CLINICAL PRACTICE

Complex Regional Pain Syndrome

Andreas Goebel, M.D., Ph.D.[1,2]

This Journal *feature begins with a case vignette highlighting a rare clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

Author affiliations are listed at the end of the article. Andreas Goebel can be contacted at andreas.goebel@nhs.net or andreasgoebel@rocketmail.com or at the University Hospital Aintree, Clinical Sciences Bldg., Lower Ln., Liverpool L9 7AL, United Kingdom.

N Engl J Med 2025;393:2338-48.
DOI: 10.1056/NEJMcp2415752

CME

A 52-year-old woman with well-controlled mild asthma presents with an 8-month history of extreme pain in her right wrist, which had been triggered by a carpal tunnel release operation. Although the earlier pins-and-needles sensations in her hand were substantially reduced by the carpal tunnel release, she now describes her pain as burning and "like a vise." The pain frequently extends to her hand and fingers, with occasional shooting into the forearm. The average pain intensity in the wrist is rated 8 on a scale of 0 to 10 (where 10 indicates the worst pain). Her right shoulder aches, with the pain intensity rated 6 on a 10-point scale. Her pain wakes her at night. Pressure on her skin is painful, and she reports fluctuating swelling across the affected region. Her skin temperature alternates between warm and cold as compared with the unaffected hand, and there is occasional mottled-blue discoloration. Her hand movement is stiff and highly painful. Analgesic medications seem to be ineffective. She has continued biweekly physical therapy, but it causes extreme pain. Recently, she noticed a reduction in her hand swelling without a change in pain. The results of an extensive workup including a physical examination, repeat nerve-conduction studies, inflammatory markers, and cervical spine magnetic resonance imaging (MRI) are all unremarkable. Radiography of the hand and wrist shows patchy osteopenia around the wrist joints; in addition, an MRI of the wrist shows mild soft-tissue swelling. How would you manage this patient's condition?

THE CLINICAL PROBLEM

Complex regional pain syndrome (CRPS) is characterized by substantial pain in a distal limb. Approximately 90% of cases are triggered by physical limb trauma such as an injury (most commonly a fracture) or operation; the condition typically commences immediately to less than 1 month after the inciting event.[1,2] CRPS is associated with two or more objectively elicited abnormalities in the affected region, such as tenderness, color change, or swelling (Fig. 1 and Table 1). CRPS is classified in the *International Classification of Diseases, 11th Revision*, as a "chronic primary pain" disorder alongside chronic migraines, fibromyalgia syndrome, and other disorders. These disorders are unique conditions and not secondary to painful somatic diseases or to psychiatric causes. In addition to involving pain, chronic primary pain disorders are identified by their association with substantial functional disability or psychological distress.[9] The predominant mechanism for chronic primary pain disorders has recently been termed "nociplastic pain," which denotes pain caused by a dysfunction of the peripheral nervous system, central nervous system, or both (Fig. 2). The history of the nomenclature for this syndrome is extensive and is summarized in Table S1 in

KEY POINTS

COMPLEX REGIONAL PAIN SYNDROME

- Complex regional pain syndrome (CRPS) is a rare post-traumatic chronic pain condition that affects a distal limb and is classified in the *International Classification of Diseases, 11th Revision*, as "chronic primary pain"; the condition may be autoimmune mediated.
- CRPS is diagnosed according to the Budapest criteria, which require the presence of objective limb abnormalities in two of four categories: sensory, vasomotor, edema or sudomotor, and motor or trophic.
- Approximately 80% of patients have substantial improvement within 18 months after disease onset; later improvement is rare.
- Patient information should emphasize the nerve-function–related cause of CRPS that explains the relentless pain despite no or minor tissue change.
- Rehabilitative treatment with CRPS-specific physical and occupational therapy is key to improving function in the impaired limb.
- Treatment with simple analgesic drugs, tricyclic agents, and serotonin–norepinephrine reuptake inhibitors may improve quality of life but will typically incompletely reduce pain. Multidisciplinary pain-management treatment that follows the principles of cognitive behavioral therapy and spinal cord stimulator treatment — in persistent CRPS — can be offered at specialist centers.

the Supplementary Appendix (available with the full text of this article at NEJM.org).

Both the Food and Drug Administration and the European Medicines Agency have designated CRPS as an orphan disease because of its low prevalence. The condition affects all races. A Dutch population–representative, retrospective, case–control study conducted with general practice registries showed that CRPS (when confirmed by a visit with an expert) had the greatest association with osteoporosis (odds ratio, 5.6; 95% confidence interval [CI], 1.8 to 17.1), asthma (odds ratio, 3.0; 95% CI, 1.1 to 8.0), and menstrual cycle–related disorders (odds ratio, 3.0; 95% CI, 1.1 to 8.7) in the year before disease onset; the study also showed a general association of CRPS with migraines (odds ratio, 2.6; 95% CI, 1.1 to 6.5)[10] and long-term use of angiotensin-converting–enzyme inhibitor medication (odds ratio, 4.6; 95% CI, 1.1 to 19.3).[11] The peak incidence of CRPS as determined in this study occurred when patients were in their 60s.[12] Approximately 80% of cases are monophasic disorders (involving a single episode without relapse) that improve substantially within 18 months after disease onset.[13] An enduring motor dysfunction, including reduced grip strength and other symptoms such as cold sensitivity, may occur as a post-CRPS syndrome associated with functional impairment.[14] Patients presenting to specialized care centers are typically in their 40s or 50s and often have persistent CRPS (lasting longer than approximately 18 months),[1] which is a considerably disabling long-term condition. Spread of CRPS to other limbs (in 5% of patients)[15] or pain in additional areas of the body will develop later in some patients. Risk factors for worse outcomes in patients with early CRPS (i.e., within the first few months after disease onset) include higher pain intensity, more-severe disability, and anxiety.[16] CRPS is rare in children and adolescents, in whom symptoms typically begin without CRPS-triggering trauma or after only minor trauma.[17]

Understanding of the pathophysiological features of CRPS has progressed over the past decade.[18] CRPS-associated regional vasomotor and sudomotor (related to sweat glands) changes are thought to be caused by both neurogenic inflammation and abnormal regional autonomic activation. Neurogenic inflammation is an inflammatory response in tissue caused by the antidromic release of neuropeptides, including substance P and calcitonin gene–related peptide, from sensory nerve endings, which causes swelling, warmth, redness, nail and hair growth, and hyperhidrosis. Abnormal regional autonomic activation is an abnormal activation of regional autonomic nerves through unknown mechanisms or an abnormal responsiveness of adrenoceptors that may independently contribute to temperature regulation, skin-color changes, swelling, sweating, and nail and hair growth. In the affected skin of patients with early CRPS, the concentration of inflamma-

tory mediators is elevated and neuropeptides are abnormally active.[19] Early CRPS is frequently accompanied by patchy regional bone changes,[7] and a subgroup of persons with CRPS has minimal injury to nerve fibers in the skin[20,21]; both changes are of uncertain relevance.

CRPS has been shown to be associated with specific microbiome signatures.[22] Patients with early CRPS and those with persistent CRPS harbor circulating autoreactive IgM and IgG antibodies, respectively, which elicit core phenotypic elements of CRPS when transferred to hind-paw–injured rodents.[23,24] White male persons with CRPS may have a permissive (facilitating but not causing the development of disease) genetic background.[25] In persistent CRPS (Fig. 1), widespread skin sensitivity may occur, which is consistent with a possible contribution of central sensitization (increased responsiveness of neurons in the central nervous system to their normal or subthreshold input), although this mechanism has not been directly proved.[8] Whether central sensitization plays a role in limb pain in persons with CRPS is unknown.

After the onset of CRPS, the degree of functional impairment and distress is affected by biologic, psychological, and social factors. CRPS is triggered by physical trauma, which can lead

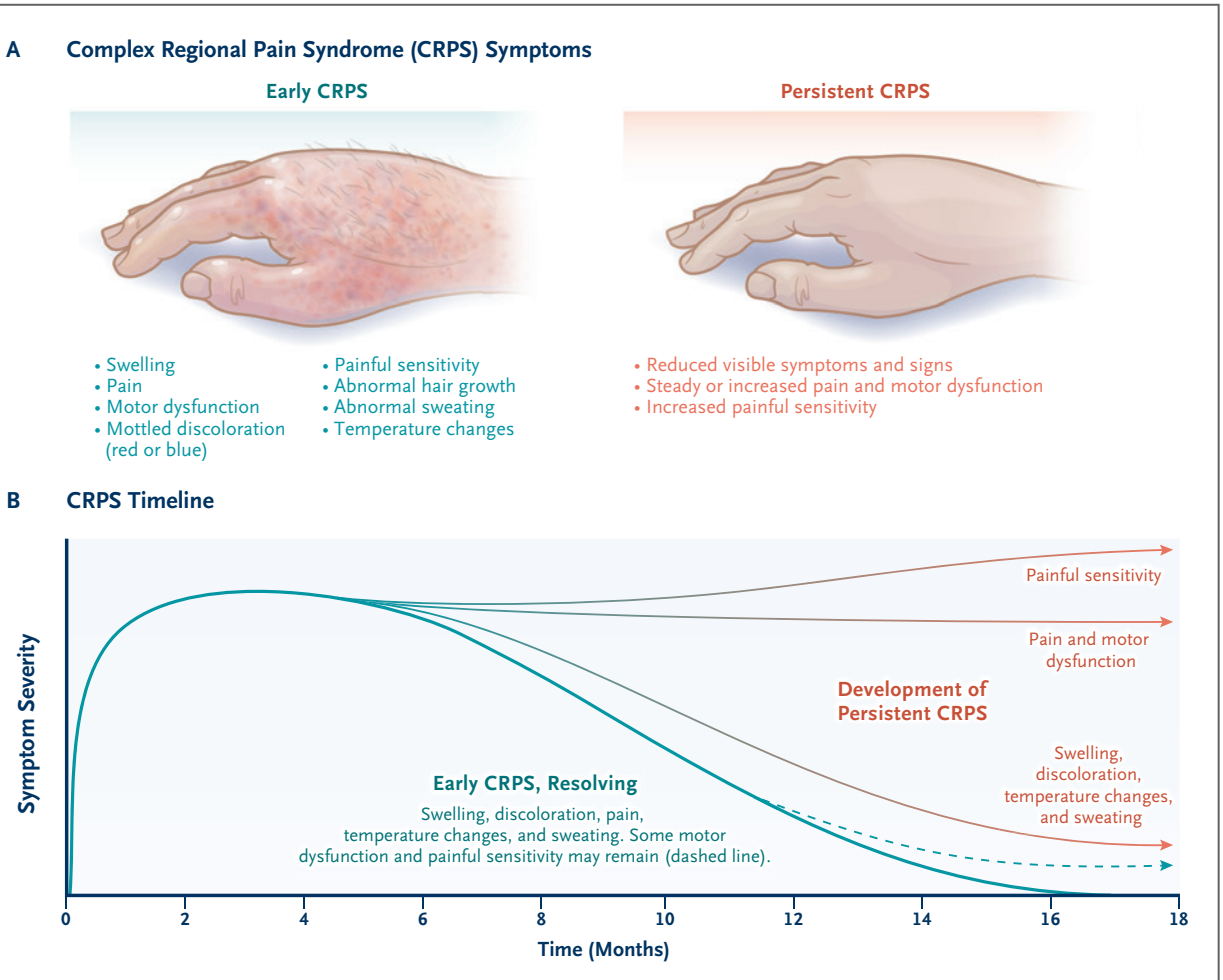


Figure 1. Symptoms and Signs of CRPS in the Affected Limb.

Panel A shows the typical features of both early CRPS (i.e., within the first few months after disease onset; obvious signs include swelling, reddish-blue mottled discoloration, increased hair growth on the back of the hand, and sweatiness) and persistent CRPS. Panel B shows the timeline of early CRPS and persistent CRPS. Among the 80% of patients with CRPS whose pain resolves naturally, the decrease in pain typically starts between 4 and 15 months after CRPS onset and almost never starts later than 18 months.

Table 1. CRPS Assessment.

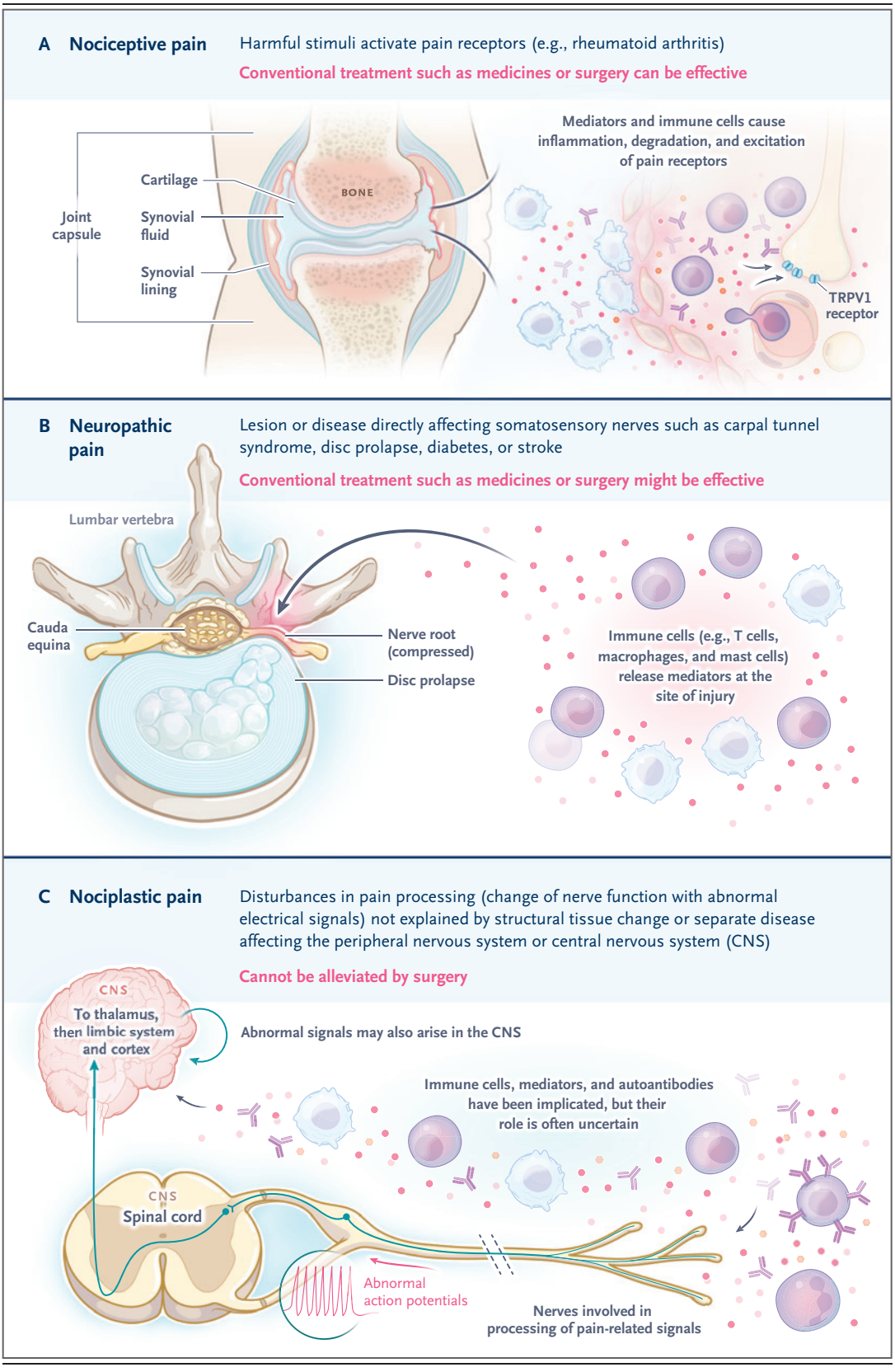
Budapest criteria for the diagnosis of CRPS*
A. Chronic pain in a limb (persistent or recurrent for longer than 3 months) is present.
B. The pain is associated with at least one symptom in three of four categories.
B.1 Sensory: hyperalgesia or allodynia
B.2 Vasomotor: temperature asymmetry, skin-color changes, or skin-color asymmetry
B.3 Sudomotor or edema: edema, sweating changes, or sweating asymmetry
B.4 Motor or trophic: decreased range of motion, motor dysfunction (weakness, tremor, or dystonia), or trophic changes (hair, nails, or skin)
C. The patient must have at least one sign at the time of evaluation in two or more of four categories.
C.1 Sensory: hyperalgesia (to pinprick) or allodynia (such as to light touch, deep somatic pressure,† or joint movement)
C.2 Vasomotor: temperature asymmetry, skin-color changes, or skin-color asymmetry
C.3 Sudomotor or edema: edema, sweating changes, or sweating asymmetry
C.4 Motor or trophic: decreased range of motion, motor dysfunction (weakness, tremor, dystonia, or myoclonus),‡ or trophic changes (hair, nails, or skin)
D. The pain is associated with at least one of two categories.
D.1 Emotional distress
D.2 Interference with daily life activities and social participation
E. The pain is not better explained by another condition.
Pain-focused medical history
How the condition started
Pain intensity§ and nature (e.g., burning or aching); improving and worsening factors
Limb awareness ("Does your limb feel strange or alien to you? Is it distorted in size or in its position in space? Do you feel like cutting it off?")[3]
Fatigue; quality of cognition including short-term memory, or "brain fog"
Medical history, medications for pain and other conditions
Other chronic pain, including back or pelvic pain, headaches or migraines, or bowel or bladder pain
Other symptoms, such as hyperacusis or bladder or bowel symptoms[4]
Biopsychosocial assessment and medical history
Patient understanding of the condition
Effect of pain
Sleep (how long, sleep interruptions, whether the bed covers are painful, whether the sleep is refreshing)
Mood (frustrated, irritable, down, anxious, angry)
Daily function, including household activities, personal hygiene, and spare-time activities
Mental response to pain that may affect function ("Do you have worrying thoughts and feelings about your pain?")[5]
Screening for anxiety and depression and post-traumatic stress disorder symptoms
Social situation and support, work history, litigation related to trauma that triggered CRPS
General medical history including mental health, first-degree relatives with diagnosed conditions such as neurodiversity conditions in biologic children[6]

* Complex regional pain syndrome (CRPS) is diagnosed on the basis of clinical symptoms and signs. Criteria A through E are met. Diagnostic symptoms and signs of type 1 CRPS (absence of nerve damage in a limb) and type 2 CRPS (presence of nerve damage in a limb) are identical. Patients who meet some but not all Budapest criteria and have never been documented as having met the Budapest criteria are considered to have CRPS not otherwise specified (NOS); little research exists on how CRPS NOS should be managed.[7] Regional osteoporosis is often present in early CRPS but does not contribute to the diagnostic algorithm. Further information about the diagnostic procedure is provided in the Supplementary Appendix.

† Pain in response to even mild blunt pressure is the signature feature, which also distinguishes CRPS from most neuropathic pain conditions.[8]

‡ Nerve conduction studies are normal; limb dystonia and myoclonus are rare, severely disruptive phenotypes within the motor category.

§ Pain intensity is measured on a scale of 0 to 10, where 0 to 3 indicates mild pain, 4 to 6 indicates moderate pain, and 7 to 10 indicates severe pain.



patients to pursue legal recourse. If a patient is involved in legal consultation regarding the CRPS-triggering trauma, the treating clinician should be made aware of it, because the legal assessment process causes additional distress and can interfere with clinical management.

STRATEGIES AND EVIDENCE

EVALUATION

CRPS is diagnosed by assessment of disease signs and symptoms in the affected limb (Fig. 1). The Budapest criteria define the diagnostic algorithm (Table 1). These empirically informed criteria were developed through a consensus process and then validated for their diagnostic sensitivity and specificity (0.99 and 0.68, respectively, for the clinical criteria).[26] Beyond diagnosis, a comprehensive biopsychosocial pain assessment can aid clinicians in determining the broader health care needs of their patients (Table 1).

Although two subtypes of CRPS are traditionally recognized, which are defined by the absence (type 1) or presence (type 2) of damage to a nerve caused by the CRPS-triggering trauma, their manifestations are similar. In the rarer type 2 CRPS, disease signs in the affected limb must extend beyond the territory of an involved nerve. Peripheral nerve damage can lead to innervation territory–restricted neuropathic pain and autonomic signs; some patients with type 2 CRPS therefore present with a mix of CRPS pain and neuropathic pain (Fig. 2).[7] Autonomic signs in the affected limb in persons with CRPS tend to abate over time; the Valencia consensus–based adaptation of the Budapest criteria clarifies that patients can receive the CRPS diagnosis (a third subtype) as long as disease signs in the limb had been documented at an earlier assessment.[7] The historical understanding that CRPS develops in stages is obsolete.

CRPS is not a diagnosis of exclusion; basic testing for important differential diagnoses should be considered (Table 1). The diagnostic workup varies according to the inciting trauma and, where appropriate, should be conducted in coordination with the trauma care team. Screening radiographs, MRI of the limb, and assessment of inflammatory markers in the blood may be needed to identify local bony, inflammatory, or infectious pathologic features unrelated to CRPS, whereas nerve-conduction studies and spinal MRI can be used to screen for possible nerve damage. Rarer differential diagnoses include lymphatic or venous obstruction, rheumatologic and systemic neuropathic conditions, and others (additional examples are provided in the Supplementary Appendix).

Figure 2 (facing page). Pain Mechanisms.
Shown are the mechanisms of nociceptive pain (Panel A), neuropathic pain (Panel B), and nociplastic pain (Panel C). CRPS itself is considered nociplastic pain; it is not considered neuropathic pain because no lesion or disease directly affecting the nervous system has been identified.

MANAGEMENT

Effective management of CRPS addresses the effect of the condition through four pillars of care: education, pain relief, physical rehabilitation, and psychological intervention.[2] The health care team typically involves physicians, physical therapists, occupational therapists, and psychologists. In some cases, this care is provided in designated pain clinics.

Education

Understanding CRPS can be difficult for both physicians and patients because of the extreme pain that appears to be disproportionate to any objective tissue damage. High-quality condition-related education is therapeutic in itself.[27] Pertinent patient-education points are listed in Table 2.

Pain Relief

In the context of the rarity of CRPS and its often self-limiting natural course, few randomized controlled trials evaluating therapies have been conducted. Most treatment recommendations are based on expert opinion in the absence of high- or moderate-certainty evidence.[2]

Regarding the prevention of CRPS, vitamin C may reduce the incidence of the condition after an initial trauma. In a meta-analysis of three randomized, placebo-controlled trials assessing the prevention of CRPS in 875 patients with wrist fractures, vitamin C (at a dose of 0.5 g taken daily for 50 days starting the day of injury) reduced the risk of CRPS (relative risk, 0.54; 95% CI, 0.33 to 0.91; P=0.02).[28]

In established CRPS with a duration of up to 18 months, most pain-relief interventions aim to reduce CRPS-related pain until the condition

Table 2. Educational Content for Patients.

The condition is caused by abnormally sensitized pain nerves.
The reason for activation of the pain nerves may be an autoimmune reaction, which was triggered by the trauma that incited CRPS or was already present but became harmful only after the CRPS-inciting trauma (e.g., because tissues were changed).
CRPS does not cause structural change except in extremely rare complications.
CRPS is not caused by a faulty surgical technique or by the patient's own actions.
Four of every five patients will naturally recover within the first 1.5 years toward a state of much less pain. After such improvement, CRPS is unlikely to recur.
If pain is unchanged by approximately 18 months, natural pain recovery becomes unlikely.
Specialized CRPS physical therapy is typically hands-off and differs from hands-on physical therapy, which the patient may have had; it is not supposed to substantially increase pain.
For physical therapy to be successful, effort and engagement are essential. Physical therapy can help to calm sensitized nerves, allowing a reduction of skin sensitivity, getting the limb moving if movement is challenging, improving activity participation, and often achieving partial pain relief. In early CRPS, specialist physical therapy may hasten recovery. Not using the limb is likely to worsen pain.
A distressing sense of the limb not belonging and of abnormal limb size and position in space is common and is attributed to poorly understood disturbed communications between the body and brain; improvement is possible with specialized CRPS physical therapy or occupational therapy.
Treatment with bisphosphonates and glucocorticoids may help to hasten recovery in patients with recent-onset CRPS; no other medication is known to modify the underlying disease process. Pain-relief medications and interventions can be tried but may have a limited effect; on the basis of recent research, several new treatment options are on the horizon.
One-to-one psychological support or group-based multidisciplinary pain management is often useful and aims to help patients understand CRPS, manage the effect of CRPS on their life, and support them in engaging in meaningful activities.
If pain persists beyond 18 months, neuromodulation treatment may be offered, which has a 50% chance of reducing CRPS pain by 50% but is also associated with certain risks.

naturally improves. Bisphosphonates may exert a therapeutic effect through antiinflammatory and antiosteoclastic actions. One meta-analysis of 10 trials (733 patients) found that bisphosphonates were associated with a 10-point improvement in score on a 100-point pain scale (95% CI, –18.9 to –1.1). This evidence is limited by unexplained statistical heterogeneity among the trials. The most substantial effects of bisphosphonates have occurred in trials that have restricted inclusion to patients with recent-onset CRPS (duration of <4 months), whereas trials involving patients with a longer average duration of CRPS (>12 months) have shown no evidence of an effect.[29]

A common practice is to prescribe a limited course of oral glucocorticoids in patients with a CRPS duration of up to 6 months, such as 100 mg of methylprednisolone for 4 days followed by a decrease of 25 mg every 4 days. However, evidence supporting this treatment is of poor quality.[30,31]

Expert consensus is that simple analgesic drugs, including nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen, and weak opioids, may mildly modify CRPS pain and can reduce proximal musculoskeletal pain in the shoulder or hip that develops in response to the intense CRPS pain affecting the distal limb.[2] Gabapentinoids (gabapentin and pregabalin), which can be effective in the treatment of neuropathic pain[32] (Fig. 2), are often tried when the nature of CRPS pain is described in neuropathic terms (such as "burning," "a vise," or "ant-crawling"). Randomized controlled trials of the appropriate dose of gabapentinoids in persons with CRPS have not been conducted.

The balance between pain relief and harm caused by potent opioids is not favorable. Opioids are far less effective in chronic primary pain, including CRPS, than in oncologic pain. In addition, tolerance develops within weeks to months, adverse effects are common, and the risk of opioid dependency is substantial.[33]

Low-dose tricyclic antidepressants administered in the evening may be prescribed, which

can improve sleep and reduce pain intensity in other chronic primary pain conditions.[33] Tricyclics often cause a "hangover" effect the next morning, which can be prevented by taking them earlier in the evening.

Serotonin–norepinephrine reuptake inhibitors such as duloxetine, milnacipran, and venlafaxine are effective in some chronic primary pain conditions and therefore may be effective in CRPS. However, dedicated randomized, controlled trials of tricyclics or serotonin–norepinephrine reuptake inhibitors in CRPS have been lacking.[33,34]

Pain medications are not considered to have disease-modifying effects in CRPS. There is evidence that they can become less efficacious over time,[35] and discontinuing the medications (gradually for gabapentinoids and antidepressants[36]) should routinely be considered.

A local injection of anesthetic to regional sympathetic ganglia appears to be effective in many patients in the short term. However, evidence suggests an overall lack of a durable effect,[37] even after repeat administration of such a nerve block.[38]

Spinal cord stimulators and dorsal root ganglion stimulators are neurologic pacemakers used in specialist centers and are thought to override painful impulses from the periphery. Small studies suggest that spinal cord stimulation may reduce CRPS pain by 50% in up to 50% of patients.[39] The effects of treatment with spinal cord stimulation slowly diminish over 5 years[40]; similar evidence from a randomized controlled trial of dorsal root ganglion stimulation is not available.[41]

Two randomized trials of intravenous infusions of low-dose ketamine showed reductions in CRPS pain, although both trials lacked an active placebo, so some participants may have been aware of their trial-group assignment.[42,43] This treatment has a time-limited effect, and adverse effects include discomforting euphoria and hallucinations.[37]

Methods involving noninvasive transcutaneous brain stimulation are emerging technologies for the treatment of neuropathic pain with few side effects, but no sufficient evidence exists with respect to CRPS.[32] The two largest medication trials involving persons with persistent CRPS have shown a lack of efficacy for the immune modulator drugs lenalidomide and low-dose (0.5 g per kilogram of body weight) intravenous immune globulin.[44,45]

Surgery

In cases of severe, recalcitrant CRPS, limb amputation has been advocated in order to improve function and reduce pain.[46] However, amputation is an extreme intervention, and the risk–benefit profile is too uncertain to allow recommendation of this approach.[2,47] Very rare complications of CRPS include skin ulcerations, malignant edema, and osteomyelitis, which have an unknown pathogenesis. A detailed protocol for the management of complications, including limb dystonia, is available in Appendix 10 and the Pain Medicine section of the U.K. CRPS guidelines.[2]

Some health care professionals advocate for therapeutic nerve decompression to treat CRPS when nerve conduction studies indicate nerve compression in part of the pain-affected area. However, controlled trials assessing the risks, including the risk of worsening of CRPS, as compared with the benefits have been lacking.

Consideration of surgical interventions indicated to treat CRPS-independent pathologic conditions in the CRPS-affected limb, such as joint instability, must balance the risk of postoperative worsening or rekindling of CRPS. Expert consensus recommends waiting for CRPS abatement first, when possible and when CRPS has been present for less than 18 months, to reduce complications of surgery in a CRPS-affected limb.[2]

Physical Rehabilitation

Appropriate limb mobilization very early after trauma may prevent CRPS development,[48] an effect that can be modeled in rodents.[49] Physical therapy or occupational therapy (or both) that uses CRPS-specific regimens is considered crucial to effective treatment in all patients with CRPS, independent of disease durations.[2] However, there is no high-certainty evidence of the effectiveness of any rehabilitative intervention in CRPS.[37] Expert consensus states that the most appropriate kind of physical therapy for persons with CRPS is gentle and typically nonmanipulating.[2] This form of gentle physical therapy can reduce the sensitivity of pain processing so that everyday activation such as movement or touch gradually becomes less painful. Limb movement is restricted in persons with CRPS not only because the limb is painful but also because of poorly understood changes in its cortical representation that interfere with movement. Appropriate physical therapy or occupational therapy that addresses

this element involves imagery techniques such as mirror therapy and graded motor imagery.[50,51] The European Pain Federation (EFIC)–curated Web application, CRPS Assist, aids physiotherapists and occupational therapists and is available for free in English, Spanish, and 28 other languages (https://crps.europeanpainfederation.eu/).

In children and adolescents, physical therapy or occupational therapy administered in accordance with the same principles used with adults is the mainstay of treatment. This method will support functional restoration in almost all cases despite the persistence of some CRPS symptoms in approximately 50% of patients.[17]

Psychological Support and Pain-Management Programs

Psychological factors assessed before or immediately after the inciting injury have not been shown to be a cause of or a risk factor for CRPS. However, depression, anxiety, and post-traumatic stress disorder are often diagnosed after CRPS onset, and their presence adversely affects the severity and prognosis.[16,52] CRPS pain is highly distressing, and psychological interventions are often warranted to support patients with long-term management of pain, as with any illness associated with mental distress. Both psychological therapy for the patient and a pain-management program involving interdisciplinary therapy are typically based on cognitive behavioral therapy or acceptance and commitment therapy.

Pain-management programs also include psychologically informed physical rehabilitation in line with the principles outlined above; they aim to reduce pain-related distress, overcome fear avoidance, and improve acceptance of and adjustment to the condition, self-efficacy, mood, and pain coping. One third of patients with persistent CRPS may have substantial functional improvement with this type of approach.[53] Substantial abatement of pain is rare because the underlying disease process is not being addressed. In our practice, pain-management programs are typically offered after medication adjustment but before neurostimulation approaches.

GUIDELINES

A systematic review in 2022, which used the Appraisal of Guidelines for Research and Evaluation tool to assess seven guidelines from six organizations, identified the U.K. Royal College of Physicians CRPS guidelines as the only high-quality consensus guidelines for the diagnosis and management of CRPS.[2,54] The CRPS management outlined in here is largely consistent with these guidelines and with more-recent German guidelines[55] and U.S. guidelines[30]; variations related to interventional treatment are listed in Table S2.

AREAS OF UNCERTAINTY

Whether the clinical phenotype of CRPS is sustained by serum IgG and IgM autoantibodies (which induce painful hypersensitivities in rodents[23]) and the CRPS-associated abnormal microbiome[22] is unknown. The efficacy in CRPS of medications used in other chronic primary pain conditions, those used in neuropathic pain, or combinations of these medications is uncertain. Whether early physiotherapy or bisphosphonate treatment, in addition to decreasing CRPS symptoms, also prevents the development of persistent CRPS or reduces long-term functional disability is unknown.[14] Given the observations with respect to immune-mediated mechanisms, trials using immunomodulating agents are needed. Finally, whether psychological factors are causes or consequences (or both) of CRPS is unclear.

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette presents with ongoing high-intensity pain 8 months after the onset of CRPS. She has been receiving physical therapy that has been exacerbating her pain and may not be appropriately applied. Much of the treatment I would provide for her would involve education (Table 2). Her prognosis for a natural recovery from her intense pain is good, but she is outside the time frame for prescribing bisphosphonates or glucocorticoids. My goal would be to support her in managing her life as best as possible until the condition abates naturally. The initiation of medications may provide a temporary mild decrease in pain and improvements in sleep and mood. I would prescribe a trial of nortriptyline at a dose of 10 mg and gradually adjust the dose to 40 mg over 4 to 6 weeks, with the main goal of improving sleep. I would add a second drug if

there is an effect with nortriptyline with acceptable adverse effects but persistent pain. If there is no effect with nortriptyline, I would switch to duloxetine and then try gabapentin or pregabalin. I may prescribe NSAIDs to reduce her reactive shoulder pain, and I may offer a prescription of mild opioids as needed to ameliorate pain flares. I would ensure she receives the specialized physical therapy and occupational therapy specific to CRPS. I would inform her about the options regarding multidisciplinary pain rehabilitation and neuromodulation therapy for the less-likely scenario that her pain would not improve by 18 months. At this point, I would recommend waiting to use stimulation therapy until all other interventions have been exhausted, because rare serious risks are associated with stimulation therapy.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

I thank the following colleagues for their contributions to the manuscript: Prof. Candy McCabe and Prof. Jenny Lewis (Bath, United Kingdom); Prof. Debbie Bean (Auckland, New Zealand); Prof. Frank Birklein (Mainz, Germany); Dr. Chris Barker (Southport, United Kingdom); Dr. Michael Ferraro (Sydney, Australia); Prof. Walter Magerl (Heidelberg, Germany); Prof. Geoff Woods and Dr. Nicholas Shenker (Cambridge, United Kingdom); and Mrs. Sharon Barnett, Mrs. Louise Haynes, Dr. Katie Herron, Dr. Selina Johnson, Dr. Kerry Matthews, and Mr. John Tetlow (Liverpool, United Kingdom).

AUTHOR INFORMATION

[1] Pain Research Institute, University Hospital Aintree, Faculty of Health and Life Sciences, University of Liverpool, Liverpool, United Kingdom; [2] Walton Centre NHS Foundation Trust, Liverpool, United Kingdom.

REFERENCES

1. Ott S, Maihöfner C. Signs and symptoms in 1,043 patients with complex regional pain syndrome. J Pain 2018;19:599-611.
2. Goebel A, Barker CH, Turner-Stokes L, et al. Complex regional pain syndrome in adults. 2nd ed. London: Royal College of Physicians, 2018 (https://www.rcp.ac.uk/improving-care/resources/complex-regional-pain-syndrome-in-adults-2nd-edition/).
3. Lewis JS, Kersten P, McCabe CS, McPherson KM, Blake DR. Body perception disturbance: a contribution to pain in complex regional pain syndrome (CRPS). Pain 2007;133:111-9.
4. Ten Brink AF, Peters L, Kompouli P-I, et al. Bodily changes and sensory sensitivity in complex regional pain syndrome and fibromyalgia. Pain 2020;161:1361-70.
5. Sullivan MJ, Thorn B, Haythornthwaite JA, et al. Theoretical perspectives on the relation between catastrophizing and pain. Clin J Pain 2001;17:52-64.
6. Hirst A, Mountford R, Berwick R, et al. Increased prevalence of autism in the children of fibromyalgia patients relative to other types of chronic pain. November 4, 2025 (https://www.medrxiv.org/content/10.1101/2025.10.20.25336737v3). preprint.
7. Harnik MA, Sodmann A, Hartmannsberger B, et al. Bone metabolism in complex regional pain syndrome. Pain Rep 2024;9(6):e1217.
8. Husk JR, Pang D, Hasnie F, Goebel A, Magerl W. Phenotype progression of complex regional pain syndrome identified by quantitative sensory testing. August 7, 2025 (https://www.medrxiv.org/content/10.1101/2025.08.05.25333054v1). preprint.
9. Nicholas M, Vlaeyen JWS, Rief W, et al. The IASP classification of chronic pain for ICD-11: chronic primary pain. Pain 2019;160:28-37.
10. de Mos M, Huygen FJPM, Dieleman JP, Koopman JSHA, Stricker CBH, Sturkenboom MCJM. Medical history and the onset of complex regional pain syndrome (CRPS). Pain 2008;139:458-66.
11. de Mos M, Huygen FJPM, Stricker CBH, Dieleman JP, Sturkenboom MCJM. The association between ACE inhibitors and the complex regional pain syndrome: suggestions for a neuro-inflammatory pathogenesis of CRPS. Pain 2009;142:218-24.
12. de Mos M, de Bruijn AGJ, Huygen FJPM, Dieleman JP, Stricker BHC, Sturkenboom MCJM. The incidence of complex regional pain syndrome: a population-based study. Pain 2007;129:12-20.
13. de Mos M, Huygen FJ, van der Hoeven-Borgman M, Dieleman JP, Stricker BHC, Sturkenboom MC. Outcome of the complex regional pain syndrome. Clin J Pain 2009;25:590-7.
14. Johnson S, Cowell F, Gillespie S, Goebel A. Complex regional pain syndrome what is the outcome? A systematic review of the course and impact of CRPS at 12 months from symptom onset and beyond. Eur J Pain 2022;26:1203-20.
15. Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet 1993;342:1012-6.
16. Louis M-H, Meyer C, Legrain V, Berquin A. Biological and psychological early prognostic factors in complex regional pain syndrome: a systematic review. Eur J Pain 2023;27:338-52.
17. Sherry DD, Mondal A, McGill M, Gmuca S. Pediatric complex regional pain syndrome with and without a history of prior physical trauma at onset. Clin J Pain 2023;39:437-41.
18. Ferraro MC, O'Connell NE, Sommer C, et al. Complex regional pain syndrome: advances in epidemiology, pathophysiology, diagnosis, and treatment. Lancet Neurol 2024;23:522-33.
19. Birklein F, Ajit SK, Goebel A, Perez RSGM, Sommer C. Complex regional pain syndrome — phenotypic characteristics and potential biomarkers. Nat Rev Neurol 2018;14:272-84.
20. Morellini N, Finch PM, Goebel A, Drummond PD. Dermal nerve fibre and mast cell density, and proximity of mast cells to nerve fibres in the skin of patients with complex regional pain syndrome. Pain 2018;159:2021-9.
21. Oaklander AL, Rissmiller JG, Gelman LB, Zheng L, Chang Y, Gott R. Evidence of focal small-fiber axonal degeneration in complex regional pain syndrome-I (reflex sympathetic dystrophy). Pain 2006;120:235-43.
22. Gonzalez E, Sahar T, Haddad M, et al. Altered gut microbiome composition and function in individuals with complex regional pain syndrome. Anesthesiology 2025;143:142-55.
23. Helyes Z, Tékus V, Szentes N, et al. Transfer of complex regional pain syndrome to mice via human autoantibodies is mediated by interleukin-1-induced mechanisms. Proc Natl Acad Sci U S A 2019;116:13067-76.
24. Guo T-Z, Wei T, Tajerian M, et al. Complex regional pain syndrome patient immunoglobulin M has pronociceptive effects in the skin and spinal cord of tibia fracture mice. Pain 2020;161:797-809.
25. Shaikh SS, Goebel A, Lee MC, et al. Evidence of a genetic background predisposing to complex regional pain syndrome type 1. J Med Genet 2024;61:163-70.
26. Harden NR, Bruehl S, Perez RSGM, et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for complex regional pain syndrome. Pain 2010;150:268-74.

27. Moore E, Braithwaite FA, Stanton TR, Bellan V, Moseley GL, Berryman C. What do I need to know? Essential educational concepts for complex regional pain syndrome. Eur J Pain 2022;26:1481-98.
28. Aïm F, Klouche S, Frison A, Bauer T, Hardy P. Efficacy of vitamin C in preventing complex regional pain syndrome after wrist fracture: a systematic review and meta-analysis. Orthop Traumatol Surg Res 2017;103:465-70.
29. Ferraro MC, O'Connell ME, Goebel A, et al. Efficacy and safety of bisphosphonates for complex regional pain syndrome: a systematic review and meta-analysis. Ann Intern Med (in press).
30. Harden RN, McCabe CS, Goebel A, et al. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 5th edition. Pain Med 2022;23:Suppl:S1-S53.
31. Kwak SG, Choo YJ, Chang MC. Effectiveness of prednisolone in complex regional pain syndrome treatment: a systematic narrative review. Pain Pract 2022; 22:381-90.
32. Soliman N, Moisset X, Ferraro MC, et al. Pharmacotherapy and non-invasive neuromodulation for neuropathic pain: a systematic review and meta-analysis. Lancet Neurol 2025;24:413-28.
33. National Institute for Health and Care Excellence. Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain. April 7, 2021 (https://www.nice.org.uk/guidance/ng193).
34. Birkinshaw H, Friedrich CM, Cole P, et al. Antidepressants for pain management in adults with chronic pain: a network meta-analysis. Cochrane Database Syst Rev 2023;5:CD014682.
35. Hashemzadeh S, Mortazavi M, Abdi Dezfouli R. Quantitative analysis of nortriptyline's analgesic properties: a comparative systematic review and meta-analysis. BMJ Open 2024;14(8):e085438.
36. Stopping antidepressants. London: Royal College of Psychiatrists, March 2024 (https://www.rcpsych.ac.uk/mental-health/treatments-and-wellbeing/stopping-antidepressants).
37. Ferraro MC, Cashin AG, Wand BM, et al. Interventions for treating pain and disability in adults with complex regional pain syndrome — an overview of systematic reviews. Cochrane Database Syst Rev 2023;6:CD009416.
38. Rodriguez RF, Bravo LE, Tovar MA, Castro F, Ramos GE, Daza P. Study of the analgesic efficacy of stellate ganglion blockade in the management of the complex regional pain syndrome in patients with pain mediated by sympathetic nervous system: preliminary study. Rev Soc Esp Dolor 2006;4:230-7.
39. Kemler MA, Barendse GAM, van Kleef M, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. N Engl J Med 2000;343:618-24.
40. Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FAJM, van Kleef M. Effect of spinal cord stimulation for chronic complex regional pain syndrome type I: five-year final follow-up of patients in a randomized controlled trial. J Neurosurg 2008;108:292-8.
41. van Bussel CM, Stronks DL, Huygen FJPM. Dorsal column stimulation vs. dorsal root ganglion stimulation for complex regional pain syndrome confined to the knee: patients' preference following the trial period. Pain Pract 2018;18:87-93.
42. Sigtermans MJ, van Hilten JJ, Bauer MCR, et al. Ketamine produces effective and long-term pain relief in patients with complex regional pain syndrome type 1. Pain 2009;145:304-11.
43. Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. Pain 2009;147:107-15.
44. Manning DC, Alexander G, Arezzo JC, et al. Lenalidomide for complex regional pain syndrome type 1: lack of efficacy in a phase II randomized study. J Pain 2014; 15:1366-76.
45. Goebel A, Bisla J, Carganillo R, et al. Low-dose intravenous immunoglobulin treatment for long-standing complex regional pain syndrome: a randomized trial. Ann Intern Med 2017;167:476-83.
46. Domerchie PN, Dijkstra PU, Geertzen JHB. Long-standing complex regional pain syndrome-type I: perspectives of patients not amputated. J Rehabil Med Clin Commun 2023;6:7789.
47. Gilanyi YL, Ferraro MC, Goebel A, et al. Amputation for complex regional pain syndrome: a systematic review. J Pain 2025 October 3 (Epub ahead of print).
48. Cowell F, Gillespie S, Cheung G, Brown D. Complex regional pain syndrome in distal radius fractures: how to implement changes to reduce incidence and facilitate early management. J Hand Ther 2018;31: 201-5.
49. Guo T-Z, Wei T, Li W-W, Li X-Q, Clark JD, Kingery WS. Immobilization contributes to exaggerated neuropeptide signaling, inflammatory changes, and nociceptive sensitization after fracture in rats. J Pain 2014;15:1033-45.
50. McCabe CS, Haigh RC, Blake DR. Mirror visual feedback for the treatment of complex regional pain syndrome (type 1). Curr Pain Headache Rep 2008;12:103-7.
51. Lotze M, Moseley GL. Clinical and neurophysiological effects of progressive movement imagery training for pathological pain. J Pain 2022;23:1480-91.
52. Beerthuizen A, van 't Spijker A, Huygen FJPM, Klein J, de Wit R. Is there an association between psychological factors and the Complex Regional Pain Syndrome type 1 (CRPS1) in adults? A systematic review. Pain 2009;145:52-9.
53. Bean DJ, Tuck NL, Magni N, Aamir T, Pollard C, Lewis GN. The efficacy of an interdisciplinary pain management program for complex regional pain syndrome compared to low back pain and chronic widespread pain: an observational study. Pain Med 2025;26:180-8.
54. Javed S, Kang WD, Black C, Chorath K, Johal J, Huh BK. Clinical practice guidelines for the management of patients with complex regional pain syndrome: a systematic appraisal using the AGREE II instrument. Pain Manag 2022;12:951-60.
55. Birklein F. Diagnosis and treatment of complex regional pain syndromes (CRPS). Berlin: Guidelines Commission of the German Neurological Society, 2018 (https://crpsselbsthilfe.de/wp-content/uploads/2024/08/030116_LL_CRPS_2018-en.pdf).