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Complex Regional Pain Syndrome: Practical Diagnostic and Treatment Guidelines, 4th Edition

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Abstract

Objective. This is the fourth edition of diagnostic and treatment guidelines for complex regional pain syndrome (CRPS; aka reflex sympathetic dystrophy).

Methods. Expert practitioners in each discipline traditionally utilized in the treatment of CRPS systematically reviewed the available and relevant literature; due to the paucity of levels 1 and 2 studies, less rigorous, preliminary research reports were included. The literature review was supplemented with knowledge gained from extensive empirical clinical experience, particularly in areas where high-quality evidence to guide therapy is lacking.

Results. The research quality, clinical relevance, and "state of the art" of diagnostic criteria or treatment modalities are discussed, sometimes in considerable detail with an eye to the expert practitioner in each therapeutic area. Levels of evidence are mentioned when available, so that the practitioner can better assess and analyze the modality under discussion, and if desired, to personally consider the citations. Tables provide details on characteristics of studies in different subject domains described in the literature.

Conclusions. In the humanitarian spirit of making the most of all current thinking in the area, balanced by a careful case-by-case analysis of the risk/cost vs benefit analysis, the authors offer these "practical" guidelines.

Key Words. Complex Regional Pain Syndrome; Reflex Sympathetic Dystrophy; Guidelines; Diagnosis; Therapy

Introduction

This is the fourth edition of diagnostic and treatment guidelines for complex regional pain syndrome (CRPS; aka reflex sympathetic dystrophy [RSD]). These guidelines have all been sponsored by the Reflex Sympathetic Dystrophy Syndrome Association and are written by expert practitioners in each discipline that is traditionally utilized in the treatment of CRPS [1]. There is an excellent, rigorous, systematic review of the treatment literature in CRPS [2] that confirmed that there is very little high-quality research in the area. Nonetheless, in this "evidence vacuum," we still have a responsibility to treat. Certainly, we must develop better evidence, but our patients cannot wait for that. Thus, although the authors of these practical guidelines all utilized a systematic approach in reviewing the available and relevant literature, they have also included less rigorous preliminary research reports supplemented by extensive empirical experience. The primary aim of this review is to present a comprehensive and detailed review of *all* the relevant literature pertaining to the diagnosis and treatment of CRPS, emphasizing the best quality evidence, but necessarily including less high-quality literature, so as to provide the practitioner with more treatment options than the four treatments with high-level evidence mentioned in a recent strict systematic review [2]. The authors perforce extrapolate from "related conditions" (e.g., neuropathy [3]), discuss the merits of more anecdotal literature, and mention techniques from their clinical experience. The research quality, clinical relevance, and "state of the art" of diagnostic criteria or treatment modalities are discussed, sometimes in considerable detail. Detailed sections are provided, with an eye to the expert practitioner in each therapeutic area. These guidelines are intended to serve as an aid to the informed practitioner. They are not intended to replace or supplant the clinician's best judgment, experience, training, and/or a careful consideration of the clinical context. Practical, easy-to-use "levels of evidence" according to the scheme used in earlier editions are utilized in this review (please see Table 1), so that the practitioner can better assess and analyze the modality under discussion, and if desired, to personally consider the citations. The authors in each section have selected a "system" for reviewing the literature in their area of expertise, and mention this in the introduction of each section. In the humanitarian spirit of making the most of all current thinking in a very poorly researched area, balanced by a careful case-by-case analysis of the risk/cost vs benefit analysis, we offer these "practical" guidelines.

Table 1 Levels of evidence used in this review

Level 1: Meta-analysis or systematic reviews.
Level 2: One or more well-powered randomized, controlled trials.
Level 3: Retrospective studies, open-label trials, pilot studies.
Level 4: Anecdotes, case reports, clinical experience, etc.

Diagnostic Considerations

Historically, among the many names that CRPS has been called, RSD and causalgia are the best known and still are commonly used. The existence of this confusing taxonomy for CRPS stems, in part, from the many nonstandardized, idiosyncratic, diagnostic schemes used throughout the past century and a half (e.g., Bonica [4], Kozin et al. [5], Blumberg [6], and Gibbons and Wilson [7]). In 1851, Claude Bernard (1813–1878) was the first to mention a pain syndrome that was linked to sympathetic nervous system dysfunction. Later, a student of Bernard, Silas Weir-Mitchell (1829–1914), employed the term "causalgia" to describe the pain he diagnosed in post-bellum union veterans (Greek: kausos = heat, algos = pain). Evans first coined the term "reflex sympathetic dystrophy" [8]. Although "RSD" became the most common name to describe this medical condition in the latter 20th century, this name is problematic for several reasons: if a true "reflex" is indeed involved, it is complicated/multisynaptic and not fully characterized; it has since been shown that the assumed "sympathetic"/autonomic changes may not be a constant or causative pain component and furthermore may not be physiologically involved throughout the entire course of the condition in every patient; and actual "dystrophy" is present in perhaps only 15% of cases. The historical lack of agreement regarding standardized nosology and diagnostic criteria for CRPS/RSD has hindered medical and scientific progress in many ways, including lack of comparison studies of treatment of the disorder, and thus has delayed progress in identifying optimal treatments and treatment sequences for its sufferers [9–12].

Primary attempts to outline diagnostic criteria for this syndrome incorporated anecdotal clinical syntheses of signs and symptoms derived from experience, such as those by Bonica [4], while attempts to identify formal criteria only appeared decades later [5,7,9]. Although commendable, the multitude of efforts added to the increasing literature of idiosyncratic, inconsistent, diagnostic schemes. To reverse this trend of "diagnostic chaos," more recent efforts to formally define the syndrome have taken place at consensus workshops. The Schloss Rettershof conference in 1988 [10] and the more definitive Orlando conference in 1994 [11,12] were international consensus efforts held to create scientifically validated diagnostic criteria designed to be inclusive, sensitive, and broad. The consequent taxonomy and criteria were adopted by the Committee for Classification of Chronic Pain of the International Association for the Study of Pain (IASP) (Table 2; the "first" IASP

criteria) [13]. These materials have greatly aided in the understanding of the syndrome, created the potential for improved clinical communication, and helped engender homogeneity within and across research samples around the world [12].

The criteria that emerged from the Orlando conference were necessary and important, yet experience gained from developing diagnostic criteria for headache and psychiatric disorders (other clinically based diagnostic schema) indicates the necessity of validating and modifying such preliminary consensus-based criteria through systematic validation research [14], as was the intent of the Orlando group. Consensus-derived criteria that are not empirically validated may lead to overdiagnosis or underdiagnosis of the syndrome and thus may reduce the ability to provide timely and optimal treatment. Because the IASP criteria for CRPS taken from the Orlando conference represent consensus, they required clinical validation [11,12]. Additionally, the use of the IASP criteria has been sporadic in the literature since their publication in 1994 [15], and the failure of the majority of researchers in the field to embrace them has continued to restrict the full and potential benefits of having a common set of criteria.

This section will describe empirical/statistical methods for validating diagnostic criteria for CRPS, discuss the results of validation studies to date, and will encapsulate the latest international consensus group's action in Budapest, Hungary, which approved and codified empirically derived criteria as a revision of the Orlando consensus group criteria. The IASP committee on taxonomy recently approved and codified these so-called Budapest Criteria as "the new IASP criteria" (Table 3).

Internal Validation

A closer study of internal validation of the 1996 IASP/CRPS criteria raises many questions concerning the integrity of the internal structure. For example, is the combination of edema, vasomotor, and sudomotor signs and symptoms in a single criterion the best, most efficient grouping (i.e., criterion 3 of old IASP/CRPS criteria; Table 2), or does this diminish diagnostic specificity and/or sensitivity? Have pivotal criteria with potential treatment implications been overlooked (i.e., motor abnormalities) [1,11,16]?

Table 2 Original International Association for the Study of Pain (Orlando) diagnostic criteria for complex regional pain syndrome

1) The presence of an initiating noxious event or a cause of immobilization.
2) Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event.
3) Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain.
4) This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

Type I: *without* evidence of major nerve damage.
Type II: *with* evidence of major nerve damage.
Modified from Merskey and Bogduk [13].

Table 3 Revised complex regional pain syndrome criteria by the Budapest consensus group (accepted and codified by the Committee for Classification of Chronic Pain of the International Association for the Study of Pain)

General Features of the Syndrome

CRPS is a syndrome characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time.

There are two versions of the proposed diagnostic criteria: a clinical version meant to maximize diagnostic sensitivity with adequate specificity, and a research version meant to more equally balance optimal sensitivity and specificity. These proposed criteria are described in Tables 5 and 6, respectively.

Distinct subgroups of CRPS can be derived from statistical pattern recognition methods such as factor analysis and cluster analysis. Such methods have been used previously for internal validation of headache diagnostic criteria [17–19], as well as psychiatric diagnostic criteria [20]. Factor analysis is a statistical method that groups coherent, and presumably conceptually linked, variables into subsets (factors) within a dataset. These subsets can then be grouped together statistically (i.e., if one sign/symptom in a given factor is present, it is more likely that another sign/symptom in that factor will also be present). Factor analysis can thus provide distinct, statistically derived subgroups of CRPS signs and symptoms (factors) as they present in the clinical setting [21]. Signs and symptoms that group together into the same factor may be reasonably assumed to share some underlying pathophysiology (e.g., color and temperature changes in the affected part are both mediated by vasomotor tone, which is an indirect indication of sympathetic tone).

Although the consensus-derived Orlando/IASP CRPS criteria suggested that signs and symptoms of CRPS cluster into two subgroups (pain/sensory and vasomotor/sudomotor/edema), internal validation research using factor analysis in a series of 123 patients revealed that characteristics of CRPS actually clustered into four

Table 4 Factors (and factor loadings) resulting from principal components factor analysis of diagnostic and associated signs and symptoms of complex regional pain syndrome

Factor 1	Factor 2	Factor 3	Factor 4
Hyperalgesia signs (0.75)	Temperature asymmetry symptoms (0.68)	Edema signs (0.69)	Decreased range of motion signs (0.81)
"Hyperesthesia" symptoms (0.78)	Color change signs (0.67)	Sweating asymmetry signs (0.62)	Decreased range of motion symptoms (0.77)
Allodynic signs (0.44)	Color change symptoms (0.52)	Edema symptoms (0.61)	Motor dysfunction signs (0.77)
			Motor dysfunction symptoms (0.61)
			Trophic symptoms (0.52)
			Trophic signs (0.51)

Factor loadings can be interpreted as correlations between individual signs/symptoms and the overall factor on which they load.

statistically distinct subgroups (Table 4; also see Harden et al. [21] and Bruehl et al. [22]). A revalidation has confirmed this finding [23]. The Orlando grouping of the statistically distinct vasomotor and sudomotor/edema subsets of signs and symptoms into a single criterion in the IASP taxonomy (criterion 3, Table 2) was demonstrated to be particularly problematic. Grouping two distinct clusters of signs/symptoms into a single diagnostic criterion lowered the clinical diagnostic threshold, leading to poor specificity and probable overdiagnosis of the disorder [21–23].

In addition to the suggested regroupings of signs and symptoms described earlier, factor analysis identified a fourth statistically distinct subgroup as well, consisting of a number of clinical characteristics not reflected in the Orlando IASP/CRPS diagnostic criteria but often seen in practice. These signs and symptoms have been frequently recognized in the older literature as fundamental features of RSD [5,7,9,11,16,24]. The older RSD literature describes various signs of motor dysfunction (e.g., dystonia, tremor) [9,16,24] and trophic features (e.g., changes in hair or nail growth, development of thin, "shiny" skin) [5,7] as being important clinical features of the syndrome. Factor analysis indicates that these motor/trophic characteristics form a fourth, distinct subset of CRPS signs and symptoms that group/factor together but do not overlap substantially with the three other subgroups described earlier [21,23]. The historical, clinical observations of the syndrome coupled with these recent findings indicate that a group of diagnostically relevant signs and symptoms of the disorder were likely omitted from the Orlando/IASP criteria.

External Validation

The external validity of the Orlando IASP/CRPS criteria has also been assessed. The external validity of the diagnostic criteria for CRPS measures its ability to distinguish CRPS patients from other neuropathic pain patients (i.e., those not involving significant evoked sensory alterations, autonomic component, etc). An ideal diagnostic criteria would make an unambiguous distinction between neuropathic pain patients based upon some clear external reference point or "gold standard" [25], but without a known pathophysiology for CRPS, such a "gold standard" does not yet exist. Thus, developing evidence for the external validity of the Orlando IASP/CRPS criteria is relatively challenging but not impossible [21–23].

The Orlando/IASP criteria themselves can be used as a reference point to test external validity [21–23,26]. For this process, a CRPS patient group should be identified using a "strict" application of the Orlando/IASP criteria that is then compared with a non-CRPS neuropathic pain group that has been diagnosed using other available diagnostic information (e.g., proven, chronic diabetes with peripheral symmetrical pain, confirmed by electrodiagnostic studies). It is important to note that this latter group does not simply consist of patients who fail to meet Orlando/IASP criteria but rather reflects a non-CRPS diagnosis derived from independent objective criteria. Therefore, by using the Orlando/IASP CRPS criteria to distinguish between the two groups of patients, the "deck has been stacked" in favor of being able to discriminate accurately between the CRPS and non-CRPS neuropathic pain patients. If the diagnostic criteria cannot distinguish accurately between CRPS and other clinically distinct neuropathic pain conditions based upon patterns of signs and symptoms, even under such favorable test conditions, the criteria are likely to be of limited utility in research and to the average clinician. A distinct disorder such as diabetic neuropathy will most likely not present a differential diagnostic challenge in clinical practice because of the clear existence of another condition "that would otherwise account for the degree of pain and dysfunction" (see criterion 4, Table 3), but the use of such disorders for testing the discriminative ability of CRPS diagnostic signs and symptoms provides an effective model for examining external validity issues.

Validation Studies

In a preliminary external validation study, 18 patients meeting Orlando IASP/CRPS criteria and 30 patients with painful diabetic peripheral neuropathy were examined. Initial study results indicated that the use of the Orlando

IASP/CRPS criteria and decision rules to make diagnostic decisions could lead to considerable overdiagnosis. If glucose tolerance status were not known and diagnoses were made *solely* based on the pattern of signs and symptoms, up to 37% of diabetic neuropathy patients would be misdiagnosed as having CRPS if one used the Orlando IASP/CRPS criteria [26].

Similar findings were determined in a larger external validation study [21,22]. The sample consisted of 117 patients meeting Orlando IASP/CRPS criteria and 43 neuropathic pain patients with established non-CRPS etiology; these 43 non-CRPS patient diagnoses included diabetic neuropathy, polyneuropathy, post-herpetic neuropathy, and radiculopathy. The Orlando/IASP criteria and decision rules (e.g., "evidence at some time" of edema or color changes or sweating changes satisfy criterion 3) discriminated appreciably between the CRPS and non-CRPS groups. However, closer examination of the results indicated that while diagnostic sensitivity (i.e., ability to detect the disorder when it is present) was quite high (.98), specificity (i.e., minimizing false positive diagnoses) was very poor (.36), and a positive diagnosis of CRPS was likely to be correct in as few as 40% of cases [22].

Sensitivity is extremely important in a clinical setting. Yet, specificity is also quite important to reduce potential morbidity (and even mortality) associated with inappropriate therapies, such as adverse reactions to medications and unnecessary invasive treatments. When sensitivity is high at the expense of specificity, CRPS may be overdiagnosed and, ultimately, overtreated in a clinical setting. High sensitivity causes the identification of pathophysiologically/mechanistically heterogeneous cohorts for research, potentially contributing to negative results in clinical trials. In order to treat patients adequately, such overdiagnosis must be balanced with the equally undesirable consequences of failing to identify clinically relevant syndromes. Therefore, although the use of the Orlando/IASP criteria in an external validation model tends to inflate diagnostic sensitivity, such a model can be useful for testing the effects of modifications to the criteria on specificity and overall diagnostic accuracy [21–23].

Statistically Derived Revision of CRPS Criteria

A set of research criteria derived from the results of the previously mentioned factor analysis and external validation, later corroborated in a revalidation study, was developed in order to provide such a test [21–23]. These adapted criteria grouped all CRPS traits into one of the four statistically derived factors described earlier (pain/sensation, vasomotor, sudomotor/edema, motor/trophic; see Table 5). In light of evidence from the Galer et al. [26], and Harden et al. and Bruehl et al. studies [21,22], which demonstrated that objective signs on examination and patient-reported symptoms both provide valuable but nonidentical data, the adapted research criteria required the incidence of signs *and* symptoms of CRPS for diagnosis.

Table 5 *Clinical* diagnostic criteria for complex regional pain syndrome

1) Continuing pain, which is disproportionate to any inciting event
2) Must report at least one symptom in *three of the four* following categories
   Sensory: Reports of hyperalgesia and/or allodynia
   Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   Sudomotor/Edema: Reports of edema and/or sweating changes and/or sweating asymmetry
   Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3) Must display at least one sign* at time of evaluation in *two or more* of the following categories
   Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
   Vasomotor: Evidence of temperature asymmetry and/or skin color changes and/or asymmetry
   Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
   Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4) There is no other diagnosis that better explains the signs and symptoms

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

A study testing the ability of these proposed criteria to differentiate between CRPS and non-CRPS neuropathic pain groups suggested that a modification of the Orlando IASP/CRPS diagnostic criteria could improve overall diagnostic accuracy [21–23]. Results showed that employing a decision rule requiring *two of four sign* categories and *four of four symptom* categories for a positive diagnosis resulted in a sensitivity of 0.70 and a specificity of 0.94. Of all those tested, this decision rule resulted in the highest probability of accurate diagnosis for both CRPS and non-CRPS patients (approximately 80% and 90% accuracy, respectively), even when a relatively low occurrence rate for CRPS was assumed [21,22]. In 2004, the Budapest IASP consensus group deemed this high level of specificity advantageous in a research context and subsequently adopted the rules as components of the proposed *research* criteria (Table 6) [27].

The significance of appropriate decision rules in the criteria is underlined by the fact that the use of these modified criteria, requiring two of four sign categories but only two of four symptom categories to be positive, resulted in a sensitivity of 0.94 but a specificity of only 0.36 [22], similar to the lack of specificity displayed by the Orlando/IASP criteria. This emphasizes the fact that both sensitivity and specificity can be strongly distorted by the decision rules acted upon [21–23]. Decision rules must be determined according to purpose: identification of stringent research

Table 6 *Research* diagnostic criteria for complex regional pain syndrome

1) Continuing pain, which is disproportionate to any inciting event
2) Must report at least one symptom in *each of the four* following categories
   Sensory: Reports of hyperalgesia and/or allodynia
   Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   Sudomotor/Edema: Reports of edema and/or sweating changes and/or sweating asymmetry
   Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3) Must display at least one sign* at time of evaluation in *two or more* of the following categories
   Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
   Vasomotor: Evidence of temperature asymmetry and/or skin color changes and/or asymmetry
   Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
   Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4) There is no other diagnosis that better explains the signs and symptoms

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

samples (minimizing false-positives) vs identification of the highest number of CRPS patients possible (minimizing false-negatives). The Budapest consensus panel therefore implemented a different set of decision rules for proposed *clinical* criteria (see Table 5), requiring *two of four sign* categories and *three of four symptom* categories to be positive [27]. This ostensibly minor adjustment (merely requiring three rather than four symptoms) resulted in a sensitivity of 0.85 and a specificity of 0.69, which represented a good compromise in identifying as many patients as possible at an acceptably accurate rate in the clinical context (see Table 5; for a summary of the sensitivity and specificity of the two criteria, see Table 7). Recently, the Committee for Classification of Chronic Pain of the IASP has accepted and codified the "Budapest" criteria for clinical and research diagnosis (Table 3). In response to the consensus group's concern with the approximately 15% of patients previously diagnosed with CRPS, a third diagnostic subtype called CRPS-not otherwise specified

Table 8 Subtypes of complex regional pain syndrome (CRPS)

CRPS I (old name: reflex sympathetic dystrophy)
CRPS II (old name: causalgia): defined earlier with electrodiagnostic or other definitive evidence of a major nerve lesion
CRPS-NOS* (not otherwise specified): partially meets CRPS criteria; not better explained by any other condition.

* This subtype was added to capture any patients previously diagnosed with CRPS who now did not meet criteria.

was created that would capture those patients who did not meet the new clinical criteria but whose signs and symptoms could not be better elucidated by any other diagnosis (Table 8). This subtype was a practical compromise and may not be necessary in the long term, as research provides specific information about mechanism(s) and thus diagnostic techniques.

CRPS Stages? CRPS Subtypes?

Is CRPS a uniform phenomenon across individuals, or are there distinct subtypes and/or stages of the syndrome? This issue addressing whether or not patient presentations (i.e., the overall pattern of CRPS signs and symptoms) tend to be similar across individuals requires validation. Historically, three progressive stages of CRPS have been cited as important in identifying and treating the syndrome (e.g., [4,28,29]), but the existence of such sequential stages is a clinical lore, an unsubstantiated theory based on certain authors' experience rather than an outcome of specific scientific study (level 4). This hypothesized staging can be tested by using cluster analysis to bracket CRPS patients into three subgroups delineated according to similarity of signs and symptoms. If the theorized stages exist, the subsequent statistically derived patient subgroups should vary considerably with regard to pain duration (i.e., predictable progress of CRPS through the three stages should take place); furthermore, the clinical presentation within the three subgroups should correspond to the three assumed stages of CRPS (best described in Bonica [4]).

One hundred and thirteen patients meeting IASP criteria for CRPS went through standardized history and physical examinations designed to evaluate CRPS signs and

Table 7 Summary of sensitivity and specificity of the clinical and research criteria

Criterion Type	Symptom Categories Required for Diagnosis	Sign Categories Required for Diagnosis	Sensitivity	Specificity
Clinical	≥3	≥2	0.85	0.69
Research	=4	≥2	0.70	0.96

symptoms in the four previously described factor analytically derived domains [30]. After preliminary assessment, K-Means cluster analysis was employed to develop three relatively homogeneous CRPS patient subgroups based on correspondence of sign/symptom patterns in these spheres. The resultant CRPS patient subgroups did not vary considerably in pain duration as might be predicted in a sequential staging model. Moreover, the most frequent signs and symptoms in each of the three patient clusters did not correspond closely to those that should have been anticipated based on published descriptions of the three stages [4]. Contrary to the tradition of time-sequenced progressive stages, the scientific analysis (i.e., cluster analysis) suggested the possible existence of three statistically distinct CRPS subtypes: 1) a relatively limited syndrome with vasomotor signs predominating; 2) a relatively limited syndrome with neuropathic pain/sensory abnormalities predominating; and 3) a florid CRPS syndrome similar to "classic RSD" descriptions [30]. Importantly, despite having the briefest pain duration of the three groups, subtype 3 displayed the greatest levels of motor/trophic signs and possible disuse-related changes (osteopenia) on bone scan. Electromyography (EMG)/nerve conduction velocity testing indicated that subtype 2 may be synonymous with CRPS type II causalgia). Even though this study did not address the individual patterns of temperature changes detected in CRPS patients (e.g., warm vs cold), research suggests that these patterns may vary over time [31]. It would therefore be constructive to see if future work examines whether or not these specific patterns relate to the patient subtypes identified.

In conclusion, these preliminary results argue against the historical three *sequential* stages of CRPS [30,32–34]. Future application of comparable analytic methods to the complexities of CRPS may permit the identification of discrete CRPS subgroups with the goal of being able to target treatment more effectively.

In 2004, the Budapest consensus group considered this information too preliminary to warrant the adoption of these subtypes (or any other scheme) into the formal diagnostic criteria. However, the consensus group *did* address the old CRPS subtypes that were reported at the Orlando conference and in the IASP criteria (1994). There was a broad consensus that problems do exist with creating a division between CRPS type I (see Table 2: without distinct "major nerve damage"; most like the old name RSD) and type II (see Table 2: "with major nerve damage," most like the old name causalgia). The consensus group found these divisions to depend on nebulous definitions of what constitutes "major nerve damage," and they discussed how objective definitions might be more accurately determined. The problem of distinguishing CRPS type I vs type II is complicated clinically by the fact that the definitive tests of nerve damage, such as EMG, are considered unnecessarily painful (even cruel) to CRPS patients. Small nerve "dropout" has been demonstrated in the skin of the affected part in most subjects studied, but there is no guidance as to whether this constitutes "major" or "minor nerve damage" [35]. Moreover, these diagnostic distinctions may not have clinical significance or affect the specific therapeutic method used. Despite these limitations, the distinction between these two existing CRPS subtypes was preserved by the Budapest group, and an eventual re-evaluation of this matter was postponed until more data pertaining to its clinical importance becomes available.

The Orlando/IASP CRPS diagnostic criteria were developed to furnish an objective means of determining whether unidentified pain conditions indicate CRPS (i.e., in which significant autonomic dysfunction is present) or some other type of neuropathic pain. Therapy for these two types of conditions may differ, and application of inappropriate (and possibly expensive) treatments due to misdiagnosis may add to unnecessary morbidity and medical costs. Worse still, misdiagnosis may delay appropriate therapy in some situations. Therefore, the statistically and empirically guided modifications described earlier, which enhance the accuracy of the CRPS diagnostic criteria, should positively affect issues of patient quality of life and reduce issues of medical overutilization, side effects, etc. Additionally, such improvements and revisions to the CRPS criteria will aid in more accurately recognizing research candidates and more effectively determining therapeutic outcomes [1]. Yet because the current understanding of the pathophysiology of the syndrome is incomplete, the statistical method described remains one of the few existing objective techniques for validating the IASP/CRPS criteria and indicating the direction of the modifications necessary to optimize their clinical and research value. Recently, the Committee for Classification of Chronic Pain of the IASP has accepted and codified the "Budapest" criteria for clinical and research diagnosis (Table 3).

Even though the validation methodology described tends to overstate diagnostic sensitivity, results thus far do suggest that the Orlando/IASP diagnostic criteria are acceptably sensitive (i.e., they rarely miss a case of actual CRPS). However, both internal and external validation research indicates a tendency toward overdiagnosis with these Orlando criteria [21–23,26,27]. This overdiagnosis may result from the grouping of discrete elements of the syndrome (vasomotor changes and sudomotor changes/edema) into the same diagnostic criterion. The information also suggests that failure to include motor/trophic signs and symptoms in the current criteria could lead to excluding vital information that may aid in discriminating CRPS from other syndromes. The closed-consensus workshop in Budapest adopted and codified the criteria in Table 3, and these criteria have been approved by the Committee for Classification of Chronic Pain of the IASP for future revisions (the next being the third) of their formal taxonomy and diagnostic criteria for pain states. A trial of these modified research diagnostic criteria suggests that a dramatic reduction of the rate of overdiagnosis is possible despite the fact that such changes also modestly diminish diagnostic sensitivity [22]. The consensus group debated the relative merits of improved specificity at the expense of diagnostic sensitivity and ultimately adopted two similar

sets of criteria differing only in the decision rules employed (summarized in Tables 5 and 6): one specifically designed for clinical settings and the other designed for research settings.

Interdisciplinary Management

This semisystematic review of interdisciplinary management of CRPS was conducted using a combination of PubMed, Ovid MEDLINE®, and Google Scholar. The key words used were: complex regional pain syndrome, CRPS, reflex sympathetic dystrophy, RSD + rehabilitation, interdisciplinary, functional restoration, physical therapy, occupational therapy, recreational therapy, vocational rehabilitation, physiotherapy, exercise therapy, conservative treatment, mirror therapy, and graded motor imagery."

A Dahlem type (think tank) conference was held in Malibu, California, in 1997 to generate consensus as to treatment guidelines for CRPS [1]. All treatments were focused primarily on functional restoration; the use of drugs, blocks, and psychotherapy was reserved for patients failing to progress in the functional algorithm (Figure 1). Interdisciplinary pain management techniques emphasizing functional restoration are thought to be the most effective therapy perhaps by resetting altered central processing and/or normalizing the distal environment (level 1) [36,37].

The principle of functional restoration is based on a gradual and steady progression from activation of presensorimotor cortices (i.e., motor imagery and visual tactile discrimination) to very gentle active movements such as progressing from active range of motion (ROM), to weight

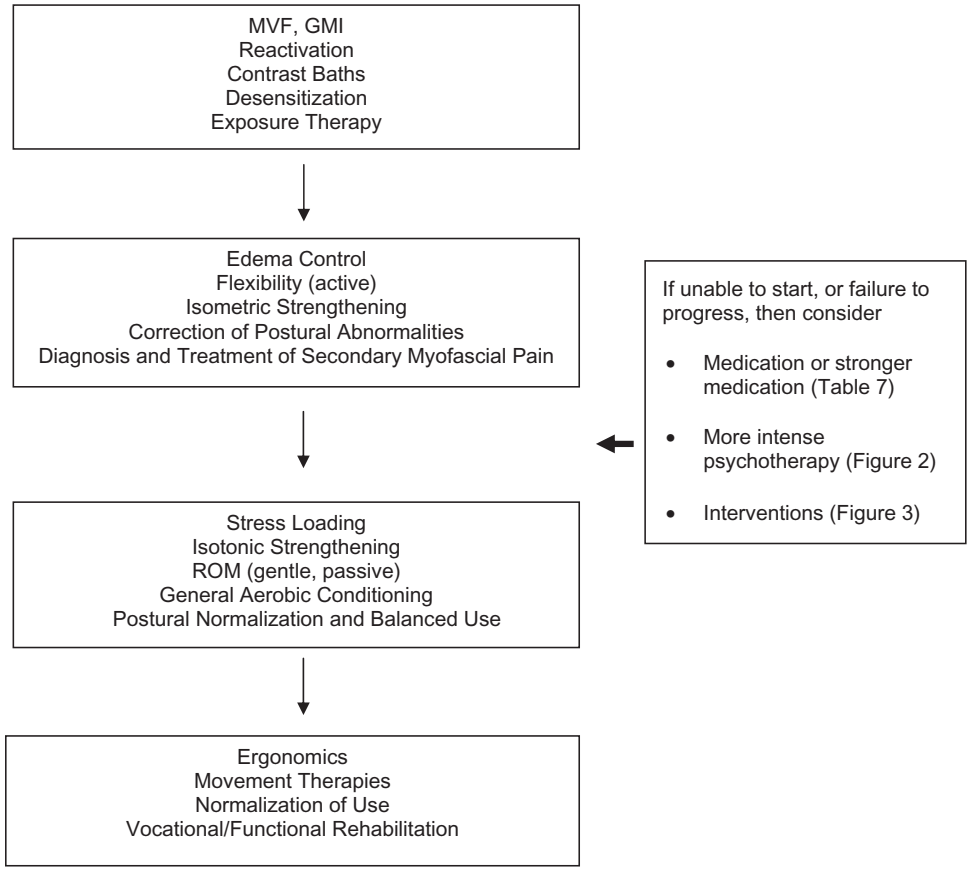

Figure 1 Overall treatment algorithm. From the outset, in appropriate cases, the patient should have access to medications and/or psychotherapy and/or injections, if needed. If the patient cannot begin, or fails to progress, at any step or in any regard, the clinical team should consider starting (or adding) more or stronger medications (see pharmacotherapy section) and/or more intensive psychotherapies (see psychological intervention section) and/or different interventions (see interventional therapy section). MVF = mirror visual feedback; GMI = graded motor imagery. (Extrapolated and modified from the three clinical consensus meetings: Malibu, Minneapolis, and Budapest [1,47,53].)

bearing such as carrying light bags with the upper extremity or putting partial weight on the lower extremity in gait training (level 4) [38]. This progresses to movements that involve more active load bearing such as the scrub and carry techniques of Carlson (level 3) [39,40]. Gradual desensitization to increasing sensory stimulus goes along with increased function. This could include such strategies as progressive stimulation with silk, progressing to other textures of cloth such as towel, or contrast baths that progressively broaden the temperature difference between the two baths. It is thought that perhaps this gradual increase in normalized sensation tends to reset the "altered central processing" in the nervous system (level 3) [41]. It is important to manage edema in order to optimize ROM and encourage general aerobic activity throughout (level 4) [42].

Another basic principle of these functional restoration guidelines is that if patients do not progress through the steps in "a reasonable time," then other interventions will be progressively added to give the patient greater comfort or confidence so that they may proceed to the next level. For instance, if the allodynic pain is too great, a sympathetic and/or somatic block may give the patient a comfort window of opportunity to begin to entertain more aggressive therapy, or if a patient has kinesiophobia [43–45], cognitive behavioral techniques could be undertaken to demonstrate to the patient that movement does not necessarily lead to negative consequences. Blocks, psychotherapy, and drugs should be used mainly in situations of failure to progress; however, if a patient presents with significant concomitant problems (e.g., depression), then certain drugs, blocks, or psychotherapies are recommended from the outset (see later) [1].

The Rationale for Functional Restoration

CRPS can be a very difficult condition to treat successfully. Not only is the syndrome biomedically multifaceted, comprising both central and peripheral pathophysiology, but it also frequently contains psychosocial components that are additional pivotal diagnostic features (and thus, critical treatment targets). The array of possible patient presentations and the fact that the presentation often changes over time also complicate successful identification and treatment [30]. To further add to the clinical challenges of managing CRPS, the epidemiology and natural history of CRPS are only superficially known; evidence concerning CRPS treatment has developed slowly due in large part to the vagaries of diagnosis (see earlier), and moreover, research data—when they are available—are challenging to interpret [46]. Given these obstacles to diagnosis, treatment, and research, how is a specialist to embark on a path toward the successful treatment of such a complicated and partially understood condition? The only treatment methodology that can possibly successfully span these gaps in medical science is a systematic and orderly interdisciplinary approach [47]. Interdisciplinary treatment is defined (here) as a dedicated, coherent, coordinated, specially trained group of relevant professionals that meet regularly to plan, coordinate care, and adapt to treatment eventualities.

Even the identification and measurement of the pain, the principal symptom of CRPS, is problematic. The defining characteristic (and critical diagnostic criterion) is "continuing pain that is disproportionate to any inciting event" [13]—pain deemed disproportionate, that is, in intensity and duration according to the (subjective) opinion of the diagnosing physician. This necessary yet biased assessment of pain is confounded by the patient's outlook; for although pain is clearly a central component of a CRPS patient's condition, its report is always a personal, private, and entirely subjective experience. Any number of factors can affect pain report, including culture, memory of past pain experiences, the meaning and context of the pain, personality type, affective state, and many other functional variables [48,49]. Furthermore, pain report is behavioral: filling out a visual analog scale (VAS) is a behavior, and any such behavior can be affected by a range of psychosocial/operant features. Unfortunately, only the subjective experience of pain is quantifiable. Limited by this subjectivity of both physician and patient, the most pragmatic assessment of pain must be based upon the patient's complete context: biological, psychological, and sociological. Obviously, the only treatment methodology that can treat all these aspects effectively is, again, the interdisciplinary approach.

It is critical to identify and aggressively treat all spheres of the pain experience. Obsessing with only the biomedical sphere often dooms the clinician and patient to failure, especially in chronic CRPS. The other equally important features for accurate diagnosis and responsive treatment targets in CRPS are psychological factors/comorbidity (see later). The psychological spheres of the pain experience can now be identified through the many psychometric, quantified measures that have been created and that have demonstrated efficacy in psychological assessment [49–51].

Psychological features are sometimes critically important diagnostic components to identify and aggressively treat; psychometric scores are also often employed as secondary outcomes in research. CRPS is not a psychological disorder, however, and it is therefore illogical to designate psychometric outcomes as primary benchmarks of improvement in treatment. Thus, solely treating psychiatric aspects of a patient's CRPS is also doomed to fail. Pain intensity and the psychological sequelae/comorbidities of pain are recognized, fundamental elements in understanding the whole patient, yet the subjective character of these elements and of their measurement deem them less suitable for research or for interpreting clinical outcomes. More objective clinical benchmarks and outcomes should be identified—standards upon which clinical decisions may be made and success may be measured. Ideally, treatment of CRPS should rely upon an intuitive, measurable, and stepwise functional restoration algorithm as the pivotal feature of treatment of CRPS [1,30,52].

Functional restoration has historically and empirically been considered a critical and necessary component of interdisciplinary pain management programs for CRPS. This contention has been codified by two large international consensus-building conferences [1,53]. Baron and Wasner concluded that physiotherapy is "of utmost importance" [54], and Birklein et al. argued that rehabilitation techniques should always be employed for the "obvious reasons" that he outlines in these manuscripts [55,56]. In a Dutch multidisciplinary evidence-based guideline for treatment of CRPS [2], physical therapy (PT) is reported to have beneficial effect with regard to functional restoration and ability to cope with the complaint and therefore should form a part of the standard treatment for CRPS. Furthermore, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials has concluded that physical functioning is a "core domain" in the assessment of pain treatment efficacy, second only to pain assessment [57,58].

Functional restoration emphasizes physical activity ("reanimation"), desensitization, and normalization of sympathetic tone in the affected limb and involves a steady progression from the most gentle, least invasive interventions to the ideal of complete rehabilitation in all aspects of the patient's life (see Figure 1). Although the benefits of functional restoration may be obvious to experienced clinicians, the evidence required to buttress these empirical impressions remains to be collected. The hard data needed to determine which aspects of treatment demonstrate efficacy, which specific components of a functional restoration program yield positive outcomes, as well as which modalities should be delivered, when, and for how long, are currently unavailable [53,59].

Evidence

The data suggesting the significance of functional restoration and reanimation are currently modest but credible. It is important to note that in a 1997 meta-analysis, Kingery notes that "CRPS trials tended to use less subjects and were less likely to use placebo controls, double-blinding, or perform statistical tests for differences in outcome measures" (than neuropathic pain) [46]. Early, uncontrolled work by several investigators focused on preliminary concepts of quantifying different facets of function and biometrics in "RSD" (aka CRPS I) [5,60–63]. In a pivotal 1988 article, Davidoff et al. conducted a prospective uncontrolled study in RSD that determined three key concepts: that objective functional components and biometric data could be quantified longitudinally, that these components were reactive enough to display change over time (in response to a functional restoration-based interdisciplinary program), and that they were associated with improvements in subjective outcomes (decreased pain) (level 3 evidence) [52]. These initial studies supplied the primary rationale for a reliance on functional measures as the basis for assessing success in the treatment of RSD/CRPS. In an open-label sample of musculoskeletal pain, Baker et al. convincingly illustrated the value of quasi-quantitative and psychometric measures in estimating functional outcome (level 3 evidence) (although this may not generalize to CRPS completely) [64].

Various uncontrolled studies suggest that CRPS patients benefited from certain physiotherapeutic modalities, including stress loading and isometric techniques (level 3 evidence) [39]. Oerlemans et al. conducted a prospective controlled study of 135 CRPS patients with pain located in an upper extremity, and she reported that both PT and occupational therapy (OT) proved valuable in managing pain, restoring mobility, and reducing impairment (level 2 evidence) [59,65]. Daly and Bialocerkowski reported in a recent well-performed meta-analysis good quality level 2 evidence that pain management PT combined with medical management to be more effective than control therapy, based on the Oerlemans et al. study [66]. In their prospective assessment of 145 patients, Birklein et al. found that pain was notably less for patients undergoing PT (level 3 evidence) [55]. In another study of 28 children meeting the IASP criteria of CRPS, 92% reduced or eliminated their pain after receiving exercise therapy (level 3 evidence) [67].

Both functional restoration and reanimation may have beneficial effects for the CRPS patient. Immobilization is a diagnostic criterion for CRPS that is recognized as a possible cause and/or perpetuating factor in the syndrome (IASP criterion l) [13]. A prevalence of motor abnormalities (dyscoordination, dystonia, weakness, and tremor in CRPS [68,69]) is a recently accepted criterion, and these have been integrated into the Budapest group's suggestions for new diagnostic criteria (see earlier). Additionally, the role of pathological involvement of local muscle spasm, reactive bracing, and disuse in the face of severe pain in relation to the syndrome should not be misjudged or underestimated; these secondary pain sites can cause severe pain and disability, and all must be assessed and actively treated in an interdisciplinary-based functional restoration or "normalization" program.

Normalized movement may also be a key aim in avoiding or inverting some of the more understated, higher central changes linked with the syndrome usually categorized under the rubric of "altered central processing" and recently, "neglect" [68]. Moseley expands on this hypothesis and suggests that the elements of CRPS indicate a central mismatch of afferent input and central representation [70] and that graded motor imagery (GMI) may "repair this dynamic central mismatch." [69] In their meta-analysis, Daly and Bialocerkowski found good to very good level 2 evidence for the efficacy of GMI PT in combination with medical management for upper and lower extremity CRPS resulting in clinically relevant and long-lasting pain reduction [66]. In a novel experiment using mirrors, sensory mismatch was demonstrated to produce sensory disturbances in normal volunteers [71] and has also been employed in a controlled pilot to successfully treat CRPS I [72]. These positive effects of mirror therapy were confirmed in randomized, controlled trial (RCT) with 48 stroke patients with CRPS (level 2 evidence)

[73], finding significant reduction of patient and enhanced upper limb motor function compared with control treatment.

In addition to these findings, positive results have been described in small-sample open-label studies aimed at sensorimotor retuning (desensitization techniques combined with motor tasks, level 3 evidence) [74] and proprioceptive feedback enhancement (using vibratory stimulation, level 3 evidence) [75] have shown reduction in pain and normalization of propriocepsis in CRPS patients [74,75]. Desensitization resulted in normalization of cortical organization in CRPS patients in the study by Pleger et al., resulting in restoration of the blood oxygen level-dependent contrast in the SI and SII lamina of the sensory cortex [74]. These interesting and technical studies provide a theoretical rationale for the more pedestrian physical and occupational therapeutic methodologies of simple functional restoration, graded exposure, and ordered normalization of movement patterns.

In addition to the reversal of immobilization, the subsequent conquest of operant-based movement phobia ("kinesiophobia") presented by so many of our patients may supply another rationale for establishing "functional restoration" as a fundamental requirement and provide a primary role for co-treatment of the physical and the psychological therapies. The research that Crombez et al. conducted on back pain, patients supported their statement, "pain-related fear is more disabling than pain itself," and this fear appears to be a dynamic clinical factor in CRPS [43]. The fear-avoidance paradigm may be very prominent in some CRPS patients, and an open-label pilot in back pain conducted by Boersma et al. has shown that "lowering" fear can reduce the ensuing avoidance of motion and use, and thereby lead to improved function [76]. Also, van de Meent et al. provided preliminary support for the efficacy of "pain exposure" PT, consisting of progressive loading exercised without the aid of medicinal pain management (level 3 evidence) [77]. In a pretest–posttest design, van de Meent et al. found significant reduction in pain and improvement of motor function, functional ability, and perceived health change. Others have also successfully exploited this concept for treating low back pain (level 3 evidence) [78,79]. A definitive investigation of this concept in CRPS has not been undertaken, but clinical experience has indicated that this approach provides a lot of positive reinforcement (at least for the clinicians!) in our clinics. The benefit of a pragmatic integration of graded, supported "exposure" to normalized movement into functional restoration programs for CRPS may be self-evident but requires validation.

The traumas usually identified in the etiology of CRPS most likely begin with peripheral nociceptive overstimulation, and this "nociceptive barrage" can eventually create and sustain the central sensitization that is indicated by the sensory factors of the syndrome. It is hypothesized that normalization of activity will adjust and normalize the afferent input and its processing; for example, an increased functional input on large fiber tracts may modulate or partly obstruct the activity on small fiber tracts, according to Melzack and Wall's gate theory of pain [80]. Blood flow and nutrition to the area may be improved by local activity in the affected part, and processes such as osteopenia (i.e., "Sudeck's atrophy") may also be reversed. Research with rats supports this concept, as do comparisons made to CRPS patients with casts. Patients with prolonged casting of a limb often present with many diagnoses considered part of the CRPS criteria: vasomotor and sudomotor asymmetry, trophic/dystrophic changes including osteopenia, and occasionally sensory disturbances [81]. Intuitively, normalizing function in such CRPS patients should reverse changes wrought by casting, and this impression has been confirmed in Guo et al.'s rat research where casting led to autonomic disturbance and allodynia [82].

These studies all support the traditional functional/physiotherapeutic rationale, although there is currently no levels 1 or 2 evidence specifically for interdisciplinary treatment for CRPS. It is important to note two meta-analyses that have shown that an interdisciplinary approach improves symptoms in patients with chronic pain: Flor et al. [36] (which included "RSD" among other diagnoses) and Guzmán et al. [37] (both level 1 evidence). (More detail of the available evidence is presented in the specific sections later.)

Principles of Functional Restoration

The Malibu Conference

In order to expedite reanimation and normalization of use of the affected extremity, functional restoration should efficiently supply a range of interventional and noninterventional treatment methods. In an effort to explore the creation of a stepwise functional restoration through a physiotherapeutic algorithm, a Dahlem-type consensus-building symposium was held in Malibu in 1987. The core principles of the algorithm generated by this group include patient motivation, desensitization, and reactivation facilitated by pain relief, the use of pharmacological and/or interventional procedures to treat specific signs and symptoms, and cognitive behavioral psychotherapeutic techniques. As a result of the conference, the symposium members produced a white paper about the purpose and usefulness of an assortment of functional restoration treatment designs; they also recommended formal treatment guidelines [1]. These treatment guidelines are considered pivotal, and the algorithm we present here is a modification of the one advocated by the Malibu group (see Figure 1).

The "Malibu" guidelines created some new problems. First, although these guidelines recognize several specific interventions to be applied (physical, medical, anesthesiological, and psychological), they offer no recommendations regarding optimal sequence or duration of these various interventions. Second, the guidelines stress the concept of time contingency, i.e., the implication that all "patients should progress through each treatment level in

two weeks or less" [1], which has proven to be far too rigid and unrealistic in this complex syndrome. Third, the guidelines assert that drugs, injections, and psychotherapy should be reserved and used only in cases where progress in the functional restoration-based algorithm has not been achieved. They fail to recognize the frequent necessity of providing medications, blocks, and psychological support from the beginning (and not "reserve" these interventions until after a patient has "failed to progress"). In our experience, it is more often than not the case that multiple interventions are required to get a patient started in a functional restoration process.

The Minneapolis Conference

Because of these and other issues, a second expert panel (the Minneapolis Group) revisited the Malibu guidelines in August 2001, along with the pertinent literature up to that time. In response to clinical evidence suggesting that sequencing and timing of the treatment guidelines could be improved (e.g., under certain circumstances, concurrent rather than linear utilization of interdisciplinary interventions provided optimum treatment), the Minneapolis group recommended the use of concurrent "pathways," which were still built upon the original domains of rehabilitation, pain management, and psychological treatment. Additionally, the Minneapolis group liberalized the use of analgesic modalities and de-emphasized time contingency while preserving the focus on function [53].

Both the Malibu and the Minneapolis groups emphasized the pivotal importance of functional restoration. Both acknowledged that pain management was important, but as a subjective operant phenomena, pain was considered secondary to function as an outcome. Both groups recognized that pain would logically drive the type, quality, intensity, and pace of other interventions used to achieve the primary, functional outcomes. The next sections provide a detailed examination of each therapy directly involved in functional restoration.

OT

OTs are the ideal therapeutic leaders in the functional restoration process, as they are trained in the biopsychosocial principles of disease and are primary in functional assessment and treatment [83,84]. The OT role begins by evaluating current functional use of the affected extremity. Active ROM is measured using a goniometer, and edema is gauged with either circumferential measurement or a volumeter [83]. Emphasis is placed on assessment of coordination/dexterity, skin/vasomotor changes, pain/sensation, and use of the extremity during activities of daily living (ADL). While the OT evaluation process has remained consistent over the past few decades, the treatment of CRPS specifically has undergone a shift.

Emerging research has now expanded the interventional focus to include the early stages of movement (activation of premotor and primary motor cortices) through GMI or mirror visual feedback (MVF) therapy. Ramachandran and Rogers-Ramachandran first described the use of mirrors to decrease pain or positional discomfort in those suffering from phantom limb pain [85]. McCabe et al. expanded the study of MVF treatment to determine its efficacy specifically in persons with CRPS [72]. This illustrated the benefits of this technique in those with early and intermediate CRPS; however, MVF demonstrated no significant effect with chronic CRPS [72]. In an effort to target those with longstanding CRPS, Moseley designed a GMI program to sequentially activate the premotor and primary motor cortices through limb laterality recognition, motor imagery, and lastly, mirror therapy [70]. This program proved to be particularly useful, in that, the premotor cortex may be initiated without setting off other cortical networks involved with movement [70]. The mechanisms that underlie MVF and GMI are still somewhat unclear. Many researchers believe that this process is partially influenced by forced attention to the affected extremity, decrease in kinesiophobia, increase in inhibition, and the reconciliation of sensorimotor incongruence [86]. The protocols outlined by McCabe for MVF and Moseley for GMI, can be considered loose treatment parameters, but both emphasize the importance of a client-centered approach that is guided by the clinical observation of presenting symptoms and response to treatment [70,86].

MVF therapy, as outlined by McCabe [86], first asks the client to close their eyes and describe both the affected and unaffected limb (i.e., size, location, and any perceived differences), followed by imagined movements of both extremities. The movements for the program are focused on painful joints and those that are just proximal and distal to the joint. The participant is then invited to look at the mirrored limb without movement in order to try to achieve ownership. The recommend frequency and duration of the home program will vary to some degree. However, the overall emphasis is on short sessions (no more than 5 minutes) occurring frequently (five to six times) throughout the day [86]. Moseley's GMI program extends over a 6-week period (2 weeks spent in each phase of treatment) and begins with limb laterality recognition using pictures. Secondly, the participant views a picture of an extremity and is asked to imagine moving into that position. The third and final stage involves viewing the reflected image of the unaffected extremity moving through different planes of movement [70]. Both researchers identify contraindications to these programs, including the inability to establish ownership of the mirrored extremity, increase in pain, and any increase in movement disorders. While the theoretical underpinnings of these techniques are still under examination, the utility of motor imagery and mirror feedback in CRPS treatment is becoming well established [70,86].

Following the implementation of MVF or GMI, the next treatment objectives for CRPS are to minimize edema, normalize sensation, promote normal positioning/decrease muscle guarding, and increase functional use of the extremity in order to increase independence in all areas—work, leisure, and ADL [42]. In severe cases of CRPS, functional splinting may be necessary to promote improved circulation/nutrition to the area as well as to

facilitate more normal tissue length/positioning during the rehabilitation process [87]. The next steps in treating CRPS are to initiate gentle active movements. manage edema, and institute preliminary desensitization techniques [1]. Edema is managed using specialized garments and manual edema mobilization [83]. Superficial or surface desensitization techniques are implemented to assist with normalizing sensation to the affected area.

The OT then introduces a stress-loading program to initiate active movement and compression of the affected joints [39,40]. Although stress loading may initially produce increased symptoms in the extremity, after several days, a decrease in pain and swelling will begin to be evident. General use of the affected extremity during daily tasks is strongly encouraged throughout the rehabilitation process [39]. Stress loading consists of two principles: scrubbing and carrying [39]. Scrubbing consists of moving the affected extremity in a back/forth motion while weight-bearing through the extremity [39,40]. The scrubbing can be accomplished using a scrub brush and is usually done with the patient in a quadruped (for upper extremity involvement) or elevated sitting (for lower extremity involvement) position. Positions can be modified to facilitate maximal performance and compliance. For example, upper extremity scrubbing can be done in a standing position or a handled scrub brush can be used for persons with carpal tunnel syndrome [87–89]. The amount of weight placed through the affected extremity and the duration of the activity are gradually increased. The Dystrophile® (The Joint Jack Company, Wethersfield, CT, USA) is a technical device designed to assist with maintaining consistent weight bearing and compliance with scrubbing by activating a light when the patient has reached the preset load. However, this device does not hold any proven advantage over a simple scrub brush.

Carrying is the second component in stress loading. In the upper extremity, weight loading continues with small objects carried in the hand, soon progressing to a handled bag, which can be loaded with increasingly heavy weights. The weight should be carried throughout the day whenever the patient is standing or walking [39,40]. The lower extremity can be loaded in a variety of ways. Walking is an important loading technique if care is taken to ensure weight bearing through the affected leg during gait, especially when an assistive device is used. Increased weight bearing can be accomplished with verbal/physical cueing or by having the patient carry a weighted object on the affected side. Loading can also be facilitated by engaging the patient in activities that promote weight shifting/balance (e.g., ball toss) or by placing the nonaffected foot onto a small footstool during static standing tasks [83]. While stress loading demonstrates great utility in the clinical setting, further study is needed to reinforce its efficacy among other functional weight-bearing interventions.

Once the patient is actively engaged in an edema management and stress loading program, treatment can progress toward increasing functional use of the extremity. As the pain and edema decrease, the patient will be better able to tolerate and participate in active ROM, coordination/dexterity, and strengthening tasks [83]. Proprioceptive neuromuscular facilitation (PNF) patterns are often well tolerated during the rehabilitation process. PNF promotes “response of the neuromuscular mechanism through stimulation of the proprioceptors” [90]. PNF patterns are spiral and diagonal combinations of motion that “permit maximum elongation of related muscle groups so that the stretch reflex can be elicited throughout the ‘pattern’ ” [90]. These patterns, similar to normal movement patterns, facilitate strength and balance while increasing ability to perform ADL.

The overall role of the OT during CRPS rehabilitation is to guide the patient through a program designed to minimize pain and edema while maximizing functional use of the extremity [83]. As CRPS varies greatly in severity and duration, it is very important for the therapist to competently upgrade/downgrade programs according to therapeutic response as well as maintain enthusiasm in support and encouragement of the patient during the rehabilitation process.

The vocational counselor and OT should work closely together (see later) when assessing return-to-work goals, especially when potential to return to a specific job is being assessed. Services including job site analysis and job-specific reconditioning or work hardening, work capacity evaluation, transferable skills analysis, and a functional capacities evaluation should be considered [91]. Allowing the patient an opportunity to participate in a trial work period before providing final release for work is often an excellent way to observe his/her ability to return to work and perform job duties, as well as further assess work behaviors. Return to work can be therapeutic, assuming that the work activities will not aggravate the problem and increase long-term pain [92]. Provision of release for work should be coordinated by the vocational counselor. Information included should be gathered from all disciplines including OT, PT, and the physician. It should include detailed instructions when releasing patients to limited duty. Functions to be considered and modified include: lifting, pushing, pulling, crouching, walking, using stairs, bending at the waist, awkward and/or sustained postures, tolerance for sitting or standing, hot and cold environments, data entry and other repetitive motion tasks, sustained grip, tool usage, and vibration factors. Releases for sedentary or light duty should always list specific physical limitations. In situations where a job is not available, vocational counseling, evaluation, and job placement services should be considered to assist patients with addressing return-to-work goals as soon as possible (see later).

PT

PT clearly plays a critical role in functional restoration, and PT activities are designed to complement those of occupational, recreational, and vocational therapy; according to the experienced Mayo anesthesia group, “Physical therapy is the cornerstone and first line treatment for

CRPS." [93] The PT can help patients increase their ROM, flexibility, and later strength through the use of gentle progressive exercise. The PT tries to improve all functional tasks, such as gait training (in lower extremity CRPS), and coordinates/collaborates on all OT, recreational, and vocational goals.

An ongoing discussion concerns the distinction between pain-contingent PT and time-contingent PT approaches. It is generally accepted that all PT must be executed within the bounds of the patients' tolerance [94] and never when the affected limb is insensate (such as after a block) or with CRPS type II patients who present with pronounced hypoesthesia. Inappropriately aggressive PT can trigger extreme pain, edema, distress, and fatigue, and may in turn exacerbate the inflammation and sympathetic symptoms of CRPS; it is therefore to be avoided. Use of assistive or ROM devices, prolonged application of ice, and inactivity may also aggravate CRPS. PTs must teach patients with CRPS that they will experience pain both when they exercise too much *and* when they exercise too little. Patients must therefore be taught to seek the "happy medium," and it is the PT's responsibility to help them find that therapeutic ground and help them to steadily advance toward a more functional and active lifestyle. In a series of RCTs, Oerleman's group has shown that PT (and to a lesser extent OT) improves pain scores and "active mobility" vs social work controls in Dutch upper extremity CRPS cohorts [59,65,95]. The principal objective of the physiotherapeutic treatment protocol as investigated by Oerlemans et al. is to enable the patient to gain the greatest possible degree of control over his or her symptoms. A specific set of questions, VAS and tests carried out during inspections, and physical examinations are used to gain an impression of the degree of segmental dysregulation and the extent to which pain can be managed. The treatment program is set up on the basis of the information obtained. It comprises a number of physiotherapy instruments, such as support, exercise therapy, improving skills and relaxation therapy. The key components of this protocol are: increasing the degree of control over the pain and improving the way the patient copes with the syndrome; extinguishing the source of pain and treating any dysregulation; and improving skills, for example, by practicing compensatory skills, training skills, and posture and movement instruction.

Efforts to improve mobility can start as soon as the pain is "under control." The emphasis here will be on active and functional movement. Attention needs to be paid throughout the entire course of treatment to maintain as normal a posture and movement pattern as possible and to prevent changes to adjacent joints and muscles (for example, changes brought about by contraction) [96].

A more recent approach to exercise in PT is directed toward activation of cortical networks presumed to be involved in chronic pain and CRPS. Based on evidence that cortical organization is altered in CRPS as a consequence of maladaptive neuroplastic activity, a comprehensive program called GMI has been developed to improve cortical organization. GMI is in essence a sequential set of brain exercises, comprising laterality training, imagined hand movements, and mirror feedback therapy [97]. There is compelling evidence that this approach leads to reduction of pain and increases functional capacity of CRPS patients [66].

In children with CRPS, a single-blind, randomized trial of PT combined with cognitive-behavioral therapy demonstrated significant improvement on five measures of "pain and function," with sustained benefit in "the majority" of subjects [67]. In a prospective review of 103 children with CRPS, "intensive PT" (aerobic, hydrotherapy, and desensitization) supplemented by "psychological counseling" (in 77%) was "effective in initially treating childhood CRPS and is associated with low rate of long-term symptoms or dysfunction" [98].

The PT should instruct the patient in the avoidance of physical stressors (i.e., the stress of extended inactivity and bed rest on one extreme, and the stress of excessive exercise at the other). The goal of the PT exercise program is the gradual increase of strength and flexibility, principally through weight-bearing. The therapy program is primarily based on functional goals and achieved through active or active-assisted means; it should encourage pacing and include rest breaks and relaxation techniques as well. PT goals can be achieved with the use of devices, including foam rubber balls succeeded by spring-grip strengtheners for the upper extremity, and Swiss balls, foam rolls, and antigravity-resistive equipment (such as a Pilates reformer) for the lower extremity. These devices help to gradually introduce a variety of weight-bearing/strengthening techniques.

Preliminary data suggest that graded exposure therapy to exercises perceived as harmful in patients with CRPS can lead to a reduction of disability and pain as a consequence of reduction of pain-related fear [99]. The program developed by Vlaeyen and colleagues consists of an educational program explaining the "fear-avoidance model" (pain leading to catastrophic thoughts, leading to avoidance and more pain and disability), combined with a tailored exercise program aimed at activities most feared by the patient.

Taking a gradual loading approach a step further is the so-called "pain exposure therapy," as described by van de Meent et al. [77] This program consists of progressive-loading exercises tailored to specific body functions using regular PT techniques such as passive and active exercises to mobilize joints and muscle stretching. The PT thereby mainly acts as an instructor, rewarding functional progression and providing schedules for exercises and activities at home. Contrary to most interventions, this approach is time-contingent, and pain severity is not used as a guideline to increase or reduce therapeutic activities. Preliminary support for this intervention includes pilot data with regard to pain reduction and decrease of functional limitations in a case series of 20 patients [77].

Mat exercises provide strengthening of both the extremity and the postural muscles in a non-weight-bearing approach. Particularly valuable mat exercises include movement therapies such as the Feldenkrais technique. Feldenkrais teaches and encourages gentle, active motions within the patient's available range to increase body awareness and promote appropriate movement patterns. A fundamental aspect of mastering proper movement patterns is the relearning of proprioception. The PT can help patients achieve mastery by teaching them neuromuscular proprioception exercises, advancing them as they gain proficiency.

Related to re-establishing body awareness in CRPS patients, behavioral programs including graded sensorimotor retuning exercises may provide decrease of pain and improvement of tactile discrimination sense, coinciding with restoration of cortical map size in the SI and SII region of the brain [74]. This pain contingent intervention, aimed at reestablishing proprioceptive abilities and desensitization, has shown preliminary efficacy in a cohort of six CRPS patients. Likewise, in a small pilot study comparing seven CRPS patients receiving low amplitude 80–100 Hz vibratory stimulation of the affected extremity combined with regular PT compared with a control group (N = 4) receiving only standard PT, Gay et al. [75] found more pronounced improvement in pain severity and ROM in the experimental group. According to the authors, the mechanism of action could be related to activation of cortical areas involved with motor command and movement representation.

Virtually, all patients with advanced CRPS will present with myofascial pain syndrome of the supporting joint. Aggressive treatment of this myofascial pain is a critical component of successful treatment and is principally the purview of the PT. Some schools of thought propone that the myofascial pain syndrome must be treated first, and if successfully treated, the CRPS will often resolve. This would reflect an "autonomic concomitant in the pain reference zone," (of the myofascial referral pattern) with vasoconstriction as a prominent feature [100].

Aquatic therapy can be quite valuable to CRPS patients because of its hydrostatic principles and its buoyancy effect [98]. Hydrostatic pressure provides a mild compressive force around the extremity that may help decrease the edema that is widespread in CRPS. Aquatic therapy also provides an outstanding opportunity for introducing lower extremity weight bearing, and the buoyancy it provides may be especially useful for early restoration of functional activities such as walking. When conducting aquatic therapy, care must be taken to maintain water temperature because excessively cold or hot water may temporarily exacerbate the CRPS. Water therapy may allow early participation in progressive PT, as nearly all exercises that are executed on land can be executed in the water, where the water adds resistance without adding full stress/weight to the joints. This of course is groundwork to full weight bearing, particularly in lower extremity.

Hands-on techniques such as massage and myofascial release can sometimes offer effective relief from the myofascial pain. Massage is often mentioned, but although it has not been formally studied (level 4 evidence), it may help decrease edema in certain cases. Electrostimulation modalities have demonstrated some efficacy in our experience, but ultrasound therapy has been less effective in our clinic. Contrast baths are another possible, if slightly controversial, treatment option for CRPS patients. Through the use of the understood principles of alternating heat and cold, contrast baths can be beneficial in mild cases to facilitate improved circulation in the affected extremity by alternating vasodilation with vasoconstriction. However, the vasomotor changes in advanced cases of CRPS do not allow for the desired response, and the immersion in the cold water may exacerbate CRPS symptoms; contrast baths for advanced cases of CRPS are therefore not recommended (all PTs mentioned are levels 3–4 evidence, except for the Oerlemans protocol and GMI, which are level 2 evidence).

Recreational Therapy

Because recreational therapy employs enjoyable activities, the recreational therapist is frequently the first clinician to succeed in getting the CRPS patient to initiate increased movement in the affected part, a primary goal of successful treatment. The incentive of returning to a favorite pastime is often the appropriate tool needed to break through the "kinesiophobia" and bracing that often attend CRPS [101]. Through the use of modifications, adaptive equipment, and creative problem solving (such as using a large-handled gardening equipment for gardeners, bowling with the nondominant hand for bowling fans, and substituting biking in place of running for athletes, etc.), a patient can find fulfillment in previously lost or new recreational activities. Recreational therapy re-establishes the patients' ability and freedom to determine their own leisure lifestyle choices. The increased social contact engendered by these activities will, in turn, heighten the patients' chances of remaining active within the community after treatment.

With a bit of advanced planning, recreational therapy can complement PT and OT treatment goals. For instance, a recreational therapist could reinforce an OT scrubbing protocol by instructing a patient to use an affected upper extremity to sand wood in a recreational project. Such planned convergence of goals affords the patient the twofold satisfaction of creating something and simultaneously accomplishing therapy goals [102]. For example, a patient who is engaged in a desensitization program and who also enjoys gardening can be assigned horticulture therapy (i.e., the use of the hands to work soil).

Additionally, recreational therapy can promote mild activity, thereby increasing flexibility and ROM. The recreational therapist should plan activities that patients find inherently enjoyable because patients are more willing to take on fine-motor grasping and releasing tasks for longer periods of time if they are engaged in an enjoyable activity

(e.g., beading a necklace, holding a watering can, playing a card game, or practicing on a keyboard). A recreational therapist must be creative because a happily engaged patient will be more inclined to fulfill therapy goals when engaged in fun activities like putting golf balls, playing balloon volleyball, or shooting pool.

In addition to advocating new leisure skills, recreational therapy concentrates on reintroducing the patient to stable community involvement. During structured community outings, the CRPS patient can focus on carrying and loading a bag (i.e., "loading") with the affected limb [39,40]. This task can be accomplished with a water bottle, shopping bag, or purse. Other tasks can involve weight bearing and follow through with gait training on unlevel surfaces within a realistic community setting. Identified and achieved appropriately, successfully completed tasks can increase patient self-confidence and promote the incorporation of these learned skills both at home and within other therapy sessions.

In summary, recreational therapy effectively combats kinesiophobia and promotes increased movement. Recreational therapists work closely with other disciplines to achieve the therapeutic goals of CRPS patients, and they implement creative tactics that achieve those goals while giving patients more decision-making freedom and more fun. Most significantly, recreational therapy can reintroduce balanced leisure activities into the lives of the patients whose conditions may have discouraged such behavior.

Vocational Rehabilitation

The vocational rehabilitation (VR) counselor helps prepare the CRPS patient for a possible return to work or the "ultimate" functional restoration. VR involves restoring a patient to their original vocational purpose as expediently and as safely as possible. Counselors use information from medical, occupational, educational, financial, and labor market fields to make return-to-work assessments. Vocational counseling addresses benefits of work and accommodations, as well as job modifications and the utilization of pain management techniques. The VR specialist can also help each patient to identify with the role of worker and assist in creating a plan for a return to work.

If possible, the VR counselor should understand all of the physical demands of the job before addressing return-to-work issues. Review of job description and consultation with employer, supervisor, employee health nurse, or other human resource specialist, and work site visit (when appropriate) are steps recommended to address specific job duties, especially when determining ability to provide a full duty release [92] or when recommending specific restrictions and modifications. The VR specialist also provides job and job site analyses, and uses that information to coordinate job-specific reconditioning or work hardening, work capacity evaluation, transferable skills analysis, and a functional capacities evaluation [91]. The VR counselor must determine whether or not a client can return to the original job. The counselor must also consider the alternatives of returning the patient to either a modified version of the previous job or an alternate job with the same employer, or whether a new job placement referral will be needed when return-to-work with the previous employer is not an option. The VR counselor and OT should work closely together when assessing return-to-work goals, especially when assessing the possibility of returning to a specific job.

The VR specialist must possess a thorough understanding of the prior job description, requirements, and, occasionally, the required vocational testing and targeted retraining of the CRPS patient who intends to return to work. Initially working with the OT, the VR specialist assesses a patient's work activities and provides a simulation of them for the patient in a controlled clinical environment. In the final steps of the VR process, the specialist can provide work capacities, along with functional capacities and targeted work hardening in order for the patient to return to gainful employment. Competent VR requires a proficient specialist capable of maintaining a methodical, informed, and experienced approach in order to grasp and successfully navigate the Byzantine social and medicolegal quagmires in which CRPS patients may find themselves. As with all the interdisciplinary specialists, the VR specialist must sustain ongoing communication with the others on the team and keep the team informed of each patient's individual vocational situation.

VR specialists regularly encounter hurdles to appropriate return-to-work functions. First, health factors are often presumed to have the greatest impact on worker disability, but social scientists have argued that the most important determinants of work status for persons with chronic disease are actually age, education, job satisfaction, and job status in the labor force [103]. Second, other factors such as work history, employment in public sector vs private, current work status, lower social class, level of education, and lack of varied work may also predict work disability for patients with chronic pain [103]. Third, long periods of unemployment or reduced employment activity may impact vocational potential. Chronic pain sufferers are often patients who have been out of work for long periods of time before they are referred to a VR specialist, and employers are often reluctant to employ persons who have chronic pain, have been unemployed for long periods of time, or who have workers' compensation cases [104]. Additionally, the ability to modify the work environment in accordance with limitations has major implications in limiting the extent of the disability and/or preventing reinjury or new injuries [103].

Although VR is frequently the final step of rehabilitation therapy, addressing return-to-work issues early is critical so as to set employment as a long-term goal [105]. Allowing the patient an opportunity to participate in a trial graduated time/effort work period before providing final release for work is often an excellent way to observe his/her ability to return to work and perform job duties, and it also provides an opportunity to further assess work

behaviors and capacity. In addition, the initial graded increase of time and effort spent at work greatly alleviates significant patient anxiety and thus improves chances of successful return-to-work. Return-to-work can be a form of therapy, provided the work activities do not exacerbate the problem or increase long-term pain.

The VR counselor should coordinate the provision of release for work by assembling information from all disciplines. Releases for sedentary or light duty should always list specific physical limitations, and the releases for limited duty should include comprehensive instructions. When preparing a release for work form, the VR specialist must take into account the abilities of the patient, including lifting, pushing, pulling, walking, crouching, using stairs, using tools, bending at the waist, maintaining awkward and/or sustained postures, maintaining a sustained grip, tolerating extended sitting or standing, tolerating extensive data-entry functions and other repetitive motion tasks, tolerating hot and cold environments, and tolerating any severe vibrational factors. Any number of these factors may require modification of the work environment, particularly in chronic or severe CRPS.

Other Therapeutic Interventions

Hyperbaric oxygen therapy was assessed in a medium-sized RCT and produced a significant decrease in pain and edema vs "normal air" (level 2 evidence) [106]. These results should be replicated, but cost-benefit considerations will also be important. Although acupuncture is mentioned in many treatment reviews, there is only one very small RCT in CRPS that failed to show a significant difference in outcomes, but this may be due to the small sample size. The authors say they are planning a "definitive trial," but this has been pending since 1999 [107]. There is no research available supporting the use of chiropractic manipulation in CRPS [108].

Because the symptoms of CRPS patients encompass all the biopsychosocial complexities of chronic pain, the best hope of helping our patients is the adoption of a systematic, stable, empathetic, and above all, interdisciplinary approach that addresses those symptoms. Drugs, psychotherapy and interventions should be efficiently deployed for patients who either cannot begin or fail to progress using the interdisciplinary approach outlined here (see corresponding sections later). Many patients will require medication and psychotherapy from the beginning to be successful in the pivotal functional restoration algorithm (see Figure 1). Treatment guidelines that center on progressive functional restoration delivered by an interdisciplinary team are traditional, have substantial empirical and anecdotal support, and have been assessed and ultimately codified by three large, expert, consensus-building conferences [1,47,53]. Although high-level evidence supporting the rationale for interdisciplinary treatment of CRPS is fairly sparse (as it is for any treatment of CRPS), much stronger evidence exists for the efficacy of the interdisciplinary approach in other pain conditions, such as chronic low back pain [36]. That functional restoration can and should be the central intervention and outcome standard in CRPS is a theory that must be tested. Until then, the interdisciplinary approach for treating patients with CRPS remains the most pragmatic, helpful, and cost-effective therapeutic approach available today.

Pharmacotherapy of CRPS

This semisystematic review of CRPS pharmacotherapy was conducted via PubMed to obtain all articles describing clinical trials using the terms "CRPS," "complex regional pain syndrome," "reflex sympathetic dystrophy," and "causalgia." All articles were read and their bibliographies searched for additional references that might not have been available in PubMed. Additionally, all major review articles and all previous meta-analyses or systematic reviews of CRPS treatment were assessed.

For the past 150 years, multiple drug treatments for CRPS have been tried—including use of laudanum (tincture of opium) by S. Weir Mitchell (who coined the term causalgia), and use of a "new invention," the hypodermic syringe, to perform cocaine nerve blocks [4,109–111]. Unfortunately, hardly any of the medications used clinically have been tested in double-blind RCTs for complex reasons that include lack of uniformly accepted diagnostic criteria and widespread suspicions of psychogenic causality [112]. The absence of a gold-standard diagnostic test or a specific mechanistically based diagnostic scheme has largely precluded well-designed trials, and scant evidence exists to guide treatment for often-desperate patients. The resourceful clinician will extrapolate from RCTs, meta-analyses, and systematic reviews concerning treatments for related neuropathic conditions [113], and ultimately utilize empirical drug trials in each patient based on consideration of what mechanisms seem most germane [110]. CRPS differs from many other neuropathic pain syndromes by having additional tissues and systems involved, including the microcirculation, bone, and inflammatory pathways [114]. Reliable data now show variable involvement of central sensitization [115], motor abnormalities [116], and sympathetic efferent features [115] at different times and in different individuals [30,114]. No one medication will treat them all [30,114].

Medications trialed specifically for CRPS include calcitonin and bisphosphonates, corticosteroids, and most recently, intravenous immunoglobulin (IVIG). Treatments better studied in other related neuralgias include tricyclics, gabapentin and pregabalin, carbamazepine, opioids, clonidine, nifedipine, α-adrenergic antagonists, 5% lidocaine patch, and topical capsaicin.

This section summarizes the outcomes from the few CRPS trials, as well as pertinent trials for other neuralgias, emphasizing those that are focal or regional such as postherpetic neuralgia (PHN). Currently, the best meta-analysis of PHN trials is that of Hempenstall et al. (free download from medicine.plosjournals.org) [117]. As with most treatments, drug therapy works best when

prescribed in conjunction with functional restoration and treatment of other comorbid conditions (please see interdisciplinary management section earlier).

Monotherapy is best to minimize adverse effects, cost, and patient noncompliance, but rational polypharmacy is often necessary, particularly to address different CRPS symptoms. This should comprise rational combinations from different classes of medications rather than multiple medications from the same class (including opioids). Most will be prophylactic drugs used daily rather than "as needed" rescue medications. The choice of medications to prescribe should include cost considerations and other patient needs. For example, tricyclics, unsurpassed in RCT for relieving neuralgia [117], also are effective for depression and insomnia, which are often comorbid with CRPS. Long-term goals should be taken into account whenever a pharmacotherapeutic regime is developed [1].

Anti-Inflammatory Drugs/Immunomodulators

Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, cyclooxygenase (COX)-2 inhibitors, and free-radical scavengers are used with the intention-to-treat pain plus inflammatory involvement in CRPS. However, CRPS inflammation may be largely neurogenic (initiated by inflammatory mediators from the terminals of afferent nociceptors) and no drugs have been studied for this type of inflammation. The assumption that efficacy against inflammation from infection, injury, or illness predicts that efficacy against neurogenic inflammation is entirely untested [118]. Of note, while these features are what distinguish CRPS from routine post-traumatic neuralgia, they are not the primary problems for most patients, and many, if not most, have spontaneous improvement in inflammatory features as their CRPS resolves.

This class of drugs can be used both for prophylaxis or rescue. Although the World Health Organization ladder recommends their early use for chronic pain [119], patients and practitioners alike have neglected this class of drugs because of the "nocebo" bias (i.e., the belief that these drugs are "too simple" to be effective against something as complicated as CRPS). If this preconception can be overcome, our clinical experience finds NSAIDs effective for some CRPS patients (level 4 evidence). A recent demonstration of modest benefit of IVIG for CRPS [120] highlights the potential utility of treating immunity and inflammation in this condition and should cause NSAIDS to be reconsidered with fresh eyes. In addition to treating CRPS, NSAIDs have also been used to treat other neuropathic pain conditions, particularly others associated with inflammation (level 3 evidence) [46,121–123].

NSAIDs inhibit COX and prevent the synthesis of prostaglandins, which mediate inflammation and hyperalgesia, and thus may block spinal nociceptive processing [122,123]. In contrast, acetaminophen has only central modes of action. A particular problem with acetaminophen is how easy it is to inadvertently overdose due to ubiquitous inclusion in combination medications with opioids. Short-acting combined opioids are often inappropriately prescribed for CRPS. If opioids are used, long-acting delivery systems and "pure" opioids are preferred, with short-acting opioids used only for breakthrough pain. Dose escalation of these combination agents (e.g., for tolerance or pain flare) not infrequently cause patients to exceed recommended acetaminophen maximums, particularly when unwittingly consumed in several different combination products. The lay perception fostered by advertisers that a nonprescription medication marketed for pediatric use could not have serious adverse effects is utterly false. In actuality, overdose from prescription combination products containing acetaminophen account for nearly half of all cases of acetaminophen-related liver failure in the United States, many of which result in liver transplant or death. The problem is so serious that in January 2011, the Food and Drug Administration (FDA) began a series of steps to counteract it (see http://www.fda.gov/acetaminophen). Overdose from prescription combination products containing acetaminophen account for nearly half of all cases of acetaminophen-related liver failure in the United States, many of which result in liver transplant or death.

NSAIDs have mixed results in small clinical trials for neuropathic pain, and in one [124], NSAIDs showed no value in treating CRPS I. Specific NSAIDs may be more useful than others. Ketoprofen, for example, may have substantial anti-bradykinin and anti-prostacyclin effects in addition to the typical anti-prostaglandin effect. Inhibitors selective for COX-2 (e.g., celecoxib) have not been tested in CRPS, although reported anecdotally to be of some use (level 4 evidence) [125]. Highly publicized concerns of cardiac risk limit widespread use of COX-2 inhibitors. Infliximab, a tumor necrosis factor (TNF)-α inhibitor, reduced cytokine levels and pain in two patients with CRPS [126], and etanercept and infliximab have been anecdotally mentioned [127]. With the proliferation of new biological agents for autoimmune inflammatory disease, more will certainly be prescribed off-label for CRPS. Thalidomide (a TNF-α, and interleukins 1 and 6 inhibitor) has shown modest promise in case reports [128] and small open-label trials [129,130]. These provided the rationale for a well-powered RCT of lenalidomide, an anti-neoplastic thalidomide derivative with greater anti-TNFα activity and lower incidence of major side effects (somnolence, constipation, neuropathy, and teratogenicity). The trial was completed but not published, so lack of efficacy can be inferred.

Oral corticosteroids are the only anti-inflammatory drugs for which there is direct clinical-trial evidence in CRPS (level 1 evidence) [46]. Most trials involved early/acute cases, when inflammation is most common, and it is unknown whether or not corticosteroids offer similar benefit for chronic CRPS, where levels of pro-inflammatory cytokines are lower [131], or for CRPS cases with only mild inflammation. Two prospective RCTs [132,133] that used a pulse of oral corticosteroids (approximately 30 mg/day for 2–12 weeks, followed by a taper) in early/acute CRPS yielded notable improvements

as compared with placebo (mean of 12 weeks' duration; level 2 evidence); a caveat is that a later systematic review of the literature [134] evaluated one of these trials [132] and found it to be low quality. Given the data, a short course of steroids may be indicated in early CRPS with prominent inflammation, but longer courses are unproven [46], and there are numerous, serious contraindications to chronic steroid use.

Reactive oxygen species contribute to inflammatory processes that may be involved in CRPS I. Free radical scavengers (e.g., dimethyl sulfoxide [DMSO] and vitamin C) may reduce the concentration of these compounds. A double-blind, placebo-controlled study of vitamin C (an antioxidant) found that it reduce the incidence of "RSD" after wrist fractures [135] (DMSO is discussed later under topicals).

Cation Channel Blockers

Drugs that block entry of sodium or calcium into neurons reduce their action potentials. Most often used as anticonvulsants, several have efficacy in neuropathic pain documented in large RCT, meta-analysis and systematic reviews (level 1 evidence) [136–140]. Gabapentin, first line for neuropathic pain, came to the attention of pain specialists in an anecdotal report of efficacy for CRPS [141]. It works at the alpha(2)-delta auxiliary subunit of voltage-dependent calcium channels, and well-powered large RCTs have proven its efficacy in PHN and diabetic peripheral neuropathy (level 2 evidence) [3,142]. A case series in adults [143] and one pediatric case report [144] suggest efficacy in CRPS (level 4 evidence) as does ubiquitous empirical use for many neuropathic pain syndromes including CRPS. As gabapentin neared end of patent-protection, Pfizer developed a closely related compound, pregabalin (Lyrica, Pfizer Pharmaceuticals LLC, Vega Baja, PR), with the same mode of action. Its major advantage is that some patients can manage with twice-daily dosing, but relative cost should be considered in when deciding between the two. There are no data evaluating pregabalin for CRPS.

Carbamazepine has a traditional place in the treatment of neuralgia and is FDA-approved for trigeminal neuralgia [145,146]. One RCT [147] of patients with CRPS indicates that 600 mg/day of carbamazepine, taken over 8 days, yields considerable pain reductions when compared with placebo (level 2 evidence). Oxcarbazepine is a similar anticonvulsant that often replaces carbamazepine because it has fewer serious adverse effects, specifically bone marrow suppression or liver failure. Headaches, dizziness, and nausea are the most common adverse effects of oxcarbazepine. An open-label trial [148] (level 3 evidence) in painful diabetic neuropathy finds equal efficacy to carbamazepine with fewer side effects. Oxcarbazepine has not been studied specifically in CRPS. Phenytoin is a third-line agent to consider for CRPS, especially in cases that seem to involve ectopic nerve firing (level 2 evidence) [149–151]. RCTs for lamotrigine have studied its effects on other neuropathic conditions, but not CRPS [152]. There is anecdotal evidence for a variety of other anticonvulsants/neuromodulators, but no compelling research at this time. In our clinics, we have found that levitiracetam and topiramate may be useful in some cases. Topiramate was extensively used off-label for neuropathic pain, but several trials failed to show efficacy.

Augmentation of Monoaminergic Neurotransmission

The brain exerts powerful inhibitory effects on the dorsal horn mediated by monoaminergic neurotransmitters, most notably norepinephrine. The tricyclic and heterocyclic drugs that augment descending inhibition by blocking presynaptic reuptake are unsurpassed in efficacy for neuralgia [153]. Although originally approved for depression, this indication has been overshadowed by use for neuropathic pain [153]. However, the antidepressant efficacy of these compounds provides additional benefit for many patients. These are "dirty drugs" with additional mechanisms including peripheral sodium-channel blockade, which may in fact contribute to efficacy [154]. Their once-daily dosing and low cost are added advantages.

A first-line option for neuropathic conditions (level 2 evidence) [155–158], heterocyclic antidepressants (HCAs) are used exclusively as prophylactic agents for migraine. Meta-analyses [136,137,157] of RCTs support their efficacy for neuropathic pain. One study [157] reported that for every 100 patients with neuropathic pain taking antidepressants, 30 would obtain at least 50% pain relief (number needed to treat [NNT] of 3) [153]. This is unsurpassed by any other treatment for neuropathic pain.

It is useful to be familiar with several tricyclic/quadracyclic drugs because each possesses specific side effects that can sometimes be used to patient advantage [158,159]. For example, an anxious, depressed, thin, insomniac patient may benefit from an anxiolytic, sedative, and antidepressant (e.g., doxepin); conversely, an overweight, hypersomnolent patient with psychomotor retardation may benefit from an antidepressant with more noradrenergic selectivity (e.g., desipramine), which can be activating and can cause anorexia [156]. Selective serotonin reuptake inhibitors (SSRIs) have not shown any analgesic efficacy (level 4 evidence) [160,161]. The NNT for SSRIs in neuropathic pain is much higher than traditional HCAs, e.g., 7.7 for citalopram, 2.9 for paroxetine [136]. Placebo medications for neuropathic pain often achieve NNTs of about 6, so medications with NNTs of 5 or greater probably are no better overall than placebo.

The older (venlafaxine) and newer combined serotonin-norepinephrine reuptake inhibitors (SNRIs) (milnacipran, duloxetine) are now FDA-approved for several chronic pain indications in addition to major depression. None has been trialed for CRPS. Venlafaxine (Effexor, Pfizer Inc, Philadelphia, PA, USA), an older SNRI, has some anecdotal value for neuropathic pain (level 4 evidence). There is a pressing need for data on comparative efficacy and safety of SNRIs and tricyclic antidepressants.

Opioids

The earliest known expert opinion of opioids in CRPS is that of S. Weir Mitchell [109], who commented that "for the easing of neurotraumatic pain . . . the morphia salts . . . are invaluable." Only one RCT has been conducted in CRPS [147], evaluating controlled-release morphine and reporting no difference in pain reduction when compared with placebo after 8 days of use. This trial would not meet today's quality standards, so the question remains open. Many studies document efficacy and safety of opioids for neuropathic pain in general (level 2 evidence) [162–164]. As neuropathic pain does not respond as universally as acute nociceptive pain [164–166], dose escalation is common, often with no added pain relief but accruing adverse effects. Patients prescribed 100 mg or more of morphine or equivalent have a nine times greater risk of serious overdose than patients prescribed less than 20 mg of morphine or equivalent daily, even after adjustment for comorbid conditions [167]. There is growing consensus that while opioids are a reasonable second- or third-line treatment option to try, dose should not be used initially and should not be escalated freely. Methadone has theoretical advantages for neuropathic pain because of its putative N-methyl-D-aspartate (NMDA) antagonism, as well as the practical advantage of low cost [168], and tramadol may be helpful due to its concomitant serotonin/norepinephrine reuptake block. Tolerance and long-term toxicity are unresolved issues for the moment [169,170], and long-term high-dose opioid use can actually worsen allodynia and/or hyperpathia [171]. Mitchell also comments on tolerance: "When continuously used, it is very curious that its hypnotic manifestations lessen, while its power to abolish pain continues, so that the patient who receives a half grain or more of morphia may become free from pain, and yet walk about with little or no desire to sleep" [109]. Opioids are not a panacea, and there are many unresolved concerns about tolerance, cognitive impairment (especially with "rescue dosing"), and opioid-induced hyperalgesia [172,173], but they are certainly reasonable to consider for CRPS on a case-by-case basis, particularly for patients in pain crisis [110]. The use of added short-acting opioids for breakthrough pain ("rescue" dosing) is controversial. Although occasionally taking an extra pill for a pain spike is unlikely to harm, too many patients end up with daily or near-daily use of "rescue" opioids, obviating their purpose and encouraging tolerance to what is effectively a higher daily dose.

NMDA Receptor Antagonists

NMDA receptor antagonists (e.g., MK-801, ketamine, amantadine, and dextromethorphan) have been evaluated for neuropathic pain and for CRPS specifically, but toxicity at effective doses has generally been too high [174–178]. Ketamine, an NMDA receptor antagonist has been used topically, orally, and intravenously (and recently, intrathecally, with no evidence support) in various doses to treat neuropathic pain, particularly CRPS. Intravenous (IV) administration of anesthetic doses over 5 days was found beneficial in an open-label phase II study of 20 patients. Although a pilot study (level 3 evidence), all 20 subjects reported "complete remission" that persisted up to 6 months in 16 subjects [179]. Ketamine is toxic and a drug of abuse, so caution is indicated and independent confirmation of these studies is needed. Use is further supported by case reports [180–182] in CRPS (level 4 evidence). Amantadine has shown some benefit in cancer-related neuropathic pain (level 2 evidence) [183] and in chronic neuropathic pain (level 4 evidence) [184]. Dextromethorphan in pill form may be better tolerated and may augment the effect of other medications, especially opioids [185].

Antihypertensives and α-Adrenergic Antagonists

Clonidine is an α_2-adrenergic agonist used more often in the past to treat CRPS, when "sympathetically maintained pain" (SMP) was thought to be a more uniform feature than it is now [186]. It can be given orally, transdermally, or epidurally (level 3 evidence) [187]. Adverse effects include sedation, dizziness, headache, and hypotension. Although a case series [188] showed that transdermal clonidine benefitted local CRPS-induced hyperalgesia and allodynia (level 4 evidence), a systematic review [46] finds no convincing support for clonidine (level 1 evidence), and indeed, it is only rarely used for CPRS lately. Nifedipine, a calcium-channel blocker, has a strong mechanistic rationale for managing vasoconstriction (level 4 evidence), and two uncontrolled case series [189,190] found doses of up to 60 mg/day useful for CRPS [189].

Phenoxybenzamine and phentolamine are α-adrenergic antagonists sometimes discussed as third-line agents for CRPS. Two case series [189,191] (level 4 evidence) support efficacy of phenoxybenzamine, which seems to work best for syndromes of less than 3-month duration [189]. Phentolamine is expensive, in limited supply, and administered by continuous IV infusion, so it is not widely used. Its primary application has been as a research tool to identify SMP, and it may have a lower rate of false-positive results than local anesthetic blockade of sympathetic ganglia.

Treatment of Bone Pain with Calcitonin or Bisphosphonates

Bone is densely innervated with small nociceptive axons. Vigorous bone remodeling can be painful because osteoclasts resorb bone by acidifying their extracellular milieu to dissolve hydroxyapatite crystals potentially activating nociceptive acid-sensing channels. Inhibiting bone resorption may thus improve pain for select CRPS patients; ideally, those with active bone resorption identified by three-phase bone scan [192]. Magnetic resonance imaging can sometimes also localize bone hyperperfusion and bone marrow edema. Such treatments can also help preserve bone mass in the affected limb, a concern in CRPS patients with disuse or immobility. Calcitonin, a polypeptide hormone produced by the thyroid, also has antinociceptive effects independent of its effects on bone, and it has been found effective for several other types of acute and chronic pain conditions. It is usually nasally administered and is without

significant adverse effects in normocalcemic individuals [193]. Calcitonin is one of few CRPS treatments studied by RCT [194–196]. Meta-analysis [197] of a limited number of controlled studies (level 1 evidence) demonstrates the value of intranasal doses of 100–300 U per day for CRPS [196–198]. Two other clinical trials [194,196] of calcitonin in CRPS, however, both identified as high-quality studies (level 2 evidence) in systematic review, reported conflicting results [134]. One found improved pain intensity after 100 IU calcitonin thrice daily for 3 weeks [196]; the other reported no improvement after 200 IU calcitonin twice daily for 4 weeks [194].

Bisphosphonates (e.g., alendronate, ibandronate, risedronate, zoledronate, etidronate, pamidronate) also slow bone resorption and can help treat CRPS. Several older oral bisphosphonates (alendronate [Fosamax, Merck & Co., Inc., Whitehouse Station, NJ, USA]), (risedronate [Actonel, Warner Chilcott LLC, North Norwich, NY, USA]) are reasonably well studied for CRPS, but there are no data on the newer longer-lasting drugs administered by periodic IV infusion (ibandronate, zoledronate, pamidronate) [199]. A systematic literature review [134] identified two high-quality studies of bisphosphonates for the treatment of CRPS [200,201] (level 2 evidence), both reported significant improvement in pain. One evaluated IV administration of clodronate (300 mg daily for 10 days) (not approved in the United States) [200], and the other evaluated IV administration of alendronate (7.5 mg daily for 3 days) [201]. One good quality, mid-sized RCT of oral alendronate finds efficacy for CRPS [202]. Two more recent small RCTs of oral pamidronate also suggest some benefit [203,204]. A case series [204] (level 4 evidence) supports efficacy of pamidronate for CRPS. The impact of these drugs on the osteopenia (Sudeck's atrophy) that is sometimes prominent in the disorder was not studied in these RCT [202]. Initial case reports linked long-term bisphosphonate use for osteoporosis with atypical femoral fracture, but a recent study of the entire Danish National Health Registry found no relationship [205]. Osteonecrosis of the jaw is a rare complication of long-term, very high-dose bisphosphonates (zoledronate, pamidronate) for breast or bone cancers at doses and order of magnitude higher than those used for osteoporosis, so this is a not a relevant concern for the CRPS population [206].

Pharmacotherapy for Other Symptoms in Chronic CRPS

Dystonia, the most common movement disorder in CRPS, often requires independent treatment. Dystonia is itself painful and can also worsen pain by impeding tissue perfusion. Treatment is complicated because prolonged tonic postures can allow tendons to shorten into fixed contractures that require orthopedic procedures including tendon release or serial casting. The standard treatments for dystonia are usually prescribed, although the mechanisms of dystonia in CRPS and other post-traumatic dystonias are distinct from the dystonias mediated by basal-ganglia dysfunction. Although trihexylphenidate can be considered, baclofen is the current first-line option. It should be prescribed orally at first, but it is very sedating, and many patients do not tolerate the high oral doses effective for dystonia. If baclofen is effective but poorly tolerated, administration by intrathecal pump should be considered, although pharmacological and mechanical complications are common. There is increasing evidence (see later) that baclofen has pain-relieving effects independent of effects on muscle contraction. In contrast, long-term use of muscle relaxants such as benzodiazepines or cyclobenzaprine (which is actually a tricyclic compound) is ineffective as well as poorly tolerated. Botulinum toxin injections are useful for focal dystonias limited to small areas, but they are too invasive and expensive for widespread regional dystonias. Amantadine can be considered for tremor, although this is only rarely present or disabling in CRPS.

Rare CRPS patients have severe edema in an arm or leg that can painfully distort their tissues and compromise tissue oxygenation and nutrition, potentially leading to skin ulceration, infection, and need for amputation in the worst cases. This should be treated with standard treatments, usually limb elevation, regular aerobic exercise to improve circulation, and compressive garments if tolerated.

Emerging Drug Treatment Options

In 2010, a single RCT found modest efficacy of IVIG for established CRPS [120]. The rationale for use is reports from a single group of detection of antibodies (to as-yet unidentified neural autoantigens) in CRPS patients [207]. IVIG is thought to work not only by interfering with autoantibodies but also by downregulating pro-inflammatory cytokines. Only 12 patients completed the trial, so independent confirmation is needed, but this trial was published in a major internal medicine journal, a first for any CRPS trial. A lower dose (0.5 g/kg) was used than is typical for other neurological indications for IVIG (2 g/kg), so higher doses are reasonable to consider, although the authors' limited experience with a few cases has not shown benefit so far. Given the expense, IVIG is not likely to become widely used.

A Cochrane Review finds efficacy of systemic administration of local anesthetic agents to relieve neuropathic pain, although there are no RCTs in CRPS [208]. Occasional patients find benefit and utility of this third-line option, but use is limited by frequent nausea. Systemic lidocaine administered by subcutaneous pump for home use is effective for neuropathic pain but difficult to organize, usually requiring a visiting nurse to change the infusion site every 3 days or so, and a special pharmacy [209,210].

Sildenafil augments the activity of nitric oxide and hinders phosphodiesterase-5 inhibitor to modulate blood flow, typically by vasodilation [211]. Some clinicians prescribe sildenafil and other agents marketed for erectile dysfunction to try and improve perfusion of CRPS-affected limbs, but no reports have been published as yet. There is emerging support for cannabinoids in peripheral and central neuropathic pain, particularly pain associated with multiple sclerosis [212]. Although not yet trialed for CRPS,

Table 9 Pharmacotherapy guide. The following strategies are suggested for patients who have been diagnosed with CRPS but who cannot begin or progress in the functional restoration algorithm

Reason for Inability to Begin or Progress	Action
Mild-to-moderate pain	Simple analgesics and/or blocks (see interventional therapy section)
Excruciating, intractable pain	Opioids and/or blocks or later, more experimental interventions (see interventional therapy section)
Inflammation/swelling and edema	Steroids, systemic or targeted (acutely) or NSAIDs (chronically); immune modulators
Depression, anxiety, insomnia	Sedative, analgesic antidepressant/anxiolytics and/or psychotherapy (see pharmacotherapy section)
Significant allodynia/hyperalgesia	Anticonvulsants and/or other sodium channel blockers and/or NMDA receptor antagonists
Significant osteopenia, immobility and trophic changes*	Calcitonin or bisphosphonates
Profound vasomotor disturbance	Calcium channel blockers, sympatholytics, and/or blocks (see interventional therapy section)

It is important to remember that these suggestions are overruled by individual patient presentation.
* It is also important to note that certain drugs, such as calcitonin, may be associated with analgesia as well as the more primary action.
CRPS = complex regional pain syndrome; NMDA = N-methyl-D-aspartate; NSAID = nonsteroidal anti-inflammatory drug.

the emerging trend of state-by-state legalization of medical marijuana improves the feasibility of such a trial.

Botulinum toxin type A used for years to weaken specific muscles in movement disorders and spasticity works by blocking acetylcholine release at cholinergic synapses. It also inhibits noncholinergic neurotransmitter (e.g., glutamate) and neuropeptide (substance P [SP] and calcitonin gene-related peptide [CGRP] release from primary afferent nerve terminals, providing the rationale for independent evaluation in neuropathic pain. Regional intradermal injections of botulinum toxin improved spontaneous pain, brush allodynia, and cold pain thresholds at the painful site of 25 patients with post-traumatic neuralgia [213] (Table 9) and, when used in conjunction with sympathetic blockade with bupivicaine, extended the duration of analgesia in a subset of CRPS patients [214]. These findings await independent confirmation.

Topical Treatments

Topical treatments must be distinguished from transdermal formulations such as the fentanyl or clonidine patches that deliver medication through the skin to reach throughout the entire body. Topical medications remain local to reach dermal nerve endings, blood vessels, and other cells in this skin. Topical medications are appealing by virtue of their lack of systemic effects; rashes and allergies are their major adverse effect, and they are currently popular with patients. Topical options to consider for CRPS include the 5% lidocaine-impregnated patch, the eutectic mixture of local anesthetics (EMLA) cream, capsaicin, and DMSO. Many clinicians endorse the use of EMLA for patients with CRPS (level 3 evidence) [215], but it must be applied under an occlusive cover (e.g., plastic food wrap) to maximize penetration. The 5% lidocaine patch is FDA-approved for treating PHN and is newly available in generic formulation [216]. It may have efficacy in some local or focal CRPS phenomena such as allodynia (level 4 evidence) [217]. Capsaicin, the vanilloid compound in chili peppers, is a highly selective agonist for the transient receptor potential channel, vanilloid-receptor type 1 (TRPV1) that is expressed on central and peripheral terminals of nociceptive primary sensory neurons. Topical capsaicin causes activation followed by dying-back of nociceptive nerve endings by allowing unchecked cation influx. Use is limited by the painful burning sensation it evokes at the site of application until this becomes denervated. In an RCT (level 2 evidence) [218], topical capsaicin showed modest efficacy for PHN. A preliminary study [219] of high-dose topical capsaicin plus regional anesthesia for CRPS demonstrated partial efficacy (level 3 evidence). We have found topical capsaicin to be intolerably painful, messy, and unacceptable to most patients [36,220–223]. In 2009, the FDA approved a high concentration 8% capsaicin patch (QUTENZA™, NeurogesX, Inc., San Mateo, CA, USA, NGX-4010) for treating PHN once every 3 months [224]. It is applied to the painful area for 1 hour after topical local anesthesia. Two additional well-powered RCTs were positive for high- vs low-dose capsaicin in peripheral neuropathic pain, including in HIV-associated distal sensory polyneuropathy [225,226].

DMSO is a free radical-scavenging agent. In a high-quality study [227] (level 2 evidence) assessed in a systematic review [134], DMSO (50% cream for 2 months) provided significant pain reduction when compared with placebo. Another as-yet untested treatment for CRPS may be more promising, specifically local injection of botulinum toxin type A, which inhibits TRPV receptors to inhibit release of glutamate and substance P. This has been found effective for focal peripheral neuropathic pain and diabetic neuropathy independently of effects on muscle tone [213].

To summarize, there are few, if any, trials for CRPS that meet current criteria for level 1 RCT. Clinicians must thus be guided by the results of RCT for other neuralgias and rely on smaller trials and clinical experience. A key is to identify the likely pain generators in individual CRPS patients, whether ischemic, dystonic, neuropathic, or bony, and to try medications effective for these mechanisms. A methodical and patient approach is essential; new drugs should be trialed one at a time and discontinued if not clearly helpful. The goal is often as much to allow progress in life activities and rehabilitation as to relieve pain. New scientific findings in CRPS may suggest drugs currently used for other conditions that may be worth considering for CRPS.

Psychological Interventions

This semisystematic review for the Psychological Interventions section was conducted by a Medline and PsychLit search using the Boolean search terms: ("Complex Regional Pain Syndrome" OR "Reflex Sympathetic Dystrophy") AND (psychological OR psychosocial OR behavioral OR biofeedback) AND (treatment or therapy).

Clinicians who work with CRPS patients recognize that successful management of the syndrome presents a significant challenge. In the absence of any definitive medical treatment [46,197], the need for multidisciplinary management of CRPS has been emphasized [1,53,228]. It is now generally agreed that successful treatment must simultaneously address the medical, psychological, and social aspects of the syndrome [1,48,53]. As will be described later, there are several reasons why addressing psychological and behavioral factors may be crucial to successful treatment in patients with CRPS. A rationale for use of psychological interventions in the management of CRPS will first be described. The treatment outcome literature regarding efficacy of psychological interventions for CRPS will then be presented, followed by a brief overview of relevant meta-analytic literature regarding efficacy of such interventions for non-CRPS chronic pain conditions. Finally, an overview of clinical recommendations for psychological care of CRPS patients based on both research literature and clinical experience will be presented.

Hypothesized Links Between CRPS and Psychological Factors

The rationale for employing psychological interventions in CRPS patients derives generally from their recognized utility in management of non-CRPS chronic pain conditions, and more specifically, from theoretical pathways through which psychological and behavioral factors *might* directly interact with pathophysiological mechanisms believed to underlie CRPS. This latter theoretical rationale suggests the possibility that psychological interventions may not only be palliative in CRPS (which is almost assured) but also could have a *potentially* beneficial impact on underlying pathophysiology of the disorder in the context of multidisciplinary treatment [229].

One pathway through which psychological factors could influence onset or maintenance of CRPS relates to the role of adrenergic mechanisms in the pathophysiology of CRPS (see Bruehl for a full review of pathophysiological mechanisms of CRPS) [230]. Diminished sympathetic outflow following peripheral nerve injury is believed to lead to localized upregulation of peripheral catecholaminergic receptors in the affected extremity [231–233]. This upregulation may lead to local hypersensitivity to circulating catecholamines, which in turn leads to excessive vasoconstriction [231,233–235], accounting for the characteristic cool, blue extremity typically seen in chronic CRPS. Following nerve injury like that which is believed to initially trigger CRPS (e.g., [35,236]), primary afferent fibers may also become sensitive to adrenergic excitation, leading to increased nociceptive firing in response to sympathetic discharge or circulating catecholamines [231,237,238]. This catecholamine-induced nociceptive firing in turn is likely to contribute to central sensitization (by maintaining elevated nociceptive input) that may underlie the allodynia and hyperalgesia associated with CRPS [239,240]. Central sensitization produces increased pain, which itself may provoke catecholamine release that further stimulates the nociceptive input maintaining the central sensitization, thereby producing a dysfunctional vicious cycle. The impact of catecholamine release in the pathophysiological mechanisms described earlier may be important to recognize given that psychological factors such as life stress and dysphoric emotional states (e.g., anxiety, anger, depression) can be associated with increased catecholamine release (e.g., Charney et al. and Light et al. [241,242]). For example, greater depressive symptoms were associated with higher levels of plasma epinephrine in a sample of 16 CRPS patients [115]. It is theoretically plausible that psychological factors such as these could, through their impact on catecholamine release, interact with adrenergically mediated pathophysiological mechanisms to contribute to onset or maintenance of CRPS.

More recent work suggests that interactions between psychological factors and inflammatory mediators may also be important to consider, given the increasingly recognized role of inflammation in CRPS [230]. For example, laboratory research in healthy individuals indicates that greater pain-related catastrophic thinking, which may be common in CRPS patients, is associated with increased pro-inflammatory cytokine activity in response to painful stimuli [243]. Moreover, in CRPS patients, psychological stress has been shown to be associated with alterations in immune function that could impact on inflammatory cytokines hypothesized to contribute to CRPS [244]. Thus, psychological stress, catastrophizing, and negative affect variables associated with an elevated pro-inflammatory state could exacerbate any underlying inflammatory mechanisms contributing to CRPS.

Examination of the historical CRPS literature indicates frequent comments from authors indicating that psychological dysfunction (usually emotional disorders) was assumed to contribute to CRPS in at least some patients. This assumption often colored physicians' conceptualization of CRPS patients despite the absence until 15 years

ago of a significant body of controlled studies testing these assumptions. Examination of this literature indicates that nearly all studies assessing the role of psychological factors in CRPS have been limited to case-series descriptions or cross-sectional psychological comparisons between CRPS patients and non-CRPS chronic pain patients. A recent review of this literature concluded that the majority of these studies do not support a role for psychological factors in onset and maintenance of CRPS [245].

Ability to make conclusions about psychological factors *contributing to onset* of CRPS depends on a prospective research design, and unfortunately, such designs are extremely rare in the CRPS literature. A prospective study in 50 postfracture patients indicated that while occurrence of CRPS was relatively common (18% incidence), personality and depression scores did not differ significantly between those who did and did not develop CRPS [246]. In contrast with these negative findings, other prospective work reported that higher levels of anxiety prior to undergoing total knee arthroplasty were associated with significantly greater likelihood of a CRPS diagnosis at 1 month post-surgery, with a similar nonsignificant trend for depression [247]. More recent findings in this dataset provide stronger evidence in support of the psychophysiological model described earlier [248]. When continuous CRPS symptom scores rather than dichotomous CRPS diagnoses were examined, increases in depression levels from presurgical baseline to 4 weeks post-surgery were found to predict significantly greater extent of CRPS symptoms at both 6- and 12-month follow-up, with similar findings at 6-months for early post-surgical increases in anxiety [248].

Even if the psychophysiological model is accurate, this should not be taken to imply that the presence of psychological "risk factors" alone would be either necessary or sufficient to cause CRPS. For example, another prospective study revealed that among 88 consecutive patients assessed shortly after acute distal radius fracture, 14 had significantly elevated life stress but did not develop CRPS, and the one patient who did develop CRPS had no apparent psychological risk factors (i.e., no major life stressors, average emotional distress levels) [249].

Until more definitive prospective studies are available, the question of whether psychological factors affect the development and maintenance of CRPS must be addressed solely on the basis of case reports and retrospective or cross-sectional research designs that do not allow causation to be inferred. Two uncontrolled retrospective case series reported a relationship between onset of CRPS and contemporaneous emotional loss or major life stressors [250,251]. The uncontrolled nature of these reports prevents any conclusions from being drawn regarding psychological factors as a contributor to onset of CRPS. One of only two controlled studies regarding the role of life stress in CRPS onset [252] found that 80% of patients in a CRPS sample recalled a stressful life event contemporaneous with the initiating physical trauma in contrast with only 20% of non-CRPS controls. Although this suggests that stressful life events may contribute to development of CRPS following physical trauma, this study was retrospective in nature; there remain no prospective tests of this life stress hypothesis. In contrast with the positive findings earlier, a more recent cross-sectional study indicated that while CRPS patients reported stressful life events at a higher rate than in the general population, they reported *fewer* stressful life events than individuals with conversion disorders or affective disorders [253]. Moreover, rates of childhood traumatic experiences were similar between CRPS patients and those with affective or conversion disorders. Results of this study do not provide strong support for a unique role of stressful life events in CRPS development.

If psychological dysfunction were somehow uniquely involved in onset or maintenance of CRPS, one might also expect increased prevalence of psychiatric disorders or elevated levels of emotional distress in this population. Based on structured interviews, estimates for prevalence of Axis I psychiatric disorders (e.g., anxiety and depressive disorders) in CRPS patients indicate a prevalence ranging from 24% to as high as 46% [254,255]. It should be noted that only Monti et al. [254] included a non-CRPS chronic pain control group, and these authors reported that Axis I prevalence was not significantly higher in CRPS compared with non-CRPS pain patients. Neither of the studies earlier documented psychiatric status *prior to* CRPS onset and therefore cannot address the issue of causality [254]. At present, there is no evidence that CRPS patients suffer from diagnosable psychiatric disorders at a higher rate than other chronic pain patients do.

Controlled studies have also addressed the issue of whether CRPS patients are more emotionally distressed than other types of chronic pain patients. Several cross-sectional studies have found that CRPS patients report being more emotionally distressed than non-CRPS pain patients in terms of depression and/or anxiety levels [256–258]. Other work indicates that patients displaying signs and symptoms of CRPS 6 months following total knee replacement reported significantly higher levels of anxiety than did patients not displaying CRPS, despite the fact that both groups were continuing to experience at least some degree of pain [115].

It is not known whether observed elevations in psychological distress in studies like those earlier are a result of CRPS pain rather than a cause. In support of the latter causal interpretation are data from a time series diary study indicating that depression levels on a given day were a significant predictor of CRPS pain intensity on the following day [259]. The other alternative, however, is that elevated distress sometimes reported in CRPS patients relative to non-CRPS chronic pain patients might be due to the unusual and sometimes dramatic symptomatology of CRPS (e.g., allodynia, hyperalgesia, vasomotor changes, significant edema, motor changes) being more distressing than experiencing more common forms of chronic pain.

Despite results of some studies suggesting that CRPS patients are more distressed than comparable non-CRPS chronic pain patients, several other studies have reported no such differences. For example, work by Ciccone and colleagues provided only partial support for this hypothesis, finding that CRPS patients reported more somatic symptoms of depression than non-CRPS patients with local neuropathy but displayed no emotional differences relative to low back pain patients [260]. Other studies have found no evidence of elevated distress among CRPS patients compared with low back pain patients [261,262] or headache patients [261]. These negative results suggest the possibility that rather than CRPS being associated inherently with greater distress, the inconsistent findings regarding this issue may be accounted for by differences in sample selection, pain duration, clinic referral patterns, and specific psychometric measures used across studies. In the absence of additional well-controlled studies, it remains unclear whether the findings suggesting uniquely elevated distress in CRPS patients are an artifact of sample selection.

Whether or not absolute levels of dysphoric emotional states are elevated in CRPS patients, two studies suggest that emotional distress, when present, may have a greater impact on pain intensity in CRPS than in other types of chronic pain [258,263]. For example, correlations between pain intensity, and both anxiety and anger expressiveness have been found to be significantly stronger in CRPS patients than in non-CRPS chronic pain patients [258,263]. These results suggest that even if CRPS patients are not uniquely distressed, the impact of that distress may be unique possibly due to the hypothesized adrenergic interactions described earlier. Such findings may also have treatment implications. For example, a small prospective treatment study in CRPS patients indicated that greater baseline anxiety predicted lower subsequent pain relief and functional improvement more than 6 months following treatment using sympathetic blocks [264]. Conversely, psychological interventions that reduce distress might be expected to contribute to reductions in CRPS symptoms (e.g., pain, vasomotor changes) and potentially enhance the efficacy of other interventions.

Another important pathophysiological mechanism that may contribute to CRPS is the sometimes dramatic disuse that patients develop in an effort to avoid stimuli that may trigger hyperalgesia and allodynia in the affected extremity. The impact of disuse is demonstrated by findings of an experimental study in 30 healthy individuals who underwent upper extremity casting for 28 days [265]. Compared with non-casted controls, experimental immobilization resulted in cold hyperalgesia and skin temperature asymmetry lasting 3 days following cast removal, as well as longer lasting reductions in mechanical pain threshold [265]. That disuse is an issue in CRPS is supported by findings that diminished active ROM is common even in early CRPS [266] and that CRPS is associated with significantly reduced mobility and impaired ability to use the affected area normally [267]. Significant inverse correlations between CRPS pain intensity and ability to carry out ADL [268] suggest that pain avoidance is a likely reason for CRPS-related activity impairments and disuse. Learned disuse reinforced by either avoidance of actual pain or reduced anxiety subsequent to avoiding *anticipated* pain exacerbations may prevent desensitization and eliminate the normal tactile and proprioceptive input from the extremity that may be necessary to restore normal central signal processing [1,39]. Learned disuse may also inhibit the natural movement-related pumping action that helps prevent accumulation of catecholamines, pronociceptive neuropeptides, and pro-inflammatory cytokines in the affected extremity, all of which may impact negatively on CRPS signs and symptoms (e.g., Drummond et al. and Weber et al. [237,269]). Pain-related learned disuse might therefore interact with other pathophysiological mechanisms to help maintain and exacerbate both the pain-related and autonomic features of CRPS [229].

In summary, while the contribution of psychophysiological interactions to CRPS is largely speculative, it is theoretically consistent and highlights the importance of addressing psychological factors in the clinical management of CRPS. A vicious cycle in which pain provokes disuse and emotional arousal, both of which in turn further exacerbate the pain, could contribute to maintenance of CRPS. Psychological/behavioral treatments may therefore play an important role in CRPS management by targeting learned disuse and both life stress and emotional distress that may contribute to maintenance or exacerbation of the disorder. Moreover, such treatments can enhance pain-coping skills that ultimately lead to improved functioning and quality of life and increase ability to self-manage pain. At minimum, such treatments are likely to enhance patients' sense of control over the condition and thereby reduce fears that may be a barrier to achieve success in functional therapies.

Efficacy of Psychological Interventions in CRPS Patients

A review of the Medline and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases reveals a number of studies that have addressed efficacy of psychological interventions for CRPS, although nearly all of these reflect uncontrolled designs that permit only limited conclusions to be drawn. An additional caveat regarding these studies is that the criteria used to diagnose CRPS were often not adequately described and in all likelihood varied substantially across studies. This lack of consistent or specified diagnostic criteria limits the ability to generalize these results to patients diagnosed according to current IASP criteria for CRPS.

A summary of studies reporting on efficacy of psychological treatments for CRPS is presented in Table 10. This table reveals that only one randomized trial specifically testing psychological interventions in CRPS patients has been published to date. Fialka et al. [270] (level 2 evidence) randomized treatment for 18 CRPS patients to receive either home PT or home PT plus once-weekly autogenic relaxation training for 10 weeks. Both groups showed similar improvements in pain, ROM, and edema, although

Table 10 Studies examining psychological/behavioral interventions for complex regional pain syndrome

Author	Design and Sample	Psychological Intervention	Outcome
Blanchard [273]	Case report N = 1 adult	Thermal biofeedback	Complete resolution of symptoms
Alioto [272]	Case report N = 2 adult/adolescent	Autogenic and breathing relaxation, thermal and muscular biofeedback	75–100% reduction in pain
Barowsky et al. [271]	Case report N = 1 child	Thermal biofeedback	Complete resolution of symptoms
Kawano et al. [274]	Case report N = 1 adolescent	Autogenic relaxation, imagery	Complete resolution of symptoms
Wesdock et al. [279]	Case series N = 36 child/adolescent	Biofeedback	Helpful in some cases, particularly in CRPS of shorter duration
Gainer [275]	Case report N = 3 adult	Hypnotic imagery, relaxation training	Complete resolution of symptoms
Wilder et al. [278]	Case series N = 70 child/adolescent	Multidisciplinary treatment including relaxation training and CBT	Significantly improved pain and function in 57% of patients
Fialka et al. [270]	Randomized trial N = 18 adult	PT (N = 9), PT+ autogenics (N = 9)	Pain improved in both groups equally. Skin temperature more improved in autogenics group.
Sherry et al. [98]	Case series N = 103 child/adolescent	Multidisciplinary treatment including psychotherapy for 77% of sample	Complete symptom resolution in 92% of sample at end of treatment, 88% symptom-free at 2 year follow-up
Oerlemans et al. [65,276]*	Randomized trial N = 135 adult	PT including relaxation training and cognitive interventions (N = 44), OT (N = 44), Social Work Control (N = 47). All patients received standard medical care.	Significantly greater improvements at 1 year follow-up for PT group than Controls on pain, temperature, active range of motion, and overall impairment scores
Lee et al. [67]	Randomized trial N = 28 child/adolescent	PT 1× week + CBT (N = 14), PT 3× week + CBT (N = 14)	Pain and function improved significantly pre-post for both groups. Recurrence rate = 50%.
Singh et al. [277]	Prospective case series N = 12 adult	4-week outpatient interdisciplinary treatment program including group psychotherapy	Function improved significantly pre-post treatment without corresponding increases in anxiety
de Jong et al. [99]	Series of prospective single-subject experiments N = 8 adult	Intensive graded exposure therapy targeting pain-related fear	Pain-related fear was significantly reduced, with corresponding decreases in pain intensity, disability, and other CRPS symptoms

Studies are listed in order of date of publication.
* Both Oerlemans et al. studies were based on same sample.
CBT = cognitive-behavioral therapy; OT = occupational therapy; PT = physical therapy.

patients in the PT + Autogenics group demonstrated significantly greater improvements in limb temperature. Although low statistical power due to the small sample limited the ability to adequately evaluate intervention efficacy, these results suggest that relaxation-based interventions may have some benefit in management of CRPS.

Although not incorporating a randomized control group design, results of a series of well-controlled single subject experiments strongly suggest the efficacy of another potential psychological therapy. In vivo graded exposure was used to target disuse and fear of movement in eight CRPS patients (level 3 evidence) [99]. This exposure therapy resulted in significant reductions in pain-related fear of movement, with pain, disability, and other symptoms of CRPS also decreasing significantly in parallel fashion [99].

Results of several published case studies and small case series suggest that the pain of CRPS may be reduced

through use of a variety of other psychological techniques. For example, Barowsky et al. [271] (level 4 evidence) reported on a 12-year-old CRPS patient in whom 10 sessions of thermal biofeedback resulted in resolution of CRPS that had been resistant to previous treatments. Alioto [272] (level 4 evidence) reported that an adult chronic CRPS patient experienced a 75% decrease in pain intensity and improved mood subsequent to a series of psychological training sessions incorporating autogenic relaxation, breathing relaxation, and muscular and temperature biofeedback. Total elimination of pain was reported by this same author in a 16-year-old CRPS patient using a similar intervention approach [272]. Dramatic improvements like those earlier were also noted in an adult chronic CRPS patient described by Blanchard (level 4 evidence) [273]. Eighteen sessions of thermal biofeedback training resulted in nearly complete elimination of pain, as well as the ability to raise digital temperature in the affected hand by 1.5°C [273]. This relief was reported to be maintained at 1-year follow-up. Autogenic relaxation and imagery training (six sessions) have been reported to result in complete resolution of CRPS-related pain of 7 months duration in a 15-year- old patient, with these gains reportedly maintained at 18-month follow-up (level 4 evidence) [274]. Hypnotic imagery combined with relaxation techniques (over a 6- to 9-month period) has additionally been reported to result in complete resolution of CRPS symptoms in a series of three adult CRPS patients (level 4 evidence) [275]. It should be noted that the complete resolution of symptoms described in some case reports using only psychological interventions is likely to be atypical and fails to recognize the number of less dramatic successes or even treatment failures no doubt encountered by these same authors. While the uncontrolled designs used in the studies described earlier prevent definitive conclusions from being drawn regarding the efficacy of psychological techniques for CRPS, they clearly support the idea that such techniques may play an important role in effective treatment.

Other research has addressed the multidisciplinary aspects of treatment, suggesting that integration of psychological methods with medical and PT may be helpful in managing CRPS [59,98,276,277]. Two RCTs examining efficacy of PT for CRPS have included components of psychological treatment in the therapy package [59,67,276]. For example, Oerlemans et al. [59,276] (level 2 evidence) tested a PT protocol that included relaxation exercises and cognitive interventions (designed to increase perceived control over pain). This combined intervention was found to produce significantly greater improvements in pain, active ROM, and impairment levels than were observed in the social work control group [59,276]. In another RCT of PT, Lee et al. [67] (level 2 evidence) examined two different frequencies of PT treatment (once per week vs three times per week) for child and adolescent CRPS patients, with both groups additionally receiving six sessions of cognitive behavioral treatment. Although no attentional control group was available for comparison, both groups were found to improve significantly in terms of pain and function when compared with their pretreatment baselines. While the multicomponent interventions in both of these studies do not permit conclusions to be drawn specifically regarding the efficacy of psychological interventions, they do suggest that psychological treatment in combination with PT may prove effective in a rehabilitation-focused approach to management of CRPS. This conclusion is supported by results of a prospective controlled case series examining efficacy of combined therapy for CRPS. A 4-week interdisciplinary pain management program including medical treatment, PT and OT, and group psychotherapy produced significant improvements in several functional outcomes without any corresponding increases in pain-related anxiety, suggesting how such treatments could potentially work synergistically (level 3 evidence) [277].

Uncontrolled trials also support inclusion of psychological interventions in the multidisciplinary treatment package, although all of these studies are in child or adolescent populations. For example, Wilder et al. [278] (level 3 evidence) described a conservative multidisciplinary treatment program used in 70 childhood CRPS patients that incorporated relaxation training and cognitive-behavioral interventions, noting that it resulted in improved pain and functioning in 57% of the sample. Even more impressive results were reported by Sherry et al. [98] (level 3 evidence) in a case series of 103 primarily adolescent CRPS patients. Multidisciplinary treatment incorporating conservative medication management, regular active PT, and psychological counseling (for 77% of the sample) reportedly resulted in 92% of this sample achieving symptom-free status [98]. Although no details are provided, Wesdock et al. [279] (level 3 evidence) noted that biofeedback was helpful in some cases of short-duration childhood CRPS in the context of multidisciplinary treatment.

While not entirely relevant regarding the specific issue of psychological interventions for CRPS, three other studies do bear mention. The first is a small RCT comparing efficacy of a motor imagery intervention (N = 7) for CRPS patients to a "standard treatment" control group (N = 6; level 2 evidence) [70]. This intervention focused on requesting that patients make repeated imaginal movements of the CRPS-affected limb (throughout the day) to match pictured movements. Despite the small sample, results indicated that the motor imagery intervention resulted in significantly greater improvements in pain intensity than did standard treatment. Although intriguing, a somewhat larger follow-up study by the same authors found that this motor imagery intervention appeared to *increase* pain and edema in a separate sample of CRPS patients (level 2 evidence) [280]. The imagery used in these studies (movement) was not identical in character to that most frequently used in psychological interventions (pain reduction or relaxing imagery), yet these findings may nonetheless be relevant to optimizing imagery interventions used in CRPS management.

Given the nearly complete absence of RCTs of psychological interventions for CRPS, results of a recent review and meta-analysis of cognitive behavioral interventions in other neuropathic pain patients may be informative (level 1

evidence) [281]. Only a single RCT of high methodological quality was identified, which demonstrated significant efficacy of cognitive behavioral interventions for reducing pain intensity, although this effect was restricted to women (level 2 evidence) [282]. Meta-analysis of all four available controlled trials indicated no overall significant effects of cognitive behavioral therapy on neuropathic pain intensity. These results do not provide unambiguous support for the likely efficacy of psychological interventions in CRPS patients, but firm conclusions cannot be drawn due to the limited number of studies available.

In summary, there is only one small RCT specifically testing the efficacy of psychological interventions for CRPS, either alone or in the multidisciplinary context. However, the clinical case reports, controlled case series, and results of single subject experiments available do suggest that psychological interventions are likely to be a useful part of a comprehensive multidisciplinary treatment program. The efficacy of such techniques for CRPS would not be surprising, given the strong evidence of their utility in other types of chronic pain. These results will be briefly summarized later.

Efficacy of Psychological Interventions in Other Non-CRPS Chronic Pain Disorders

Numerous RCTs have documented the efficacy of various psychological approaches to the management of chronic pain in general, and these have been quantitatively summarized in several published meta-analyses. Treatment approaches examined include many of the same interventions used in the CRPS studies described previously, including relaxation techniques, autogenic training, biofeedback, behavioral therapy, and cognitive behavioral therapy. Results of several meta-analyses clearly document the efficacy of these techniques for non-CRPS chronic pain conditions. For example, a meta-analysis of clinical trials testing progressive muscle relaxation techniques found significant effects in various chronic pain conditions, reflecting a moderate effect size (level 1 evidence) [283]. Meta-analysis specifically of autogenic training, another self-relaxation procedure, also indicated a significant and at least moderate effect size in controlled trials for patients with headache and somatoform pain disorder (level 1 evidence) [284]. Significant efficacy for biofeedback training is also indicated by meta-analyses in populations including temporomandibular joint pain and migraine headache patients (both level 1 evidence) [285,286]. More generally, meta-analyses of RCTs across psychological treatment types (various treatments provided both alone and in combination) indicate significant efficacy of this class of techniques for a variety of chronic pain conditions, including low back pain, fibromyalgia, rheumatoid arthritis, and cancer-related pain (all level 1 evidence) [287–293]. Results of one available meta-analysis also confirm that cognitive behavioral interventions are significantly effective for children and adolescents with chronic pain (level 1 evidence) [294]. Overall, the results of RCTs of psychological treatment approaches consistently indicate at least a moderate benefit in terms of experienced pain, mood, and function for patients with a variety of chronic pain conditions. Given the proven efficacy of these interventions for various non-CRPS chronic pain conditions, their utility specifically in the management of CRPS might also be expected. These meta-analytic findings provide additional support, albeit indirect, for the reported efficacy of psychological interventions in CRPS patients described in uncontrolled trials.

Clinical Recommendations

There is little well-controlled CRPS-specific outcome research on which to base psychological treatment recommendations for the condition. However, clinical experience and available data do suggest several specific strategies that may be helpful. A suggested psychological intervention algorithm is summarized in Figure 2.

While there are indications that many cases of acute CRPS may resolve relatively quickly without any need for specific psychological intervention, a low cost and potentially helpful intervention recommended for all *acute or chronic* CRPS patients is a comprehensive education about the condition. Specifically, it is recommended that all patients *and their families* receive detailed information early in treatment that addresses the negative effects of disuse, the importance of reactivation, and the need for an active self-management approach to treatment, and that provides an explanation of how possible psychophysiological interactions could affect severity of CRPS. Such education may help prevent development of dysfunctional behavior patterns (e.g., elevated distress and severe disuse) that could contribute to the severity, disability, and chronicity of the condition. For more chronic CRPS patients or those who do not respond to limited intervention, individualized psychological evaluation is recommended, followed by focused psychological pain management treatment. An overview of several key issues to address in this assessment and treatment is provided later.

Assessment

Several specific areas of relevance to CRPS management should be addressed in the psychological evaluation, including: 1) presence of comorbid Axis I psychiatric disorders; 2) cognitive, behavioral, and emotional responses to CRPS; 3) ongoing life stressors; and 4) responses by significant others to the patient's CRPS. As noted previously, Axis I psychiatric disorders such as major depression, panic disorder, generalized anxiety disorder, and post-traumatic stress disorder are at least as common in CRPS patients as in other chronic pain patients [254]. The importance of assessing for disorders such as major depression is highlighted by the fact that diminished energy level and motivation related to clinical depression may be a significant barrier to success in active physically focused treatment modalities (e.g., PT and OT). Identification of specific life stressors and general emotional arousal (depressed, anxious, fearful, or angry mood) even in the absence of clinically diagnosable psychiatric

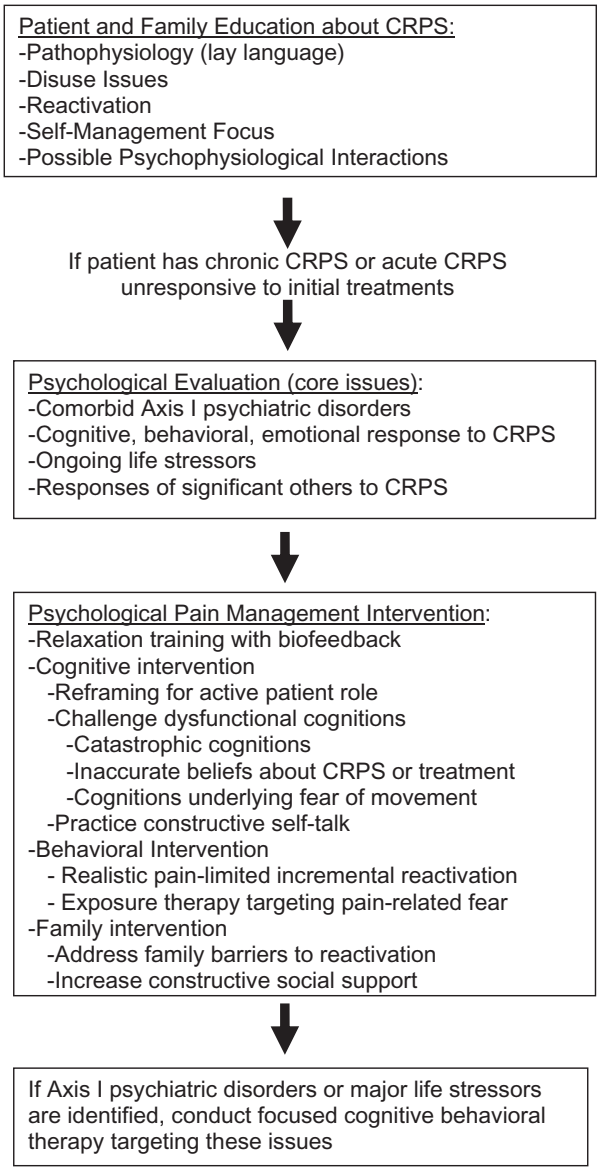

Figure 2 Psychological intervention treatment algorithm. CRPS = complex regional pain syndrome.

disorder may be equally important given possible psychophysiological interactions hypothesized earlier.

Research in chronic back pain patients indicates that pain-related disability is more strongly related to *fear* of pain than it is to the level of pain intensity itself [43]. Therefore, assessment of CRPS patients' fear of their pain is also important. Evidence from studies in chronic back pain patients indicates that pain-related fear contributes to elevated pain intensity and disability in part by leading to chronic guarding, bracing, and disuse in response to fears that movement will lead to increased pain and re-injury [295]. This is particularly important for CRPS patients, in whom disuse may interact directly with the pathophysiology of the disorder and in whom severe guarding may contribute to secondary proximal myofascial pain that can mimic spreading of the disorder (and further increase fear). Not all activity avoidance in CRPS patients is unreasonable (e.g., avoiding heavy lifting with the affected hand), and therefore, the focus should be on identifying activity avoidance that is extreme and unreasonable. For example, some CRPS patients may appear to be experiencing agoraphobia based on their reports of an intense desire to avoid crowded environments. However, further assessment in many cases reveals that this avoidance is motivated by excessive fears that someone will accidentally make contact with the affected extremity and provoke extreme pain. While patients admit that this is unlikely to occur, the behavior persists. This pattern highlights the fact that activity avoidance and disuse in chronic pain can be operantly reinforced by the decreased fear that accompanies avoidance of expected pain exacerbations [296].

Assessment of the cognitive impact of CRPS should include thorough exploration of the patient's beliefs regarding CRPS. Several misconceptions are common among patients, particularly those who have failed previous treatments. For example, patients may believe that CRPS is an untreatable, progressively deteriorating condition and that it will necessarily spread throughout the body (a belief not supported by empirical studies). Catastrophic cognitions such as these are often a contributor to negative emotional states that may have a deleterious impact on CRPS and responses to treatment [264]. The importance of addressing catastrophic cognitions in CRPS treatment is highlighted by results of a prospective study in non-CRPS neuropathic pain patients, which indicated that level of catastrophizing at study baseline predicted level of pain 8 weeks later, independent of baseline pain and depression [297]. Patients may also possess incorrect beliefs regarding the meaning of CRPS pain. Not surprisingly given the intensity and unusual nature of allodynic pain, patients may assume that pain signals damage, and as a corollary, "if it hurts, don't do it." Such beliefs may be a primary contributor to pain-related fear and, consequently, exacerbate disuse. It is therefore important that patients understand that neuropathic pain as in CRPS does not signal tissue damage. Unrealistic beliefs regarding how CRPS treatment should progress may also be problematic. Common misconceptions include beliefs that sympathetic blocks alone are curative and that treatments that exacerbate pain temporarily cannot contribute to long-term improvements. Invasive and expensive interventional procedures, such as spinal cord stimulation (SCS), may prove valuable for some patients in the later stages of treatment. However, excessive focus early in treatment upon invasive interventions viewed as a "quick fix" before patients have participated in a comprehensive multidisciplinary program leads to reduced motivation to engage actively in multidisciplinary care, and outcomes are likely to suffer. The importance of considering treatment expectations is underscored by recent qualitative research examining the content of CRPS Internet message boards, which found that many CRPS

patients have unrealistic expectations regarding likely outcomes of medical interventions for CRPS [298].

Psychological Pain Management Intervention

The pain management intervention component of CRPS treatment should include relaxation training (preferably in conjunction with thermal and/or electromyographic biofeedback), training in cognitive pain coping skills, and behavioral intervention to address disuse and activity avoidance issues, as well as family reinforcement issues. In addition to the earlier reports, other targeted cognitive behavioral therapy interventions may be helpful if specific issues are identified during evaluation, which may impact on the condition or ability to engage effectively in treatment (e.g., major ongoing life stressors or Axis I psychiatric disorders).

The goal of relaxation training with biofeedback is to increase patients' ability to control their pain and decrease emotional arousal (and associated sympathetic discharge) that may impact negatively on the condition. Clinical trial data in non-CRPS chronic pain suggest that breathing-focused relaxation, progressive muscle relaxation, relaxing imagery, and autogenic training all may prove beneficial. There is no clear evidence of the superiority of any one of these interventions, and thus, the specific techniques employed are generally determined by patient and therapist preference. With all relaxation/biofeedback techniques, the key factor determining their clinical efficacy is the degree to which patients practice the techniques at home and integrate them into their pain coping during regular activities on a daily basis.

A second aspect of the pain management treatment component is cognitive intervention. Given the emphasis in recent consensus guidelines for CRPS management using an active rehabilitation approach [1,53], it is important to reframe the CRPS patient's role as that of an active participant in the treatment process rather than a passive recipient of treatment interventions. As part of this active treatment focus, pain exacerbations should be identified as a cue to practice self-management interventions that may help the patient gain control over their situation. As patients learn relaxation skills and begin to understand the cognitive and behavioral aspects of the syndrome, they will have increasing resources for exerting at least some degree of control over their CRPS. Increased sense of perceived control, even if that control is limited in scope, may be an important factor in determining outcomes in chronic pain treatment (e.g., [299]). Dysfunctional cognitions may be common in CRPS patients [258], including catastrophic interpretations about symptoms or implications of CRPS for the future fearful pain-related cognitions, like those described earlier, and unrealistic beliefs about treatment. Cognitions like those earlier can contribute to elevated distress, which may impact on sympathetic outflow and catecholamine release, and potentially aggravate CRPS pain and vasomotor changes. Moreover, in the absence of *in vivo* reactivation experiments in which constructive self-talk is practiced, fear of pain may prevent improved daily function even in the face of objectively improved capabilities during therapy. It is therefore important that cognitive interventions be employed to help patients learn to identify and modify their specific dysfunctional cognitions regarding reactivation, CRPS, and its treatment.

Given the impact of learned disuse as a potential barrier to reactivation, behavioral interventions targeting this disuse can also be an integral component of the overall treatment program. Reactivation and behavioral goals must necessarily balance disuse concerns with avoiding *severe* pain exacerbations that could potentially contribute to maintenance of CRPS and reinforce learned disuse. *Realistic* pain-limited incremental reactivation is a key, with the psychologist and functional therapists coordinating efforts to insure that appropriate activity goals are set and that problems encountered in this reactivation process (e.g., pain-related fear of movement) are effectively addressed. As noted earlier, there is some experimental evidence supporting the efficacy of graded in vivo exposure therapy to address pain-related fear in CRPS, with apparent beneficial effects on pain and other CRPS symptoms as well [99].

With regards to family intervention, the most crucial issue to address is the possibility that some family members may be a barrier to reactivation due to solicitous responses and fear of pain exacerbations. Unless detailed education regarding CRPS and disuse issues is provided, family members may consider any activity that increases pain as dangerous to the patient and something to be discouraged. It is therefore important to ensure that family members understand the necessity of reactivation and that this might be associated with transient increases in pain. In contrast, family members may, due to a lack of understanding, incorrectly assume that unusual symptoms such as allodynia are exaggerated and as a consequence, be less than fully supportive. Adequate positive family support can have a significant impact on ultimate efficacy of treatment. Family members should therefore be guided in how they can best respond to the patient's pain in a way that encourages and facilitates appropriate reactivation and helps keep the patient focused on constructive management of the condition. The importance of addressing family issues is highlighted by findings demonstrating that more than half of caregivers of CRPS patients experience negative mood and significant strain, and these factors in turn are associated with greater patient disability [300]. While one might assume that this family distress and strain is a *result* of having to handle greater patient disability, the possibility of bidirectional causal influences must at least be considered.

Summary

There is no solid evidence that psychological factors are necessarily involved in the onset of chronic CRPS. However, there are theoretically plausible pathways through which psychological factors in some cases *could* affect the development of CRPS. There is no consistent

experimental support for the idea that CRPS patients are in any way psychologically unique compared with other chronic pain patients. Once CRPS has developed, emotional factors may have a greater impact on CRPS pain intensity than in non-CRPS pain conditions possibly through the impact of dysphoric psychological states on catecholamines. Meta-analytic reviews document the efficacy of various psychological interventions for many types of non-CRPS chronic pain and suggest that such interventions are likely to be beneficial for CRPS patients as well. Adequate randomized, controlled studies of psychological interventions in CRPS patients are not available to guide this aspect of CRPS management, although numerous uncontrolled studies suggest the likely utility of several approaches. These approaches include various forms of relaxation training, biofeedback, and cognitive and behaviorally focused interventions including graded exposure therapy. Successful implementation of these interventions requires recognition of the unique issues in CRPS patients, particularly the pervasive learned disuse often seen in such patients. Clinical experience using techniques, like those described earlier, in an integrated multidisciplinary context indicates that many CRPS patients can achieve significant improvements in functioning and ability to control pain.

Interventional Therapies

This semisystematic review for the Interventional Therapies section included a PubMed search for "RSD, CRPS + interventional pain, sympathetic block, nerve blocks, neural blockade, spinal stimulation, neuromodulation, dorsal column stimulation."

The Role of Interventional Therapies in the Treatment of CRPS

Interventional therapies, including nerve blocks, drug infusions, and implantable pain treatment devices have all been advocated for the treatment of CRPS. This section will present information about the role of each block or technique individually and present an algorithm for a "best practices" utilization of these procedures to treat CRPS, citing the best available evidence where available.

As the mechanisms of CRPS are better understood, mechanistic-based treatments should be forthcoming; but in the meanwhile, different interventional and non-interventional treatment modalities are applied empirically in a timely manner to facilitate reanimation of the affected extremity. In this section, the historical basis and evidence for the use of nerve blocks in the treatment of CRPS will be reviewed. There have been several topical reviews/meta-analysis articles on this topic, and they will be included. An updated PubMed and Google Scholar search was done in 2011 to update this work from the previous edition. Individual studies will be included periodically for several reasons: to highlight a good quality study, to note a novel (or newer) treatment, or to highlight some aspects of clinical decision making. Blocks included in this section include: sympathetic nerve blocks (SNBs), IV regional techniques (IVRAs), "other" blocks (including somatic and spinal infusions), neurolytic sympathetic blockade, and implantable therapies (including neurostimulators and intrathecal pumps).

SNBs

Over time, much research and clinical experience has provided evidence that CRPS is a post-traumatic painful neurological and inflammatory syndrome involving the somatosensory, sympathetic, and often the somatomotor systems [114]. This evolution of mechanistic thinking reveals a complex condition that consists of local inflammation (and perhaps neurogenic inflammation) out of proportion to injury; severe pain in the skin, subcutaneous tissues, and joints; evidence of central hyperexcitability; and sympathetic dysfunction and asymmetry (which represents a logical target for injection therapy) [301]. The SNB is traditionally recognized as an important procedure both in the diagnosis and treatment of CRPS, with ablative surgical techniques described back to the 1940s or earlier [302]. Historically, the nomenclature RSD implied mechanistic involvement of the sympathetic nervous system, which led to the belief that the diagnosis of RSD could be confirmed with a positive clinical response to sympathetic blockade [303]. In the subgroup of CRPS with SMP, there is considerable evidence of coupling of sympathetic nerves with several types of afferent nerve fiber types in the peripheral and central nervous system [304].

Blockade of the sympathetic nervous system is traditionally accomplished at the level of the stellate ganglion block (SGB) or lumbar sympathetic block (LSB) chain, depending on the location of the painful syndrome (upper vs lower extremity). The pain relief following SNB generally outlasts the effects of the local anesthetic and may be long lasting in some cases [305,306]. In addition to these anatomic local anesthetic blocks, other sympatholytic procedures, including IV phentolamine, IVRA with either lidocaine, bretylium, clonidine, reserpine, or guanethidine, and epidural infusion (for sympathetic blockade) have been described [187,307–310]. The role of the sympathetic block has been called into question, yet most treatment algorithms still consider at least one sympathetic block (or infusion of sympatholytic agents) necessary to classify CRPS as SMP or sympathetically independent pain (SIP) [311,312]. There is considerable difficulty in "clinically assessing" the successful sympathetic block, and many "clinically successful" blocks provide a varying degree of sympatholysis (see later) [313]. Thus, the role of this block is in the realm of practical treatments based on traditional patterns. With a new understanding of CRPS as including both SIP and SMP, and the realization that it is clinically difficult to assess the degree of sympathectomy provided by SNB, the role of these blocks in a treatment algorithm is largely empirical (lack of a solid evidence base), but clinically important in individual cases as far as it facilitates amelioration of pain and function, and provides a less painful "window of opportunity" for rehabilitation techniques.

A systematic review by Cepeda et al. was published in 2002, which reviewed all available literature regarding local anesthetic sympathetic nerve blockade from 1916 through 1999 [314]. They screened 79 reports of which 50 were rejected due to small sample size, lack of validated or methodical assessments, or undisclosed CRPS patient selection details. The remaining 29 studies were evaluated in detail. These included 19 retrospective reports, 5 prospective case series, 2 nonrandomized controlled studies, and 3 RCTs. For multiple reasons, including evolving diagnostic criterion for CRPS and the recent increase in the sophistication of pain and functional assessment tools, these older reports tend to be relatively imprecise and performed on heterogeneous/nonspecific cohorts. Sixteen of the studies quantified the magnitude of response.

Another significant confounding factor is lack of consensus on defining the criterion of a successful sympathetic block. There are several studies available to clarify relevant issues. Price et al. did an interesting study of local anesthetic vs saline SGB or LSB in seven CRPS patients in a double-blind, crossover fashion [305]. Onset of analgesic effect occurred within 30 minutes in *both* groups, with the local anesthetic group (lidocaine/bupivacaine mixture) having a significantly greater duration (mean of 3 days 18 hours vs 19 hours) [305], thus showing at least short-term analgesic efficacy of local anesthetic sympathetic blockade for CRPS (level 3 evidence). Bonelli et al. did a randomized trial of SGB vs "active control" (in the form of guanethidine IV regional block) [61]. They found significant improvement in both groups, with no significant difference between the SGB and IVRA guanethidine groups (level 3 evidence).

Raja et al. undertook a blinded prospective trial of IV phentolamine infusion vs local anesthetic sympathetic blockade in 20 patients (10 upper and 10 lower extremity SMP patients). They found a high correlation between analgesia with SNB and IV phentolamine infusion and concluded that either technique could distinguish between SMP and SIP (level 3 evidence) [315].

Malmqvist et al. defined strict sympathetic block success criterion (4 out of 5 equals success: [1] Horner's syndrome, [2] increase in skin temperature >34°C, [3] increased skin blood flow >50% by laser Doppler flowmetry, [4] abolished skin resistance response ulnar, and [5] abolished skin resistance response radial) in an observational study of 54 SGBs. Only 15 of 54 blocks met this strict criterion for a successful block [316], thus indicating the relatively high rate of partial or incomplete sympathetic blockade clinically. Less than 20% of the articles reviewed by Cepeda et al. critically evaluated the success of their blocks [314]. Schurmann et al. showed the clinical difficulty regarding correlation of limb temperature elevation, Horner's syndrome, and complete sympathetic block as measured by an elegant complex experimental design in a large group of CRPS type I patients [313]. This study clearly showed that even in the case of significant limb temperature elevation, the sympatholysis may be incomplete, with the same holding true for the Horner's syndrome. Additionally, even in patients with a complete sympatholysis, the rate of analgesia obtained following the SGB was a little higher than 50%, clearly demonstrating subgroups of SIP and SMP within this group of 33 CRPS type I patients.

To summarize, there is some (albeit level 3) evidence for the efficacy of the classic SGB and LSB, but they remain in most CRPS treatment algorithms in order to differentiate SMP from SMP, realizing the clinical interpretive difficulty of a "successful" block as outlined earlier. If the block provides good analgesia in a patient, then a short series of blocks in conjunction with active reanimation physiotherapy is advocated based on consensus recommendations [53]. A future direction for further research involved combining bupivacaine plus botulinum toxin vs bupivacaine alone in a trial comparing nine patients undergoing LSB for CRPS. These authors found botulinum toxin prolonged the duration of analgesia from a mean of 10 days to 71 days [214].

IVRA

IVRA has been used for years to empirically treat CRPS [317]. Numerous IVRA medications alone and in combination have been reported to have efficacy in treating CRPS. IVRA with guanethidine, lidocaine, bretylium, clonidine, droperidol, ketanserin, or reserpine have been described and reviewed critically by Perez et al., Forouzanfar et al., and Kingery [46,134,197].

Perez et al. undertook a meta-analysis of the highest quality (blinded, with re-evaluation of included trials, statistical methodology, and inclusion only of trials meeting strict inclusion criterion such as randomization, blinding, sample size, dropout rate, and others), finding 11 acceptable trials of "sympathetic suppressors," nine being IVRA studies and six concerning guanethidine in particular [197]. Perez et al. applied a quantitative analysis of effect size that compares the difference in pain relief between experimental and control groups, with a correction factor applied for trial size. This method has become acceptable in meta-analysis to analyze aggregate treatment effect from numerous studies. Their aggregate analysis showed *lack of proven effect* of IVRA and lack of proven effect more specifically of guanethidine IVRA (thus level 1 evidence for *lack* of proven effect of these therapies).

Several good quality studies have also reported a negative outcome of the IVRA intervention (no better than placebo). Ramamurthy et al. did a double-blind, crossover, controlled outcome study with 60 CRPS I patients randomized to receive IVRA blocks every 4 days for a total of four blocks with either guanethidine (one, two, or four guanethidine blocks) or placebo in 0.5% lidocaine. After the first block, placebo response was higher than guanethidine and 6 months after the last block (up to four), 35% of patients had significant pain relief, without difference between placebo and guanethidine arms (level 2 evidence for *lack* of effect of guanethidine over placebo) [318]. Confounding factors in this study include the fact

that the "placebo" group received an IVRA using local anesthetic (0.5% lidocaine) and a tourniquet, which may confer some type of analgesic effect following the block; thus, in reality, the "placebo" control is an active treatment comparison group.

Jadad et al. used an enriched trial design and prospectively enrolled patients who reported pain relief with open-label guanethidine IVRA to a double-blind treatment phase with crossover design. No differences between guanethidine and placebo were seen, and this study was terminated early for side effects (level 2 evidence for *lack* of effect) [319]. Blanchard et al. compared the effects of IVRA with guanethidine vs reserpine vs saline (placebo arm). This was a crossover design, changing to another agent if inadequate analgesia occurred with a block. Only 21 patients were studied, but no differences between treatment types were discernable at short-term follow-up [310]. The placebo saline infusion is done with a tourniquet in similar fashion to the active drug block; thus, this does not control for a tourniquet induced effect on the extremity (e.g., tourniquet-induced analgesia, compression-induced alteration of local cytokines) leading to methodological problems with the "control" group for most IVRA studies [197]. Rocco et al. did a small double-blind, active RCT of reserpine and guanethidine (at different times) vs lidocaine alone in IVRA [320]. They noted significant relief following the block with no difference between the reserpine, guanethidine, or "control" (lidocaine) group.

The notable exception to these negative trials was Hord et al., who found a positive response with bretylium in a prospective, randomized, double-blind fashion vs lidocaine (level 2 evidence) [308]. However, bretylium is unavailable in the United States. Bonelli et al. compared IVRA guanethidine to SGB in a cohort of 19 "RSD" patients [61] and demonstrated "comparable efficacy."

To summarize, the IVRA technique is a procedure that allows placement of medications directly into the affected extremity. Again, efficacy is poor based on the available literature, with most of the guanethidine trials failing to show improvement in efficacy of guanethidine over lidocaine. There is lower quality evidence available to support the use of other agents—including bretylium, phentolamine, clonidine, lidocaine, and ketorolac—alone and in combinations. Ultimately, as our understanding of the peripheral alterations in cytokines is clarified, this technique may allow targeted pharmacotherapy to the affected limb [321].

IV Infusions

A phentolamine infusion has been postulated as a test for SMP. This short-acting alpha-adrenergic blocking agent needs to be given by infusion. Arner reported a critical analysis of the use of phentolamine infusion, followed by IVRA guanethidine to assess clinical response to: 1) the phentolamine infusion, and 2) to assess the positive predictive value of the phentolamine infusion on a subsequent IVRA guanethidine block's success [307]. Arner divided the results into causalgia and RSD adults vs causalgia and RSD children. In adults, Arner found that approximately 50% obtained markedly positive analgesia with IVRA phentolamine infusion and a complete correlation to an excellent response to guanethidine. In children, 37/47 obtained markedly positive analgesia to phentolamine infusion and a very strong correlation to an excellent response to IVRA guanethidine (32/37 excellent response). Arner concluded that phentolamine caused no complications and provided "diagnostic" information as to the presence of SMP and prognostic information about subsequent response to guanethidine (level 3 evidence for IV phenolamine) [307]. A major weakness of the Arner study was the lack of a control or placebo group. By contrast, Verdugo and Ochoa found that neither placebo, phentolamine, nor phenylephrine infusions gave any significant changes in pain, quantitative sensory testing, regional blood flow, or hyperalgesia—with no difference between groups in a prospective, single-blinded, nonrandomized study (level 3 evidence for *lack* of effect of phentolamine) [322].

A critical evaluation of IV infusion of lidocaine was undertaken by Wallace et al. in a randomized, double-blind trial [323]. They studied 16 patients with CRPS I or II with three different levels of lidocaine infusion (1, 2, and 3 mcg/mL, and placebo infusion)—during which the patients underwent spontaneous and evoked pain scores and detailed quantitative psychophysical testing. During the lidocaine (but not placebo) infusion, the patients showed evidence of a decrease in pain response to cold stimuli, a decreased response to cold or touch allodynia in previously allodynic areas, and a decrease in spontaneous pain (but only at the highest serum infusion level). Thus, the predominant effect was decreased pain in response to cool stimuli more so than with mechanical or spontaneous pain. There was no effect on pain induced by punctate stimuli (level 3 evidence for short-term decrease in pain response to IV lidocaine infusion).

IV phentolamine infusion has been used largely as a diagnostic tool to differentiate SIP from SMP. These techniques have fallen out of favor and are lacking evidence of efficacy.

Other (Brachial Plexus/Spinal Block Infusions) Blocks

There are numerous case reports of the use of brachial plexus blockade in the literature. Indications for continuous brachial plexus infusion include: perioperative post-trauma and postoperative pain relief, vascular compromise, intractable pain from CRPS I and II, and phantom limb pain. The brachial plexus is an ideal location for a continuous regional technique because of its well-defined perivascular compartment and the close approximation of the large number of nerves supplying the upper extremity. Catheters have been kept in place in the same position for as long as 3 weeks (level 4 evidence) [324]. The brachial plexus catheter may be connected to a constant infusion of local anesthetic, opioid, clonidine, and other agents.

Sympatholysis can still be maintained for up to 2–3 weeks with 0.1–0.2% ropivacaine in a reliably anchored catheter (level 4 evidence) [325].

Wang et al. reported placement of an axillary catheter in a patient with severe CRPS II 30 days post-carpal tunnel release (level 4 evidence) [326]. These authors started with a concentration of bupivacaine of 0.1% at 2.5 mL/h and noted a dense motor and sensory block with excellent analgesia. Within 1 day, they decreased the infusion to 0.05% bupivacaine, stopped the basal infusion, and allowed a 1-mL patient-controlled dose every 15 minutes. The patient had continued good analgesia with resolution of the motor block allowing active motion PT, with the catheter left in place for 1 week.

The complications of a continuous brachial plexus infusion are similar to those of a brachial plexus block plus the infectious risks of a long-term catheter. These include bleeding, infection, intravascular injection, intrathecal injection, pneumothorax, and phrenic nerve paralysis.

Epidural infusions are relatively straightforward to initiate, and allow one to vary local anesthetic concentration and infusion volume in order to titrate to desired effect. Other medications such as clonidine and/or opioids can be added to provide spinal analgesia and potentiate the degree of relief. The most commonly used combination of epidural medications today includes clonidine with/without bupivacaine. Opioids should be added if the pain relief is inadequate or if the local anesthetic concentration required to produce pain relief also prohibits ambulation or full participation in the physiotherapy program. The primary benefit of continuous regional analgesia is that one is able to effectively control the intense degree of relief and promote as aggressive a PT program as can be tolerated. Furthermore, with patient-activated bolus programming, these continuous regional techniques allow patients to self-administer small boluses for optimal analgesia as the pain levels dictate. For example, after a strenuous exercise program that may elevate pain, swelling, or allodynia, patients have ready access to improved relief simply by self-administering extra doses of medication within certain preprogrammed parameters. The effectiveness of epidural analgesia for the treatment of CRPS has been borne out by several studies.

Rauck et al. did an excellent randomized, blinded, placebo-controlled trial utilizing epidural clonidine [187]. They randomized 26 patients with CRPS to receive daily epidural infusions (for 3 consecutive days) of clonidine 300 or 600 mcg, or placebo. If patients responded to the clonidine with analgesia (and did not respond to placebo), they were placed on an open-label infusion for a mean of 32 days at a mean dose of 32 mcg/h. All patients had "good relief" with both the 300- and 700-μg dose. Of the 26 patients, 19 elected to receive continuous infusions of clonidine for an average of 43 days, with an average dose 32 ± 6 μg/h. Seventeen of 19 patients had statistically significant improvement in pain (level 3 evidence). Side effects were dizziness, dry mouth, mouth sores, and nausea. Six of 19 patients developed catheter-related infection, and one developed meningitis [187].

Cooper et al. studied 14 patients in a prospective open-label trial and demonstrated improved pain relief and ROM in patients receiving an epidural bupivacaine-opioid mixture for an average of 4 days (level 3 evidence) [327]. Thirteen of 14 patients had significant improvement with 11 of the 14 achieving "resolution of their CRPS" (at least at the end of the trial) with no activity restrictions. Koning et al. studied 26 patients using continuous cervical epidural analgesia of bupivacaine (0.25%) for 7 days coupled with PT (level 3 evidence) [328]. Eighty-three percent of patients had "improvement in pain." Edema, sweating abnormalities, and dysfunction of the hand responded particularly well. Sixty-three percent of patients considered their condition to be acceptable, whereas only 8% were completely pain-free. Reduction in use pain medications was also noted. Finally, Buchheit and Crews describe a single case report where continuous epidural infusion markedly improved ROM (level 4 evidence) [329].

The reported rates of infection in epidural catheters used to treat CRPS are as high as 31% [187]. Thus, epidural catheters that are meant for longer term use should be performed as minor surgical procedures requiring standard surgical sterility techniques. Catheters should be tunneled away from the midline entrance point in the spine to minimize the colonization by bacteria that is inherently a greater risk with extended duration infusions. In spite of precautions, CRPS patients may be predisposed to an increased chance of infection. Standard catheter dressings such as those required for extended central venous catheters should be followed. Dressings should be changed weekly in meticulous sterile fashion as with a central venous line. The hallmarks of an epidural abscess include the triad of back pain, sensorimotor loss, and loss of bowel and bladder function. Epidural abscesses usually have some earlier prodromal symptoms, such as fever, neck pain, or photophobia. Careful attention to early symptoms is paramount for early diagnosis. A previous study has demonstrated a catheter-related infection rate of 19 out of 350 patients. All of these patients were treated with antibiotics and catheter removal, and none required surgical intervention [330].

Intrathecal analgesia has been less well studied, with Lundborg reporting a series of three patients with highly refractory CRPS who did not have a good clinical response to intrathecal bupivacaine. In spite of initial analgesia, all of these patients had progression of their CRPS (level 4 evidence) [331]. In a small subset of patients ($N = 7$) with refractory CRPS and severe dystonia, van Hilten et al. had good outcomes of analgesia with functional restoration using intrathecal baclofen injected in a double-blind fashion, followed by intrathecal infusion (level 3 evidence for intrathecal baclofen in *dystonic* CRPS) [332].

Many have adopted epidural infusion techniques as next-line therapy for patients failing intermittent blocks with moderate evidence for efficacy of epidural clonidine. This

procedure is technically easy to perform, with level 3 evidence supporting epidural clonidine infusion as outlined earlier. Some centers have utilized the plexus infusions described earlier, but the epidural techniques are more common. The main drawback to these infusion techniques is the rate of infection, which remains to be defined by further prospective study on infusion techniques in CRPS patients. Intrathecal baclofen infusion (via implanted pump) is advised in patients with a dystonic component to their CRPS, with level 3 evidence supporting this treatment. Intrathecal infusion for CRPS without dystonia has only limited supporting literature.

Neurolytic Sympathetic Blocks (Radio Frequency/Alcohol-Phenol)

Surgical sympathectomy has been utilized to treat SMP and other hyperactive sympathetic syndromes (including hyperhidrosis and Raynaud's phenomenon among others) since 1889 and historically was an important treatment for RSD [302,333]. These surgical techniques were performed in an open operation, but recently, both upper and lower extremity sympathectomy are being done via endoscopy with a minimally invasive technique, as initially described in the 1950s and recently "re-discovered" in a small prospective case series (level 3 evidence) [303]. More recently, radio frequency (RF) techniques have been described in a large case series (level 3 evidence) [334].

Kim et al. reviewed the available literature for surgical sympathectomy and found an initial failure rate of up to 35%, usually ascribed to poor patient selection [333]. Other possibilities for failure to achieve analgesia include incorrect diagnosis, inadequate resection, reinnervation, and contralateral innervation. In light of the difficulty of clinically assessing adequacy of sympathetic blockade based on clinical criterion, it is easy to understand the difficulty in assessing the local anesthetic sympathetic block's predictive value for surgical sympathectomy [313]. The ablative sympathectomy techniques have been available for many years, but as yet, no high-level evidence exists to support their widespread use.

Another significant problem with ablative sympathectomy is recurrence of former symptoms and "post-sympathectomy neuralgia" 6 months to 2 years post-sympathectomy. These post-ablative neuralgic syndromes may respond to re-resection or SCS [335]. The reported incidence of this clinical phenomenon is up to 44% in a series of open sympathectomy for causalgia [336]. Due to the refractory nature of these post-neurectomy pain syndromes, neurectomy is not advocated by this author.

Wilkinson reports the largest series of percutaneous RF lesioning of the thoracic T2 distribution sympathetic outflow (RF sympathectomy), with over 350 procedures performed with 86% signs of sustained sympathectomy at 3-year follow-up, without any assessment of clinical analgesic or functional outcomes (level 3 evidence for *interruption of sympathetic activity* in a prolonged fashion with RF techniques) [334]. Wilkinson reports difficulty with lumbar percutaneous RF techniques due to variability of the lumbar anatomy vs the thoracic ganglion. He also reports a low rate of postprocedure neuralgic syndromes (around 5%), although this is recorded in an unpublished data format within a book chapter [333]. This author could find no published data yet on pulsed RF sympathetic ganglion techniques.

Sympathetic ablation techniques have been advocated for many years, mainly by surgeons. In general, neurodestructive techniques to treat chronic pain syndromes due to deafferentation syndromes or "post-sympathectomy neuralgia" have fallen from favor. The same holds true for neurolytic blocks utilizing alcohol or phenol, which have largely been relegated to the terminally ill. The RF ablative techniques are much more controllable than neurolytic solution injections and less invasive than surgical ablation. Preliminary reports in the form of case series are promising, but the exact role of RF ablation sympathectomy vs periodic blockade vs neurostimulation is uncertain.

Neurostimulation

Research of high quality regarding SCS and CRPS is limited, but existing data is positive in terms of pain reduction, quality of life, analgesic usage and function.

Kemler et al. published a prospective, randomized, comparative trial to compare SCS vs conservative therapy for CRPS [337]. Patients with a 6-month history of CRPS of the upper extremities were randomized to undergo trial SCS (and implant if successful) + physiotherapy vs physiotherapy alone. In this study, 36 patients were assigned to receive a PT program together with SCS, whereas 18 patients were assigned to receive therapy alone. In 24 of the 36 patients randomized to SCS, the trial was successful, and permanent implantation was performed. At a 6-month follow-up assessment, the patients in the SCS group had a significant reduction in pain, and a significant percentage graded the global perceived effect as improved. However, there were no clinically significant improvements in functional status. The authors concluded that in the short-term, SCS reduces pain and improves the quality of life for patients with CRPS involving the upper extremities. The improvement in pain scores, global perceived effect, and overall health-related quality of life, although modest, were significant and sustained for 2 years follow-up as published in a subsequent manuscript (level 2 evidence) [338]. Further analysis of this patient subgroup has revealed no difference in outcomes for cervical vs lumbar SCS in terms of effectiveness or complication rate [339].

Several important case series have been published on the use of neurostimulation in the treatment of CRPS. Calvillo et al. reported a series of 36 patients with advanced stages of CRPS (at least 2 years duration) who had undergone successful SCS trial (>50% reduction of pain) [340]. They were treated with either SCS or peripheral nerve stimulation, and in some cases, with both modalities.

Thirty-six months after implantation, the reported pain measured on VASs was an average of 53% better, and this change was statistically significant. Analgesic consumption decreased in the majority of patients. Forty-one percent of patients had returned to work (on modified duty). The authors concluded that in late stages of CRPS, neurostimulation (with SCS or PNS) is a reasonable option when alternative therapies have failed. Two groups have critically reviewed these and other studies and case report literature and concluded that there is moderate evidence that SCS is effective in treating CRPS-related pain (Table 11) [341,342].

With a new understanding of CRPS as encompassing *both* SIP and SMP, sympatholysis remains an important diagnostic and therapeutic modality (in the SIP subgroup). Because of the considerable difficulty in "clinically assessing" the successful sympathetic block and because "clinically successful" blocks provide varying degrees of sympatholysis [313], the role of local anesthetic injection sympathetic blockade vs IVRA, IV, or epidural sympatholysis is unknown and largely based on local practice patterns. Additionally, with the notable paucity of good quality supportive outcomes studies, the clinician is left to utilize these blocks or sympathectomy-inducing infusions within the context of a broad algorithm of treatment while awaiting further pathophysiological data and outcomes research to guide our practice to the most beneficial treatments.

The decision to proceed with RF ablative techniques vs other nondestructive alternatives is a complex one, with less evidence for the ablative vs augmentative treatments. Due to the adverse long-term post-sympathectomy syndromes, this author currently recommends against surgical ablative sympathectomy. Future studies may expand on the role of pulsed RF (cold RF) techniques or such unstudied techniques as cryosurgery as alternative therapies to treat SMP.

Our recommended strategy (and tactic) is to use interventional treatments for CRPS patients who are having difficulty either starting or progressing in the functional restoration/interdisciplinary algorithm. If patients are not progressing because of high pain levels (especially associated with autonomic dysfunction), then a stepwise progression—from the less invasive blocks to infusions or catheter infusion therapies, and ultimately perhaps to neurostimulation—is recommended in order to facilitate the patient's functional improvement and pain control. One suggested algorithm developed by an expert panel for the integrated use of these procedures is shown in Figure 3 and has been previously published [53].

Table 11 Summary of evidence for interventional pain management of complex regional pain syndrome (modified from van Eijs et al. [343])

Technique	Score
Stellate ganglion block	3
Lumbar sympathetic block	3
Brachial plexus block	4
Epidural analgesic infusion	3
Spinal cord stimulation	2
Peripheral nerve stimulation	3

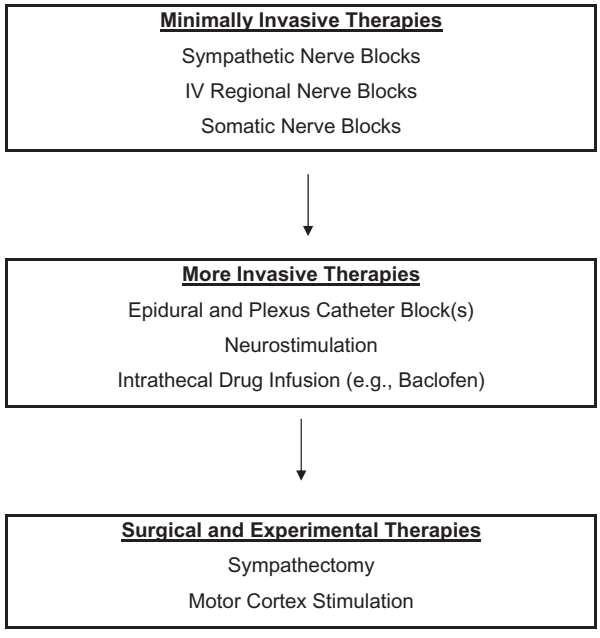

Figure 3 Interventional pain treatment algorithm for complex regional pain syndrome (modified from Stanton-Hicks et al. [53]). Inadequate or partial response to any given therapy should lead to a stepwise progression down through theses modalities (moving from less to more invasive) in conjunction with other noninterventional treatments. IV = intravenous.

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