathways.

For patients with an excellent response, the standard follow-up care protocol, other than physical therapy or continuing pain relief, will be determined by the degree of any impairment and the particular level of function in each case. Throughout the course of treatment, patients must be reassessed relative to QOL—in terms of psychological well being, functional status, and pain relief. Treatment regimens are then amended relative to the progression within each of the 3 domains (responses) proposed. Patients might graduate from requiring regular sessions with a physical or occupational therapist, but continue on a regimen of active, self-managed home exercise to restore functionality; active participation in their therapeutic regi- men is necessary for a successful outcome. Patients who have developed severe tendon contractures or nonfunctional joints (eg, extreme equinovarus deformity) limiting progress or conclusion of their rehabilitation can safely have corrective surgery (eg, tendon lengthening, arthrodesis, amputation). This is possible if continuous regional analgesia can be assured, not only for the operative procedure, but also for several weeks afterwards.

REVIEW OF REHABILITATION, PSYCHOLOGICAL THERAPY AND PAIN MANAGEMENT LITERATURE

Ongoing research continues to evaluate treatment methodologies for CRPS patients. Recent scientific evidence supports the inclusion of these 3 key modalities in the clinical pathway and lends credence to the proposed interdisciplinary approach.

Rehabilitation

As stated already, rehabilitation is the mainstay of treatment in CRPS: Baron and Wasner concur that physiotherapy is "of utmost importance,"82 and Birklein and Handwerker contend that rehabilitation be applied "for obvious reasons."83 Researchers as early as 1987 have shown that specific stress loading and isometric techniques benefited patients.84 Oerlemans et al conducted a prospective controlled study of 135 CRPS patients with pain located in an upper extremity, reporting that both PT and OT proved helpful in management of pain and restoration of mobility.85 Birklein et al reported that pain was significantly less for patients receiving physical therapy in their prospective evaluation of 145 patients.42 In another report of 103 children meeting the IASP criteria of CRPS, 92% experienced resolution or reduction of pain after undergoing exercise therapy.86

Psychological Therapy

Psychotherapy for patients with CRPS should be employed to assist in the general rehabilitation of patients, including cognitive behavioral therapy, stress management, coping skills, relaxation techniques, imagery, and self-hypnosis.8 Biofeedback is used extensively; techniques employed include electromyograph biofeedback, autogenic (limb warming) training, progressive muscle relaxation, meditation, and sleep hygiene.8 There are no randomized prospective studies that demonstrate the scientific merit of psychological therapy in the treatment of CRPS, although the efficacy of such techniques more generally in chronic pain management have been documented in controlled trials.53,57
Pain Management

There are a plethora of pain management techniques available, from less invasive pharmacological management to more invasive neurostimulation. While recent literature describes their use in CRPS patients, future studies should include scientific design components of randomization, blinding, and adequate sample sizes, the latter implying multicenter participation if data are to be acquired in a timely manner.

Pharmacologic Management. Pharmacologic agents that have been used to manage patients with CRPS include: nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic and heterocyclic antidepressants, sodium channel blocking agents, corticosteroids, opioids, calcitonin, adrenoceptor antagonists and agonists, GABA agonists, NMDA-receptor antagonists, and the topical agents, capsaicin and dimethyl sulfoxide. In patients with early CRPS, prednisone and methylprednisolone have been reported to have significant analgesic effects, including long duration of effect and 75% clinical improvement in the prednisone arm until remission at 12 weeks. In a randomized trial of topical DMSO vs. regional IV guanethidine, Geertzen et al reported that the 13 patients in the DMSO arm had significantly improved Visual Analogue Scores compared with patients receiving guanethidine after 9 weeks. Gobelet et al demonstrated some pain relief with subcutaneous injections of calcitonin. Of recent interest is a report of a randomized controlled trial in which the incidence of CRPS after surgical correction of Colles fracture was significantly reduced by the prophylactic use of ascorbic acid (Vitamin C).

Regional Anesthetic Techniques. There is a lack of prospective studies evaluating regional anesthetic techniques, and few, if any, discuss intermittent sympathetic blockades, although stellate ganglion and local anesthetic sympathetic blocks are still traditional first-line treatments. Rauck et al conducted the largest randomized, blinded trial (n = 26) of epidural analgesia and demonstrated that patients receiving clonidine had significantly reduced pain indices compared to placebo. Sedation and hypotension were also reported.

In their reviews of various treatment modalities, Kingery et al and Tanelian et al reported only limited support for IV regional anesthesia, although investigators assessed numerous agents. In their randomized, double-blinded trial of bretyllium plus lidocaine vs. lidocaine alone, Hord et al found that bretyllium/lidocaine provided significantly more pain relief of greater duration than the control. Data from a randomized study of 9 in which IV ketanserin blocks were compared against placebo indicated that patients in the ketanserin arm had significant, sustained pain relief. Tolerability was acceptable, and side effects were mild. Although these prospective studies, demonstrated significant improvement with each IV regional agent, their numbers were small. Verification in larger randomized controlled trials (RCTs) is needed if general conclusions are to be drawn. Additionally, none of these regional anesthesia studies discussed the effect of lidocaine on sensory nerve endings, which confounds interpretation of the results.

Neurostimulation. Although most studies of neurostimulation are noncontrolled, the majority have demonstrated beneficial effects of spinal cord stimulation (SCS) for the symptomatic management of CRPS, and their contribution to an understanding of this treatment modality is all the more significant in the light of the recent prospective, randomized trial by Kemler et al. Most studies emphasize the importance of patient selection prior to SCS trial.

Spinal Cord Stimulation. In a randomized prospective study of 54 patients in which SCS combined with PT vs. PT alone were compared, the SCS/PT group reported significantly reduced pain intensity and a significantly higher Global Perceived Effect. Multivariate analysis demonstrated that only treatment assignment influenced the size of the effect. Pain reduction was not predicted by upper vs. lower extremity involvement, age, gender, duration of pain, pain rating on VAS, overall distress, or health-related QOL at baseline. Functional status at 6 months was not affected by treatment assignment, nor was it predicted by any baseline variables. The complication rate was 25% (6/24), mostly malposition of the electrode.

Oakley and Weiner reported results from 19 CRPS patients, a subgroup enrolled in a prospective multicenter SCS trial. In 10 assessable patients, significant improvement in pain was reported. The complication rate of 21% (4/19 requiring minor revision). While the numerous outcome measures plus a well-defined population were strengths of the study, the small number of assessable patients confounds the results with a potential selection bias.
Many retrospective studies of SCS in the treatment of CRPS have also been reported. Bennett and colleagues reported on a multicenter series of 101 assessable patients and found significantly favorable outcomes with good pain control in most patients.\textsuperscript{96} Calvillo et al examined various outcomes after stellate ganglion block followed by SCS, PNS, or both in 36 patients with CRPS of the upper extremity.\textsuperscript{97} Pain was 45% significantly “better” in the SCS group, 51% in the PNS group, and 64% in those receiving both therapies. In a preliminary report, Mekhail et al\textsuperscript{98} in a 127 chronic pain patient study (60% diagnosed with CRPS) reported trends toward positive utilization of health-care resources, daily living, overall health, satisfaction, and cost-effectiveness. Pallares and coworkers reported 86% (67/7) of the patients had 75% improvement in symptoms after SCS.\textsuperscript{99} Preceding their randomized prospective study of SCS in patients with CRPS, Klemmer et al reported retrospective data on a different group of 23 CRPS patients. SCS patients had a significant reduction of mean pain scores vs. baseline, while in contrast to the control group.\textsuperscript{100} Successful pain relief outcomes in the treatment of CRPS with SCS reported by Barolat et al, Sanchez-Ledesma et al, and Kumar et al have also been reported in the literature.\textsuperscript{101-103} Common to all the reports is a complication rate of 20% to 30%, which is mostly due to a shift (positional change) of the percutaneous lead.

**Peripheral Nerve Stimulation.** Recent reports have indicated a more consistent response than earlier reported for PNS patients.\textsuperscript{104,105} In 1 series, 6 patients with causalgia responded to PNS and SCS.\textsuperscript{106} In a study of 48 patients (4 with phantom limb pain), Buschmann and Oppel reported that 47 of 52 procedures were regarded as satisfactory.\textsuperscript{107} Hassenbusch and colleagues reported favorable results in a prospective trial of 32 consecutive patients with CRPS.\textsuperscript{108} They noted a long-term response rate, based on good or fair pain relief, of 63%; 20% returned to work. Compared to pre-implant levels, allodynia and spontaneous pain were significantly reduced in responders.\textsuperscript{108} The authors concluded that PNS provided good relief for pain that is limited to the distribution of a major peripheral nerve. Although most protocols, techniques, and electrode designs for PNS are far from ideal, they are improving. In particular, specific electrode development is needed to improve the nerve-electrode interface, in some areas such as the dorsum of the foot.

**Intrathecal Drug Delivery.** In non-cancer patients, long-term intraspinal drug infusions are increasingly used; however, most data are from anecdotal reports, small, uncontrolled studies with short follow-up, or retrospective studies. Of the prospective studies in patients with CRPS, Kanoff administered intraspinal morphine to 15 patients with chronic, intractable pain (5 with CRPS).\textsuperscript{109} There were few complications, with “good” to “excellent” pain relief in 11 patients, and 6 returning to work. In a randomized, double-blinded, placebo-controlled study conducted by Van Hilten et al, bolus intrathecal injections of bupivacaine were given to 7 women with CRPS-I or CRPS-II.\textsuperscript{112} Six subjects crossed over and received continuous intrathecal bupivacaine. Eighty-six percent of patients receiving bolus bupivacaine achieved complete or partial resolution of dystonia of the hands. Fifty percent of patients receiving continuous bupivacaine regained normal hand function, and 33% also regained their ability to walk. Side effects were mild to moderate. The authors concluded that CRPS associated dystonia responded to intrathecal bupivacaine. Validation of the foregoing data are needed in large, randomized, prospective trials to determine a role for intrathecal drug delivery in the management of CRPS.

**Sympathectomy.** The phenomenon of sympathetically mediated pain in CRPS must be confirmed by regional anesthetic procedures before sympathectomy can be considered in the treatment of CRPS.\textsuperscript{110,111} Evidence to support the use of sympathectomy is limited. Only anecdotal reports exist for radiofrequency in the treatment of CRPS.\textsuperscript{112,113} Retrospective studies of surgical sympathectomy for the treatment of CRPS demonstrate long-term successful outcomes in 70% to 85% of the cases of thoracic, and slightly less, on lumbar sympathectomy.\textsuperscript{114} Schwartzman in a 29-patient retrospective study showed patients with unsuccessful surgical outcomes had significantly longer duration of symptoms before surgery than those with successful outcomes (median 36 and 16 months respectively).\textsuperscript{110} In a similar study, 20 of 21 patients who had surgical sympathectomy 12 months following injury had satisfactory outcomes.\textsuperscript{111} These successful outcomes must be balanced with reports of the negative impact of surgical sympathectomy in some cases.\textsuperscript{115-117} The role of sympathectomy in the treatment of CRPS needs to be determined in large, randomized, prospective trials.

**Deep Brain and Motor Cortex Stimulation.** Brain stimulation for pain has traditionally involved stimulation of the thalamic sensory nucleus and/or the periventricular/periaqueductal gray. A review of the DBS literature
shows that 30% to 40% of patients with intractable neuropathic pain have adequate pain control. While there is no study specifically evaluating DBS for CRPS, the few reported cases have demonstrated comparable outcomes. A more recent brain stimulation technique involving stimulation of the motor cortex has provided early promising results for the treatment of neuropathic pain. Epidural motor cortex stimulation, first proposed by Tsukabawa et al for the treatment of central pain, is safer, less invasive, and easier to perform than deep brain stimulation. As an experimental procedure in patients with CRPS, the efficacy of motor cortex stimulation, particularly for heat hyperalgesia is >60% based on small numbers of patients with CRPS treated. * Nguyen et al reported data from a prospective study of 32 patients with refractory central and neuropathic facial pain treated with chronic stimulation of the motor cortex. Seventy-seven percent of patients with central pain and 75% with neuropathic facial pain experienced substantial pain relief, as measured by Visual Analogue Scale. Nevertheless, randomized, prospective studies are required and technical areas such as electrode design and stimulation parameters require further research.

CONCLUSIONS

An update of the existing clinical guidelines for CRPS is proposed, with the goal of treatment being minimization of pain and optimization of function through rehabilitation, pain management, and psychological therapy. Several new features of the updated clinical pathway include incorporation of neurostimulation techniques, and consensus guidelines on the timing of more invasive therapies. There is widespread agreement among experts that patients who do not respond to an acceptable level of treatment by 12 to 16 weeks should be given a trial of more interventional therapies as discussed. The proposed CRPS clinical pathway presented here will require validation through the conduction of RCTs. The QOL focus of the clinical pathway emphasizes an interdisciplinary approach (rehabilitation, pain management, and psychological treatment) that the panel believes is the foundation for successful treatment of patients with CRPS.

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