J Clin Psychol Med Settings (2013) 20:247–254
DOI 10.1007/s10880-012-9322-3

A Review of Psychosocial Factors in Complex Regional Pain Syndrome

Jessica A. Lohnberg · Elizabeth M. Altmaier

Published online: 9 September 2012

Abstract Complex regional pain syndrome (CRPS) is a disabling pain condition poorly understood by medical professionals. Because CRPS is particularly enigmatic, and has significant impact on patient function, researchers have examined psychological processes present among patients with this diagnosis. This systematic review examines psychosocial factors associated with CRPS, both predictors and sequelae. Our conclusions are that CRPS is associated with negative outcomes, both psychological (e.g., increased depression and anxiety) and psychosocial (e.g., reduced quality of life, impaired occupational function) in nature. However, research does not reveal support for specific personality or psychopathology predictors of the condition.

Keywords Causalgia · Chronic pain · Complex regional pain syndrome · Psychosocial factors · Reflex sympathetic dystrophy (RSD)

CRPS is a pain syndrome that develops as a disproportionate consequence of extremity trauma or nerve lesion (Baron & Wasner, 2001). According to the National Institute of Neurological Disorders and Stroke (NINDS, 2008), pain is experienced in excess of what one would expect given the injury that occurred and most often affects an extremity such as an arm, hand, leg or foot. NINDS additionally describes typical features of the disorder as dramatic changes in color and temperature of the skin over the affected body part, intense burning pain, skin sensitivity, sweating, and swelling. While CRPS has properties similar to that of a peripheral neuropathy (e.g., persistent neuropathic pain often peripherally distributed), it is distinguished by the sudomotor or vasomotor symptoms that accompany the syndrome (Merskey & Bogduk, 1994). CRPS is unique compared to some of the other chronic pain conditions in that several of the distinguishing features are these observable signs (e.g., changes in skin color or temperature) that occur in addition to the subjective symptom of pain.

CRPS challenges the healthcare community with its poorly understood etiology and complex constellation of symptoms accompanied by psychological comorbidities (Lynch, 1992). Because of the uncertain origins of the condition, professionals have considered the role of psychological factors, either in the development of the condition or in its continuance. This review begins with a brief history and description of CRPS along with known etiology, pathophysiology, and prevalence. The review then focuses on findings regarding the role of psychosocial factors in CRPS: anxiety, depression, general distress, disability, quality of life, and psychiatric conditions. In order to identify relevant research, the following search criteria were used: *complex regional pain syndrome* (CRPS) or *reflex sympathetic dystrophy* (RSD) combined with *depression, anxiety, disability, quality of life,* or *psychopathology.* Since earlier reviews (Ochoa, 1992; Van Houdenhove et al., 1992; Weiss, 1994) were published

This manuscript is based on a doctoral dissertation conducted at the University of Iowa.

J. A. Lohnberg (✉)
Psychology Service, VA Palo Alto Health Care System, (116B), 3801 Miranda Ave., Palo Alto, CA, USA
e-mail: jessica-lohnberg@uiowa.edu

E. M. Altmaier
Department of Psychological and Quantitative Foundations, University of Iowa, Iowa City, IA, USA

E. M. Altmaier
Department of Community and Behavioral Health, University of Iowa, Iowa City, IA, USA

prior to the development of current diagnostic criteria and terminology, articles selected for review concerning psychosocial factors in CRPS were published after 1994 in order to present a more updated review of the role of psychosocial factors in this disorder. The reference lists of selected articles were also reviewed to identify additional studies for inclusion in this review. Studies whose primary focus was the role of psychosocial factors in CRPS were retained for this review. Dissertations and other unpublished research were not included.

CRPS: History, Etiology, Pathophysiology

The first documented descriptions of the symptoms of CRPS date back to the American Civil War (see Feliu & Edwards, 2010) where an exaggerated presentation of pain followed battlefield injury. Over the years, signs and symptoms currently known as CRPS have been labeled causalgia, Sudeck's atrophy, osteodystrophy, shoulder-hand syndrome, algodystrophy, RSD, and sympathetically-maintained pain (Borg, 1996; Turner-Stokes, 2002). The evolution of names reflects poorly understood mechanisms underlying the condition as well as disagreement on a universally accepted set of diagnostic criteria. In 1995, following a consensus conference, Stanton-Hicks et al. presented a taxonomic system for diagnosis along with the proposed name change from RSD and causalgia to CRPS.

The International Association for the Study of Pain (IASP) developed the following four diagnostic criteria: (1) the presence of an initiating noxious event or cause of immobilization; (2) continuing pain, allodynia, or hyperalgesia in which the pain is disproportionate to any known inciting event; (3) evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain; and (4) the diagnosis is excluded by the existence of other conditions that would account for the degree of pain and dysfunction (Merskey & Bogduk, 1994). In addition, IASP noted that if the condition does not include major nerve damage, the diagnosis of CRPS I is given, whereas the diagnosis of CRPS II includes the presence of major nerve damage.

The most recent set of diagnostic criteria was proposed by Harden, Bruehl, Stanton-Hicks, and Wilson (2007) after determining that the previous CRPS diagnostic criteria were found to be sensitive (i.e., able to detect actual cases) but not adequately specific. Harden et al. based their criteria on the results of a diagnostic criteria workshop held in Budapest, Hungary in 2003 to reevaluate the terminology of CRPS. Based on this workshop, the committee proposed the following definition of CRPS:

> "CRPS describes an array of painful conditions that are 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" (p. 330).

In order to make a full clinical diagnosis, Harden et al. proposed that the following four criteria be met (known as the Budapest criteria): (1) continuing pain that is disproportionate to the inciting event; (2) at least one *symptom* in three of the four following categories: (a) sensory: reports of hyperesthesia and/or allodynia, (b) vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry, (c) sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry, (d) motor/trophic: reports of decreased range of motion and/or motor dysfunction and/or trophic changes; (3) at least one *sign* in two or more of the following categories: (a) sensory: evidence of hyperalgesia and/or allodynia, (b) vasomotor: evidence of temperature asymmetry and/or skin color changes and/or sweating asymmetry, (c) sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry, (d) motor/trophic: evidence of decreased range of motion and/or motor dysfunction and/or trophic changes; and (4) there is no other diagnosis that better explains the signs and symptoms. The Budapest Criteria have been validated compared to IASP criteria as having enhanced specificity with regard to diagnosis of CRPS (Harden et al., 2010).

Though the specifics of what constitutes an official diagnosis have varied (e.g., number of signs or symptoms required, exact temperature difference), certain key signs and symptoms are common among the diagnostic criteria. Brunner, Lienhardt, Kissling, Bachmann, and Weber (2008) surveyed international experts for their opinion on which parameters were most important in determining diagnosis and follow-up of CRPS type I patients. Experts agreed that pain, signs of edema and color change, and decreased mobility were the most relevant diagnostic parameters. The Budapest criteria outlined above have not yet been accepted by the IASP; therefore, a clinically accurate diagnosis can currently be made using the existing IASP criteria.

CRPS type I, previously known as RSD, is more common than type II. The condition was first termed Sudeck's dystrophy because it was described by Sudeck in the early twentieth century (Baron & Wasner, 2001). Because the name RSD did not accurately reflect the pathophysiology of the disorder, the name was changed to CRPS to highlight the complex interaction of somatic, psychological, and behavioral factors along with the regional distribution of

symptoms (Turner-Stokes, 2002). CRPS type I can begin with an inciting event such as a fracture, soft tissue damage, low-grade infection, frostbite, burns, or even stroke or myocardial infarction (Baron, Levine, & Fields, 1999). Because CRPS type I often responds to a sympathetic nerve block and shows signs of autonomic nervous system abnormalities, researchers have suggested the syndrome is an exaggerated sympathetic response to post-traumatic inflammatory responses instead of sympathetic damage (Baron et al., 1999; Turner-Stokes, 2002).

CRPS type II, previously known as causalgia, has the same signs and symptoms as type I, but is distinguished by the identification of a peripheral nerve injury (Nelson, 2002), usually occurring to large named nerves such as the median or sciatic nerve (Stanton-Hicks et al., 1995). The pain, however, may extend beyond the distribution of the injured nerve to a general region of the body (Baron & Wasner, 2001). Because the other symptoms (swelling, temperature changes, sweating, hypersensitivity to pain) are similar to CRPS type I, the name was changed from causalgia to CRPS type II (Baron & Wasner, 2001).

There are several currently held theories regarding contributing factors in the etiology of CRPS. These hypotheses include disuse of the affected body part following an injury (Galer, Schwartz, & Allen, 2001), myofasical dysfunction (Galer et al., 2001), and exaggerated regional inflammatory response to injury (Veldman, Reynen, Arntz, & Goris,1993). The specific symptoms in CRPS have also been linked to sympathetic nervous system dysfunction (Baron & Wasner, 2001). The response of symptoms to sympathetic nerve blocks supports this explanation (Turner-Stokes, 2002); however, it does not explain why certain individuals develop the syndrome and others do not or the striking association and interaction with psychological factors.

Although CRPS can develop following common injuries and events, the actual number of people who develop CRPS is small. It has been shown to occur in 20–90 persons per 100,000 compared to fibromyalgia (FM), another chronic pain condition, which occurs in 700–3,200 persons per 100,000 (Marinus & Van Hilten, 2006). Furthermore, because CRPS pathophysiology is not fully understood, it is hard to determine who is at risk for developing the syndrome. Only a few epidemiological studies have explored the incidence of the condition and the demographics of the individuals who develop the condition.

Sandroni, Benrud-Larson, McClelland, and Low (2003) performed the first population based study to establish the incidence, prevalence, natural history, and response to treatment of CRPS type I in Olmsted County, Minnesota. They determined an incidence of 5.46 per 100,000 person years and a period prevalence of 20.57 per 100,000. In their population, CRPS type I was more likely in females than males (4:1) and the median age at onset was 46 years old. The upper limb was affected twice as often as the lower limb and a fracture was the most common inciting incident. Another study (de Mos et al., 2007) that investigated the incidence of the disorder via medical record review in the Netherlands estimated the incidence to be 26.2 per 100,000 persons. These authors found that women were affected three times more often than men (3.4:1) and the highest incidence occurred in females in the age category 61–70 years old. Other demographics noted were that the upper extremity was the most affected body part and a fracture was the most common precipitating event. While this study investigated the records of 600,000 patients, the sample was exclusively from the Netherlands and the results differ from other epidemiological studies performed. Of note, this study did not specify which type of CRPS was included while the previously described population-based study (Sandroni et al., 2003) limited their investigation to CRPS type I.

More recently, an internet-based study focused on a diverse geographic population (Sharma, Agarwal, Broatch, & Raja, 2009) and the researchers questioned individuals with CRPS about symptoms, demographics, treatments, and psychosocial factors. Eight hundred and eighty eight individuals met inclusion criteria and completed the survey. In this sample, women were significantly more affected than men (5:1). The precipitating event was most commonly trauma, lower extremities (56 %) and upper extremities (38 %) were primarily affected, and the syndrome usually progressed to other body areas. Many participants were refractory to both pharmacological and nonpharmacological interventions. The authors noted a disability rate of approximately 62 % with significant interference in sleep, mobility, and self-care.

Certain medical treatment procedures function to assist in a diagnosis of CRPS based on whether the procedure relieves symptoms. Pappagallo and Rosenberg (2001) described procedures for both diagnostic and treatment purposes: a stellate ganglion block for upper extremity pain, a lumbar sympathetic nerve block for lower extremity pain, and pharmacotherapy. Pappagallo and Rosenberg noted that antiepileptic drugs, opioids, NMDA antagonists, cannabinoids, antidepressants (TCAs and SSRIs), topical analgesics, and biphosphates have been used for treatment of CRPS. In addition, physical therapy and rehabilitation are incorporated into treatment since immobilization has been hypothesized to be a contributing factor to the development of CRPS.

Borg (1996) discussed the use of sympathetic nervous system blockades, physical therapy, and drugs such as calcitonin, corticosteroids, beta-blockers, nifedipine, and TCAs in the treatment of CRPS. In reviewing pharmacologic treatments used for CRPS, Baron and Wasner (2001) noted that only glucocorticoids, transdermal clonidine, intrathecal baclofen, and gabapentin have been shown to

provide relief to CRPS patients. Although there are additional medications that show promise in the treatment of CRPS, there are limited studies on the efficacy of certain drugs. In addition, the ones that have shown benefit often only help with some of the symptoms.

Of particular note is the finding that time since diagnosis predicts poor response to any treatment. In one study (Schwartzman, Erwin, & Alexander, 2009) 1 year after diagnosis, signs and symptoms of the syndrome had become well developed and were refractory to most current therapies. This finding demonstrates the importance of early detection and intervention for optimal treatment, but it also suggests that factors other than pathophysiological are influencing the course of the disease.

Psychosocial Predictors and Sequelae

Debate concerning whether CRPS is a legitimate pain condition or a result of a psychiatric state has stimulated researchers to study differences between CRPS and non-CRPS pain patients. Several researchers (Beerthuizen, van't Spijker, Huygen, Klein, & de Wit, 2009; Feliu & Edwards, 2010; Steger, Bruehl, & Harden, 1999) have considered whether CRPS patients have predisposing diatheses or personality traits that lead to the development of the disorder without arriving at a definitive response. A related line of research considers whether personality factors play an influential role in either the development or the maintenance of the syndrome. This section reviews and critiques studies that have examined these hypotheses regarding the role of psychosocial factors in CRPS.

de Mos et al. (2008) evaluated prior medical and psychological conditions that might serve as risk factors for CRPS. Participants included CRPS patients ($N = 186$) identified by search of the Dutch Health Care System who were compared to age, gender, and injury-matched controls ($N = 697$). They found that history of migraine headaches or osteoporosis was related to CRPS and that CRPS patients in the past year had reported more menstrual cycle-related problems and neuropathies. Of the medical conditions that have a potentially similar pathogenesis/etiology as CRPS, only asthma was found to be associated. de Mos et al. also evaluated preexisting psychological factors including depression, anxiety, psychosocial problems, and stress and found none of them to be associated with CRPS onset. Because the authors investigated medical records, they did not have to rely on self-report of preexisting conditions being affected by recall bias. One limitation of the study was that they determined preexisting conditions by categorizing each general practitioner contact into some type of episode or medical problem. This method might minimize reported psychological conditions since each visit was to a physician, and if anxiety and depression were not the focus of the physician contact, those conditions would not have been classified even if the patients met psychiatric diagnostic criteria.

Limited research prospectively has also assessed the association between depression and pain among CRPS patients. Feldman, Downey, and Schaffer-Neitz (1999) considered the relationship between daily pain, negative mood, and social support in a prospective daily diary study. Participants ($N = 109$) with RSD (CRPS, type I) completed 28 daily diaries with responses to questions about pain, mood and social support. Overall, findings revealed that previous day pain was a significant predictor of next day negative and depressed mood, anxiety, and anger. Previous day negative mood did not significantly predict next day pain but previous day depressed mood did. Because depressed mood both predicted pain and resulted from pain, the causal relationship between them cannot be established.

Another way to determine whether depression affects pain is to evaluate whether treatment of the depression can alleviate pain symptoms. McDaniel (2003) presented three case reports in which CRPS patients (onset after fractures) with comorbid depression sought electroconvulsive therapy (ECT) for depression. In each of the cases, ECT treatments resolved both the depression and the CRPS symptoms. Because of the previously suggested central nervous system etiology (Turner-Stokes, 2002), these results cannot rule out the idea that the ECT might directly affect CRPS pathology irrespective of the alleviation of depression.

Geertzen, de Bruijn-Kofman, de Bruijn, van de Wiel, and Dijkstra (1998) examined the role that stressful life events and psychological dysfunction may play in the pathogenesis of CRPS. The authors compared a study population of CRPS patients in the early phase of the syndrome ($N = 24$) with a control group of preoperative patients with hand pathology ($N = 42$). Both groups were interviewed by a psychologist prior to treatment of CRPS or hand pathology to assess history of stressful life events. Results showed that stressful life events were more frequently present in the CRPS group compared to the control group. In addition, female CRPS patients scored higher in depression, feelings of inadequacy, and emotional instability than the control group, and male CRPS patients were higher in anxiety than the control group. Harden et al. (2003) completed a prospective study of psychological factors predicting the development of CRPS following total knee arthroplasty (TKA). Because this surgery is associated with onset of CRPS, the authors studied a sample of patients ($N = 77$) who were scheduled to undergo TKA and administered assessments preoperatively, and at 1 month ($N = 77$), 3 months ($N = 69$), and 6 months follow-up ($N = 55$). At each of the assessment periods, patients filled out measures of pain, anxiety and depression.

Prevalence of signs and symptoms meeting criteria for CRPS was 21 % at 1 month, 13 % at 3 months, and 12.7 % at 6 months. Although CRPS patients reported more depression and anxiety at 1 month and 6 months, respectively, pre-TKA anxiety and depression did not predict the development of CRPS, whereas preoperative pain did predict CRPS status at 3-months and 6-months. Overall, these results suggest that depression and anxiety follow the onset of CRPS and are not predispositional factors.

Another prospective study examining risk factors for the development of CRPS was conducted by Dijkstra, Groothoff, ten Duis, and Geertzen (2003). These authors followed 88 patients who reported to an emergency department with a fracture of the distal radius. Participants were queried concerning risk factors associated with their injury at the time of the fracture, such as cast changes and repositions. Patients also provided data on social life events and psychological history. Only one patient developed CRPS and she did not report any psychological or life event abnormalities.

Puchalski and Zyluk (2005) conducted a prospective study of 62 patients who underwent surgical closed reduction and percutaneous fixation with K-wires of a displaced radial fracture. In this study participants were administered psychological questionnaires the day after surgery and followed for 2 months to assess signs and symptoms of CRPS. Nine patients developed CRPS and 41 did not over the two month follow up, but no differences between these groups were demonstrated on personality or psychological factors, thus supporting previous findings that fail to establish a link between preexisting psychological symptoms and a greater likelihood of developing CRPS.

Another psychological factor implicated in the development of CRPS is psychopathology. In research selected for review summarized below, psychopathology within CRPS patients is compared to that displayed by other pain patients. Van der Laan, van Spaendock, Horstink, and Goris (1999) considered patients with CRPS-dystonia (a subset of CRPS patients who additionally have fixed abnormal posture of the affected extremity) and a population of patients suffering from a somatic disorder that required rehabilitation. The authors found that insomnia was higher in the CRPS-dystonia population than in the rehabilitation group, and that the rehabilitation group had higher somatization scores than the CRPS-dystonia group. They concluded that their results suggest a psychogenic factor in the presentation of CRPS-dystonia. In a better controlled study, Bruehl, Husfeldt, Lubenow, Nath, and Ivankovich (1996) examined psychological differences between RSD patients ($N = 34$), non-RSD chronic low back pain (CLBP) patients ($N = 165$), and non-RSD limb pain patients ($N = 50$). To better isolate the potential psychological differences among the specific groups, the authors controlled statistically for age and pain duration. RSD patients reported more somatization and phobic anxiety than LBP patients and also reported more use of diversion of attention as a coping strategy than LBP patients. The only difference found between RSD and non-RSD limb pain patients was greater somatization among the RSD group. Although the authors concluded that RSD patients were more dysfunctional than other chronic pain patients, the RSD patients and limb pain patients were similar on almost all measures, which confound the authors' statements about RSD patients presenting with impaired psychological profiles.

Verbunt, Pernot, and Smeets (2008) examined disability and quality of life in FM patients. Although the purpose of the study was to compare FM patients to other chronic pain patients, one comparison group was CRPS patients. FM patients ($N = 54$) were compared to chronic CLBP patients ($N = 35$) and CRPS patients ($N = 22$) on psychological distress and quality of life. The FM group reported significantly greater total psychological distress as compared to CRPS and CLBP patients. FM patients also reported a lower quality of life than published data on other pain populations. This study provides some support to the hypothesis that CRPS patients are not psychologically more disturbed than other chronic pain patients, though conclusions from this study must be weighed against its limitations.

A narrative literature review compared CRPS type I patients to FM and Repetitive Strain Injury (RSI) patients by evaluating the existing literature on these conditions. Marinus and Van Hilten (2006) identified studies on the clinical manifestations, disease course, risk factors, and demographic characteristics for the three pain groups (59 studies on CRPS, 73 on FM, seven on a specific RSI). Published data suggested similarities in age distribution, male–female ratio, pain characteristics, and sensory signs and symptoms among the three conditions. The authors conclude that the numerous similarities may suggest a common pathway for these three conditions is involved. While the previous study focused on disease characteristics of several conditions, Shiri, Tsenter, Livai, Schwartz, and Vatine (2003) compared psychological profiles of CRPS patients ($N = 17$) and Conversion Disorder (CD) patients ($N = 20$). CRPS and CD patients were recruited from Hadassah University Hospital in Jerusalem, Israel and were interviewed and tested by rehabilitation psychologists. Results showed no statistical differences between personality profiles of both patient groups. In addition, based on interviews and psychological testing, the authors suggested that about one third of patients from both groups suffered from an Axis I disorder, most often depression or post-traumatic stress disorder (PTSD). The significant similarities between the CRPS and the CD groups suggest that

CRPS has marked somatoform features. Of note, the majority of the CRPS sample was male (94 %) compared to the CD sample (30 % male). Given previous studies that rely on primarily female samples (consistent with the gender distribution of CRPS), these results should be tempered against potential gender differences.

An additional area of study is the health-related quality of life of CRPS patients over time. Savaş, Baloglu, Ay, and Cerçi (2008) compared CRPS type 1 patients ($N = 30$) discharged with good outcome to healthy controls ($N = 38$). Participants completed measures on arm, shoulder and hand function; physical measures including range of motion and touch perception threshold; and health-related quality of life. None of the CRPS patients met full criteria for the disorder at the time of the study, but only three were symptom free. CRPS patients exhibited decreased grip strength, increased disability, and increased touch perception threshold compared to controls. On quality of life measures, CRPS patients reported impaired physical function, increased bodily pain, and reduced social and emotional function compared to controls. Of equal interest in this study is that CRPS patients demonstrated some ongoing symptoms that continued to cause pain and disability, but were not different from normal controls on other measures including mental health and vitality. It may be that a limited number of signs and symptoms associated with CRPS are responsible for the increased pathology and decreased quality of life noted in other studies of the psychological effects of CRPS.

The issue of limitations created in employment among CRPS patients after treatment is similar to that of any patient population with ongoing fluctuating symptomology such as FM or CLBP. However, empirical studies of this issue are limited. In an early small-sample study, Galer, Henderson, Perander, and Jensen (2000) surveyed 21 patients who had been given a diagnosis of CRPS. Quality of life was assessed as the degree to which pain interfered with daily activities, such as work, sleep, self-care, and social activities. Patients reported significant interference with functional activities, and more than 50 % of the patients reported substantial interference with all daily activities except self-care. Loss of or limited physical functioning is common among chronic pain disorders. A review of the psychological and behavioral aspects of CRPS (Bruehl & Chung, 2006) argues that the disuse associated with CRPS may be a significant contributor to the impairments in quality of life. Additionally, work withdrawal or avoidance provoked by pain may lead to emotional arousal, thus exacerbating the pain and maintaining dysfunction. This suggests that the physical disability associated with CRPS may account for variations in mood and quality of life in affected individuals.

Summary and Conclusions

Bruehl (2001) points out that although the specific medical pathogenic mechanisms of CRPS remain unclear, "absence of definitive evidence for the disorder may be incorrectly assumed to be evidence of absence of the disorder" (p. 279). Researchers and clinicians agree on the biopsychosocial nature of pain and the reciprocal relationships between physical and psychosocial factors. While the precipitating role of psychosocial factors in the development of CRPS is not fully supported, it is clear that CRPS results in psychological sequelae such as depression, anxiety, reduced quality of life, and functional/occupational disability for a number of individuals. The important clinical implications of this review are that an interdisciplinary approach is crucial in understanding and treating patients with CRPS. Addressing the physical/medical as well as psychosocial factors involved in patients with CRPS is an essential goal. Factors that have been identified that are critical for treatment planning are early identification and intervention; reduction of both preexisting depression and anxiety as well as depression and anxiety in response to pain; and focus on occupational and functional impairment.

It should also be noted that current research advances are illuminating the connections between neuroendocrine and immunological processes that are psychologically moderated. As examples, Miller, Chen, and Cole (2009) have identified depression as a key contributor to the development of increased levels of neuroendocrine mediators and immune alteration; these processes are then linked to delayed healing and increased systemic inflammatory activity. More recent advances (O'Connell, Rao, & Baltimore, 2012) have targeted a class of noncoding RNAs in managing the inflammatory process. Treatment for CRPS will likely make significant advances as both prevention and remediation strategies reduce the likelihood of disease onset and diminish functional impairment after onset.

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