Review Article

Modern Principles of Diagnosis and Treatment in Complex Regional Pain Syndrome

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Summary

Background: Complex regional pain syndrome (CRPS) is a relatively common complication, occurring in 5% of cases after injury or surgery, particularly in the limbs. The incidence of CPRS is around 5–26/100 000. The latest revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-11) now categorizes CRPS as a primary pain condition of multifactorial origin, rather than a disease of the skeletal system or the autonomic nervous system.

Method: Based on a selective search of the literature, we summarize current principles for the diagnosis and treatment of CRPS.

Results: Regional findings in CRPS are accompanied by systemic symptoms, especially by neurocognitive disorders of body perception and of symptom processing. The therapeutic focus is shifting from predominantly passive peripheral measures to early active treatments acting both centrally and peripherally. The treatment is centered on physiotherapy and occupational therapy to improve sensory perception, strength, (fine) motor skills, and sensorimotor integration/ body perception. This is supported by stepped psychological interventions to reduce anxiety and avoidance behavior, medication to decrease inflammation and pain, passive physical measures for reduction of edema and of pain, and medical aids to improve functioning in daily life. Interventional procedures should be limited to exceptional cases and only be performed in specialized centers. Spinal cord and dorsal root ganglion stimulation, respectively, are the interventions with the best evidence.

Conclusion: The modern principles for the diagnosis and treatment of CRPS consider both, physiological and psychological mechanisms, with the primary goal of restoring function and participation. More research is needed to strengthen the evidence base in this field.

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In 1994, after a number of previous different historical terms (e1–e10), complex regional pain syndrome (CRPS) was conceptualized for the first time by the "International Association for the Study of Pain" (IASP) (e10). Consensus criteria were established ten years later. They were revised in 2010 and slightly adapted in 2021 (*Box 1*) (1, 2).

The penultimate revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-9) had still classified essentially identical clinical conditions as "sympathetic reflex dystrophy" or "algoneurodystrophy". On the one hand, ICD-10 mentions "neurodystrophy/algodystrophy" (which included sympathetic reflex dystrophy, Sudeck's bone atrophy, shoulder-hand syndrome), while using the term "causalgia" if it developed after a nerve injury. In 2019, the term CRPS was included in the ICD-10. A distinction was made between Type 1 without nerve injury and Type 2 with nerve injury. Only shoulder-hand syndrome remained as "neurodystrophy/algodystrophy".

On 1 December 2022, ICD-11 came into effect and is meanwhile also available as a German draft version

BOX 1

Budapest criteria

1. Continuing pain, which is disproportionate to any inciting event

2. The patient must report at least one symptom in three of the four following categories:

a) sensory:
hyperalgesia (increased sensitivity to pain stimuli); hyperesthesia (increased sensitivity to light touch, allodynia)

b) vasomotor:
skin temperature asymmetry; changes or asymmetry of skin color

c) sudomotor:
changes or asymmetry of local sweating; edema

d) motor/trophic:
decreased range of motion; motor dysfunction (weakness, dystonia, tremor); trophic changes (hair or nail growth, skin)

3. The patient must display at least one sign in two or more of the four following categories at the time of the examination:

a) sensory:
hyperalgesia to sharp stimuli (e.g., toothpick); allodynia (evoked by light touch / brushstroke; pain on deep somatic pressure to joints/bones/muscles, with joint movement)

b) vasomotor:
skin temperature asymmetry; changes or asymmetry of skin color

c) sudomotor:
changes or asymmetry of local sweating; edema

d) motor/trophic:
decreased range of motion; motor dysfunction (weakness, dystonia, tremor); trophic changes (hair or nail growth, skin)

4. There is no other diagnosis that better explains the signs and symptoms.

(3, 4). It assigns both CRPS types and, for the first time, shoulder-hand syndrome together to a new symptom category—with a cross reference to chronic postoperative/post-traumatic pain (3, 4). "Chronic primary pain" now comprises, in addition to CRPS, other regional and widespread pain syndromes, such as chronic widespread pain/fibromyalgia syndrome, chronic primary low back pain, chronic primary visceral pain, and chronic primary headache. Common features, such as persistency, high emotional burden, and significant functional limitations are highlighted (2–4, e11). Chronic primary pain is referred to as "multifactorial" and sometimes as "nociplastic", as opposed to nociceptive (thermic, mechanical) pain and neuropathic (nerve injury) pain (3, 4, e11–e14). "Nociplastic" is understood as a potentially reversible central hypersensitivity to stimuli without tissue or nerve damage (e12–e20). Indeed, the mechanisms of developing CRPS are nowadays assumed primarily to be peripheral, spinal, and cerebral sensitization processes due to neurogenic inflammatory (auto-)immune response, autonomic dysregulation, and maladaptive protective behavior (learned disuse) (5–14, e15, e21–e25).

What are the implications of the new ICD-11 conceptual framework for clinical practical diagnostic and therapeutic strategies for CRPS?

Methods

The present review article takes a clinical interdisciplinary view of new diagnostic aspects and function-focuseded forms of treatment of CRPS. It follows the current German (15) and international CRPS guidelines and expert recommendations (16–18). A selective literature search was also conducted in PubMed for original articles and reviews published in English or German relating to the clinical presentation, course, (differential) diagnostics, and treatment of CRPS in adults. The search terms were "CPRS", "complex regional pain syndrome", "diagnosis", "treatment", "guideline", "consensus", and "recommendation". The clinically most useful articles are cited directly, and a list of further reading is provided as e-references.

Diagnosis

Incidence, inciting causes, risk factors

The incidence of CRPS is between 5 and 26 per 100 000 per year, its prevalence is about 20/100 000 (19, 20); numbers fluctuate strongly, depending on diagnostic criteria (8, 19, 20). Women are more commonly affected than men, with a ratio of 2–4 : 1 (19–21, e26–e28). The age peak is around the 40th to 70th year of life (19–21, e26–e28). However, CRPS occurs at any age, also affecting children and adolescents at a rate of about 1 to 5 per 100 000 (19–21, e26, e27, e29, e30).

In 0.2 to 9% of cases, CRPS develops after peripheral fractures or ligament injuries, in 2 to 5% after nerve injury, and in 1 to 13% after surgery of the extremities (8, e22–e25, e28, e31–e39). On the other hand, 40 to 50% of all CRPS cases are preceded by fractures, and 30 to 40% are the result of other injuries or surgical procedures (1, 8, 19–21, e26, e27). Type and degree of tissue or nerve damage, immobilization, and high initial pain intensity increase the risk of developing CRPS (*Box 2*) (e28, e34–e42). Yet even mild tissue injury can result in CRPS, for example, following arthroscopy, tourniquet application, snowball injury, injection, vaccination, or local infection (19, 20, e26, e27, e43–e45). CRPS of the limbs (e.g., shoulder-hand syndrome) can also follow cerebral, spinal, and cardiac ischemia, degeneration, injuries, surgical procedures and, in isolated cases, malignant neoplasm, even though the tissue injury may lie far proximal to the site of manifestation (20, e27, e41, e46–e52, e45–e51). No initial event is clearly defined in about three to ten percent of cases (19–21, e27, e53). Painful pre-existing conditions (e54–e57) and stressful life events (6, 22, e58, e59), even without tissue injury (6), can precede CRPS (*Box 2*).

There is conflicting data on psychological risk factors for developing CRPS. Overall, the rate of premorbid and comorbid post-traumatic stress disorders (PTSD) appears to be increased: 27 to 38% fulfill all, 56% most criteria (22, e59). Anxiousness and pain catastrophizing appear to both increase the risk of disease (e60) and worsen its prognosis (e61–e63). Most studies, however, do not show an increased rate

of depression, anxiety disorders, or personality disorders as compared with other diseases (22, e33, e37, e42, e57–e66) (*Box 2*).

Clinical presentations and diagnostic criteria

The cardinal symptoms of CRPS are regional pain and other sensory, motor, autonomic, and trophic disturbances (*Box 1*). Distal extremities are by far the most common sites of manifestation of CRPS, with the hands being affected more often than the feet. The symptoms have a "glove-" or "sock-like" distribution and do not correspond to a dermatome or area of innervation. There have been isolated reports of CRPS affecting, amongst other sites, the face and trunk (e45, e67–e69).

To establish a CRPS diagnosis, the Budapest criteria must be met—as per the current guidelines, too (*Box 1*) (1–4, 15–18). Their sensitivity is around 98 to 99%, their specificity about 36 to 68% (1, 8, e46, e57). The entry criterion is continuing pain disproportionate to any inciting event (in 1994 it was still "harmful event or immobilization" [e10]). Neither the disproportionality nor the potential inciting cause is defined more precisely. No other disorder, including the primary injury, better explains the signs and symptoms (1, 15–18). There is no time criteria; the CRPS guideline of the German Neurological Society (DGN) specifies two to three months as a reasonable time point (15) by which all criteria must be fulfilled, bearing in mind that the healing process of the primary injury still needs to be awaited.

The majority of patients present other symptoms, in particular top-down disturbances of body perception and symptom processing (7–12, 15–17, 22, 23, e70–e108) (*Box 3*). For example, between 32 and 84% have neuropsychological symptoms relating to the affected limb, i.e., disturbances of alertness/attentiveness, sense of body ownership/sense of position, experience of authorship/control of actions, and attribution of meaning/emotions (7, 23, e69–e81), even in the form of depersonalization (e82) or alexithymia, i.e., a reduced ability to identify emotions experienced by themselves and others (e83). A combination of finger misperception and body image disturbance differentiated between patients with CRPS and those with fractures with a specificity of 85% and a positive predictive value of 84% (e84).

There appear to be clinical, possibly pathophysiological, overlaps with neuropathic pain syndromes (15–18, e101–e103), as well as with other chronic primary pain syndromes (3, 4, 18, e11–e14, e104–e108) and functional (e18), (especially functional neurological) disorders, defined as involuntary discontinuity of the normal integration of motor, sensory, cognitive functions (7, 9, 11, 12, e109–e114), and PTSD (6, 22, e59, e80). Modern guidelines recommend assessing affective disturbances and body perception disturbances, especially post-traumatic stress symptoms, attentional disturbances, fear of touch or of movement (15–18). So far, however, such features have not been included in any diagnostic criteria (1–4) (*Box 3*).

BOX 2

Potential risk factors for developing CRPS

- female sex, in particular postmenopausal women (women of middle age also sustain fractures three times more often than men)
- severe injuries, in particular crush injuries, displaced, juxta-articular or intra-articular fractures (especially distal radius fractures); ankle injuries; nerve injuries; prolonged anesthesia/ischemia, manipulation procedures such as secondary fracture reductions; restricted range of motion and functional impairment, prolonged immobilization
- high pain intensity initially or directly after surgery, sensory disturbances and low skin temperature (for example, persistent pain ≥5 on a numerical rating scale of 10 points for more than a week after conservative treatment of a distal radius fracture)
- chronic or widespread pain and hypersensitivity, such as migraine, fibromyalgia, back/period pain, neuropathies, osteoporosis, osteoarthritis, rheumatoid arthritis; also, asthma/allergies
- high anxiety level, depressiveness, passivity, avoidance tendency, pain catastrophizing, or manifest disorders associated with anxiety and trauma/stress; previous critical life events; desire for compensation and litigation

Technical and laboratory findings are not included in the diagnostic criteria either (1–4): CRPS is and remains a clinical diagnosis. If history and clinical examination have established the diagnosis, then no guideline recommends any further diagnostic investigations (15–18). To help substantiate the diagnosis, the DGN CRPS guideline recommends a three-phase bone scan only during the first year of disease in cases of doubt or if an expert opinion is required in the foreseeable future (15). Additional diagnostic investigations, however, allow sound differential diagnostics in accordance with the 4th Budapest criterion (*eBox*) (15, 16, 18, e115–126).

Subtypes, clinical course, prognosis

Differentiation between CRPS 1 and 2 is controversial, given that, clinically, there is no difference (2, 8, 15–18, e28). Modern guidelines do not express any difference in recommendations between the two (15–18). The distinction between "warm" and "cold" CRPS subtypes or stages, however, is of some clinically relevance with regard to treatment (see below) (8, 15, 17, e127–e129). The "warm" subtype is often described as "red", "sweaty", and "early". The "cold" subtype is characterized as "blue", "dystrophic/atrophic", "late" and regarded as having a less favorable prognosis. Depending on the situation, vasomotor and sudomotor symptoms, such as skin color changes and sweating, may fluctuate (2–4, 10, 13) as an indication of central neurogenic regulation – there is possibly a peripheral inflammatory etiology behind "warm" CRPS signs and symptoms, while "cold" CRPS is of a central nervous nociplastic origin (13, e21). The DGN CRPS guideline refers to acute (less than 6 months) as opposed to chronic CRPS (15), while current US-American and British

BOX 3

Additional clinical findings in CRPS

Allodynia
- pain on light movement/touch/pressure (e.g., draught, brush, finger [pressure less than 100 g/cm^2 or load less than 500 g])
- pain from vibration (e.g. tuning fork on a bony prominence), cold, heat

Hyperalgesia
- periarticular pressure hyperalgesia distal to the site of injury/surgery
- solitary sharp stimulus (pinprick) is felt stronger/longer

Disturbance of body perception/interoception
- attention: exerted, hypervigilant focussing or disregarding (neglect-like/dissociation)
- shape, size, weight, position, posture, laterality, symmetry, ownership, e.g., as if limbs were detached, foreign, dead ("as if wooden", "like part of a dead body")
- attribution of meaning or affective evaluation, e.g., threatening, disgusting, or hated limb; caution: desire for amputation

(Functional) disturbances of voluntary motor function
- protective posture, slowed, reduced or non-movement
- reduced experience of motor action, control, intention (agency)
- weakness, disturbances of fine motor skills, coordination or movement
- sometimes several types of disturbance inone and the same limb, e.g.
  - myoclonus or tremor (with "entrainment", i.e. unconscious synchronization with rhythmic movements of the unaffected limb)
  - dystonia (usually in fixed flexion/supination)
- increase during manipulation, decrease when distracted, no decrease with sensory tricks ("gestes antagonistes")

Trophic, vasomotor and sudomotor disturbances
- non-pitting edema (circumference measurements where possible)
- skin color usually reddish-blue, with time more waxy-pale (skin care?)
- skin temperature about 1–2 degrees difference to the contralateral side
- hair growth: usually increased, thick, dark, sometimes reduced, finer hair (shaved?)
- nail growth: usually harder, brittle, faster or slower nail growth (nail care?)
- increased, with time reduced, sweating
- trophic skin lesions or pressure lesions (rarely: differential diagnosis self-harm)

Tendency to spread and become generalized
- at times tendency to spread proximally or to other limbs
- other pain sites; contralateral and generalized reduced pain threshold/body image disturbance
- sensitivity to noise, light, smell, touch, at times with autonomic arousal
- cardiovascular dysregulation, increased heart rate, reduced heart rate variability
- micturition and digestive problems

Affective, cognitive, general signs and symptoms; behavioral changes
- fear, particularly of touch, movement, and disease progression
- avoidance of sensory stimuli from clothes, wind, movement, other people, etc.
- signs and symptoms of trauma-related disorders (helplessness, flashbacks, dissociation, depersonalization, avoidance, hypervigilance/hyperarousal)
- mood fluctuations, depressiveness, alexithymia (reduced awareness of one's own emotions and those of others), withdrawal
- fatigue, sleeping problems, and cognitive disturbances

recommendations distinguish between early (less than 18 months) and persistent CRPS (18). New CRPS subtypes ("CRPS with remission of some features" and "not otherwise specified") were proposed for subsyndromal courses which no longer fully meet the diagnostic criteria or never have (2).

CRPS usually settles within three to 13 months, sometimes even without treatment (20, 21, 24, e28, e74, e130, e131). Complete remissions are rare, though, and difficult to define (21, 24, e132). In more than one half of adult patients at least some of the signs and symptoms persist, especially pain and motor symptoms (20, 24, e28, e74, e130). Although most patients return to work, one third require workplace adaptations, and one third remain permanently unfit for work (20, 24, e74, e130). In about 7%, the CRPS spreads to involve other limbs without any further traumatic event (2, 16, 17, e74, e133, e134).

Differential diagnostic challenges

The differential diagnosis of CRPS is wide-ranging, which inevitably carries with it the risk of being missed or even becoming subject to diagnostic inflation or a diagnosis of convenience (*Table 1*) (15–17, 20, 25, e135). Findings are sometimes difficult to objectify, resulting in discrepancies between history and examination as well as between one examination situation to another (2, 15–18, 25, e136). The fact that the CRPS diagnostic criteria demand that the pain should be disproportionate to the inciting event can lead to it being wrongly attributed to trivial trauma (11). Focus is therefore on a detailed history, clinical examination, and differential diagnostic considerations from an interdisciplinary perspective, together with a careful assessment of the primary injury and repeated (photographic) documentation (2, 15–18, 25). The Budapest criteria are assessed in comparison with the healthy side, paying due respect to risk factors and additional symptoms (*Box 1*, *Box 3*).

A particular distinction must be made from rheumatic, vascular/vasomotor, infectious, (functional) neurological, psychosomatic/psychiatric disorders, and complications from previous treatment (*Table 1*) (11, 15–17, 20, 25, e23–25, e110–e114, e135–e142). The longer CRPS has been present, the more difficult is the differentiation from chronic non-use/underuse of other origin (15). Referral to an interdisciplinary center should be arranged if there are any doubts, complications (symptom spread, fixed dystonia, skin lesions/infections, malignant edema, severe psychological burden, desire for amputation), or no improvement after about two months (15–18) (*Table 1*).

Examinations in the medicolegal setting reveal high rates of simulation, somatoform/functional disorders, opioid dependency (e143–e145), as well as deterioration of signs and symptoms instead of improvement over time (e136). For the purposes of an expert opinion with near complete proof of causality, the diagnosis of CRPS is often insufficient: The German pain assessment guideline refers to CRPS as an "extraordinary chronic pain syndrome" and a "special case", and rejects trivial trauma as a negligible and interchangeable cause (e135, e146). For confirmation of a comprehensible causal relationship, it demands a (contentiously early) onset of symptoms within a few days to two weeks after the inciting event.

Treatment

Treatment is centered around an inflammatory and particularly sensitive acute phase and an early and late rehabilitation (*Table 2*) (15–18, e147). Prior to that, it is worth considering prevention even before CRPS becomes manifest. The key therapeutic principle is functional restoration, guided by graded occupational

TABLE 1

Subspecialties involved in interdisciplinary clinical diagnostic workup of complex regional pain syndrome (CRPS)

Specialty	Main issues	Differential diagnoses or comorbid diagnoses relevant for the further clinical course (selection)
Trauma/hand/foot surgery, possibly vascular surgery	• CRPS-related or independent structural damage • indication for surgical intervention	• osteoarthritis, arthritis, ligament injury, (unstable) fracture, non-union • soft-tissue infection, compression syndrome, thrombosis, vasculitis, erythromelalgia, lipedema//lymphedema • plate break, foreign body, factitious manipulation (ligature mark? frostbite?)
Neurology, possibly neurosurgery	• (differential) diagnostics of peripheral nerves • differentiated assessment of sensorimotor function • pain differentiation • consider cerebral imaging and functional diagnostics • pharmacological, or possibly interventional, treatment	• peripheral nerve/plexus injury, mono/polyneuropathy • neuralgic shoulder amyotrophy, syringomyelia, neuroborreliosis, post-zoster neuralgia • neuroma, glomus tumor • central thalamic pain • motor dysfunction, e.g. focal dystonia, Parkinson's syndrome • functional neurological disorder, including clenched fist syndrome*1
Pain therapy, possibly rheumatology	• pain differentiation (local, regional, widespread, nociceptive, neuropathic, nociplastic) • chronification risks, substance abuse, resources • pharmacological, or possibly interventional, treatment	• generalized pain disorder, e.g., fibromyalgia syndrome, rheumatism • comorbid/pre-existing pain disorder, e.g. migraine • drug dependence or opioid-induced hyperalgesia
Clinical psychology, psychosomatics, psychiatry, psychological or medical psychotherapy	• psychological symptoms/comorbidity • context factors (above all psychosocial burden, identification with the sick role, resources)	• functional/dissociative/somatoform (ICD-11: bodily distress) disorder*2 • self-harm, factitious disorder*3, e.g. Secretan's syndrome*4 • body integrity identity disorder*5 • anxiety/post-traumatic stress disorder, depression • suicidal tendencies
Rehabilitation medicine, occupational therapy, and physiotherapy	• range of motion/flexibility and limb use • self-care ability and ability to work	• non-physiological movement patterns • sensorimotor or body perception disturbances • inactivity atrophy, joint stiffness • deconditioning or muscle imbalance, even beyond the CRPS region itself • activities of daily living and functional capacity • distinction from aggravation/simulation/dissimulation

*1 usually painful, tightly clenched fingers with no vaso- or sudomotor changes
*2 continuing pain, sensory or motor disorders, without or with only slight vaso- or sudomotor changes, yet with underuse, psychosocial burden, and dysfunctional attention/expectations/behavior (numerous overlaps with functional neurological disorders)
*3 e.g., constrained postures; manipulations such as ligature marks, hypothermia, discoloration; desire for amputation
*4 from blows (e.g., against the wall, table edge; known as wall-banging) resulting in inflammatory, often bluish, edematous, peritendinous fibrosis extending from the dorsum of the hand to the wrist
*5 desire for a physical disability, often dating back to the teens, and often associated with body image disturbance and desire for amputation

therapy and physiotherapy—Harden et al. (18) even spoke of "reanimation". This is facilitated by psychological, physical, pharmacological, and, in individual cases, invasive pain management (15–18). The primary therapeutic goal is a lasting improvement of function and participation. With this in mind, chances and risks of all therapeutic measures must be weighed up against each other. Possible barriers to recovery, including iatrogenic issues, must be taken into account (15–18). Throughout every phase of treatment, all passive, fear or pain amplifying, and movement restricting measures against the patient's will or outside the patient's control, including unannounced touching and nocebo messages, are contraindicated (15–18).

Prevention

Of central importance are as little tissue traumatization and immobilization as possible, adequate pain relief, and detailed information for the patient with regard to normal findings and ranges of movement (*Table 2*) (8, 15–18, e23–25, e125, e148–e154). The incidence of CRPS after radius fractures appears to fall if patients are taught light range-of-motion exercises early on (e153); physiotherapy and occupational therapy, together with explicit motor imagery (see below), appear to reduce pain and improve function (e154). There is some controversy concerning any preventive anti-inflammatory effect of ascorbic acid (16–18, e155, e156); this agent does not find mention in the DGN CRPS guideline (15).

The treatment of manifest CRPS

Treatments are usually delivered within individually tailored, multimodal programs that have been shown to be effective (15–18, 26–28, e23–e25, e146, e157–e162). Available data supporting specific individual interventions (see below) are insufficient, comprising only a few randomized controlled trials, mostly

TABLE 2

Principles of staged treatment of complex regional pain syndrome (CRPS)

Strategy	Examples
Primary and secondary prevention	
• as little tissue traumatization and immobilization as possible • psychoeducation with a reassuring and activity-orientated approach • good post-traumatic or peri-/postoperative analgesia	• avoid unnecessary invasive operative techniques, repeated fracture reductions and restrictive, malpositioned immobilization • encourage and provide guidance for early use, e.g. "It is good for the healing process if you touch and move your fingers; I'll show you how to do it." • explain transient, physiological signs of injury/immobilization*, e.g., "temporary pain, swelling, sensitivity to touch, sometimes even slightly increased hair growth, often develop after such disorders / injuries / operations and usually settle quite soon." • monitor closely, especially in the presence of risk factors
Acute phase and early rehabilitation	
• Instructions on using and reintegrating the limb • Symptomatic therapy In particular, passive measures must not interfere with function and participation.	• early, active physiotherapy and occupational therapy together with identification and reduction of dysfunctional movement patterns, fears and avoidance behavior • integration of playful and distracting exercises at home, relevant to everyday life, e.g. by using MindMotion GO, Orientate app, Recognize app • integration of imagination, relaxation, hypnosis, learning, biofeedback, distraction and acceptance and commitment techniques • tolerable physical measures, such as contrast baths /carbonic acid baths, heat and cold application, electrotherapy/transcutaneous electrical nerve stimulation (TENS), acupuncture • early anti-inflammatory drug therapy and individually tailored analgesic pharmacotherapy • medical aids: e.g. flat-knit custom-made compression gloves and stockings (class 1), (night) positioning splint, functional or, possibly, gentle static/dynamic correction splint (e.g. Moberg); crutches, wheelchair • consider supplementary options such as concentrative movement therapy, Feldenkrais method, yoga, Tai-Chi, aerobic exercise, aquatic physiotherapy, pacing, sleep hygiene
Late rehabilitation and reintegration	
• Promote autonomy and participation • Use individual resources, consider individual barriers to recovery	• assess and support social and vocational rehabilitation or home/workplace modifications • realistic information about pension/compensation claims; consider whether short-term or partial disability pension might be better than a full disability pension • in cases of treatment stagnation/setback: – consider widening assessment of findings and differential diagnoses – guideline-based treatment of somatic and mental comorbidities – identification of conflicting goals, consider developing alternatives to the sick role

* dolor, associated also with allodynia/hyperalgesia, tumor, rubor, calor, functio laesa, occasionally also trophic changes such as excessive hair growth or disuse osteopenia

involving small or (considering the low specifity of diagnostic criteria) heterogeneous populations (*Table 2*).

Active forms of treatment

Physiotherapy and occupational therapy

The key recommendation of current guidelines throughout all treatment phases is physiotherapy and occupational therapy, together with neurocognitive elements or components of behavioral therapy aiming at the normalization of sensorimotor integration. This is achieved by graded exposure to strength and movement as well as visuo-tactile stimulation and discrimination (*Table 2*) (8, 15–18, 29–31, e23–e25, e163–e185):

- The Perfetti method and graded motor imagery are directed towards cortical reorganization by means of left-right discrimination training (recognizing photos of limbs in different positions of function), explicit motor imagery, and mirror therapy (projecting the healthy, positively connotated limb onto the affected side) (8, 15–18, 29–31, e23–e25, e80, e163–e172). The patient is introduced as early as possible to individual leisure activities/work requirements by self-exercises, also with the help of computer applications (e173–e181). Mirror therapy appears to be particularly effective for post-stroke CRPS (15, 29 e168), but it is not sufficient on its own for the majority of cases. Indeed, mirror therapy can even make individual cases worse, or result in the development of symptoms on the contralateral side, (15, 29, e169). Overall, neurocognitive procedures appear to improve function more than alleviate pain (27, 29, e169).
- There is adequate proof that graded exposure can improve function, pain, and fear (15–18, 26, e182).

Perceptual disturbances, kinesiophobia and dysfunctional protective behavior are adressed and gradually reduced by graded exposure and the violation of dysfunctional expectations. In such an approach, occupational therapy, physiotherapy and psychology work closely together.

Pain exposure without psychological support is a subject of controversy because of frequent discontinuations of treatment; therefore, it is no longer recommended (15, 18, 26, 31). Self-efficacy, fitness and body-mind techniques, integrated into an overall treatment concept which includes playful or meditative methods, often in groups, can additionally improve body perception and control in a cost-effective way with few side effects (*Table 2*, 16, 17, 26, e24). Studies dealing with this, however, are lacking.

Psychological treatment

Current guidelines recommend stepped psychological interventions (*Table 2*) (15–18):

- Teaching a biopsychosocial explanatory model which provides motivation and instructions for the best possible active and fear-free use of the limb (psychoeducation) is conducted immediately by the attending "somatic" healthcare staff (15–18, e152, e153). For this purpose, patients need information, repeated often and in reassuring, layman's language, which they can then put into action.
- Within the framework of multimodal treatment, clinical psychologists conduct a more differentiated form of psychological pain therapy, oriented predominantly towards cognitive behavioral therapy and often also in groups to enable exchange with fellow patients (15–18).
- Guideline-based psychotherapy provided by board-certified medical/psychological psychotherapists may be indicated for intractable cases and patients with considerable biographical or current stresses and strains and/or mental comorbidity (15–18).

However, the level of evidence covering psychoeducative/psychological and, above all, psychotherapeutic interventions for CRPS is low and for the most part derived from other chronic pain disorders (8, 15–18, 34, e23–e25, e159, e186–e192).

Passive forms of treatment

Medication

The focus of pharmacotherapy (*eTable 1*) is also primarily on maintaining function (15–18): Sedatives, for example, improve tension and sleep disturbances, yet interfere with treatment cooperation and participation (fitness to drive!). It is important to inform patients in detail about risks/side effects, the need to gradually increase the dose until adequate levels are reached, to consider a possible delayed, sometimes absent, effect, and to discontinue or withdraw if necessary (15–18, 34, e193). Medication needs decrease and self-efficacy improves by incorporating active, non-pharmacological interventions such as relaxation methods.

Pharmacotherapy is based almost without exception on off-label drugs where evidence is limited (*eTable 1*) (8, 15–18, 26–28, 32, e23–e25, e194–e209). Current treatment recommendations vary: The German guideline recommends anti-inflammatory bis-phosphonates and steroids which are of equal value for the acute inflammatory phase (15), the British guideline recommends only bisphosphonates (16), while the position paper of the European Pain Federation recommends neither (17). The DGN CRPS guideline regards oral pain pharmacotherapy as a basic measure (15) and recommends gabapentinoids with some reservations and ketamine with strict indications (15). Other guidelines are more cautious and recommend prescribing analgesics only when stopping rules are established due to their frequent ineffectiveness and side effects (17) or only when functional restoration is not possible without them (18). Beyond that, many guidelines refer to the more established treatment recommendations that exist for neuropathic pain (for example, the use of gabapentinoids, antidepressants, possibly botulinum toxin, 15–17, 33, e209), although even CRPS 2 only partially meets the definition of neuropathic pain (18, e210).

Current guidelines hardly mention the use of topical agents with their various chemical properties (15–18). Their advantage lies in their minimal side effects. In addition, the tactile stimulus when applied by the patients themselves provides better somatotopic representation and motor control. The German guideline points out that dimethyl sulfoxide cream is standard therapy in the Netherlands (15, 26). Other substances with an effect on the central nervous system, such as naltrexone and memantine, as well as immunomodulatory drugs are regarded as experimental and thus not yet recommended (15–18, 26–28, 32, e24, e160, e211, e212).

Physical therapy and medical aids

Passive physical measures, including transcutaneous electrical nerve stimulation (TENS) and acupuncture, are directed primarily at edema and pain relief, and medical aids towards better functionality (*Table 2*). According to modern guidelines, manual lymphatic drainage is suitable for edema treatment (15, 17), while other procedures are either not mentioned at all or only briefly touched (16–18, 26). There are hardly any studies on this, and these are contradictory. (15–18, 26–28, e24, e213–e217).

Interventional therapies

Where interventional measures reduce—albeit temporarily—pain and restricted movement, they open a window of opportunity for active rehabilitation. Given that they are associated with higher costs, risks and, possibly, repeated experience of pain and helplessness, however, they require a strict indication, especially when they are demanded by the patients themselves (15–18). They are reserved for unequivocal, severe

CRPS where conservative measures have been exhausted (15–18).

According to current guidelines, including the DGN CRPS guideline, there is the option of spinal cord stimulation for intractable CRPS of the lower limbs (*eTable 2*) (15–18, 26, e218). Recent reviews and a current randomized comparative study suggest that direct dorsal nerve root stimulation has probably fewer side effects and is longer lasting than spinal cord stimulation (15, 18, 34, e219–e224). Intrathecal baclofen may be considered for intractable dystonia (15, 16, 18). So far the evidence is not convincing for any other approaches; for example, with regard to the duration of action of transcranial magnetic stimulation, and the risk-benefit profile of more invasive methods *(eTable 2)* (15–18, 26–28, e23–e25, 34, e225–e237).

Future prospects

Peripheral and central, physiological and psychological mechanisms appear to work together in CRPS. Diagnosis specificity and treatment effectiveness seem to improve when neuropsychobehavioral findings are taken into consideration. This is reflected in modern guidelines and the IDC-11, but not yet in the CRPS diagnostic criteria. Sensitive early warning signals, specific clinical criteria and biomarkers, as well as properly targeted prevention/treatment strategies should be further developed—while still maintaining a differentiated look at comorbidities und differential diagnosis.

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► **Supplementary material**

eReferences, eTables, eBox:
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eBOX

Technical investigations, useful for differential diagnostics of CRPS*

Three-phase bone scan with technetium-99m diphosphonate (qualitative evaluation)
- Normal result does not exclude CRPS
- Possible demonstration of a not very sensitive (31–50%), but specific (77–100%) band-like juxta-articular radionuclide scan uptake
- May support the diagnosis, especially during the first year—but its validity decreases with increasing duration of illness

Conventional X-ray diagnostics and computed tomography (bone density tests)
- Normal result does not exclude CRPS.
- Common, nonspecific asymmetrical juxta-articular patchy osteopenia as compared with the contralateral side, in about one half of CRPS patients after 4–8 weeks, as also seen in other disorders
- Not to be confused with osteoporosis secondary to physical inactivity

Magnetic resonance imaging
- Normal result does not exclude CRPS
- Sometimes, subcutaneous/periarticular contrast uptake and (nonspecific) bone marrow edema/bone bruises
- Occasional demonstration of nerve injury in cases of CRPS 2
- But does not reliably differentiate CPRS, serves instead to exclude some differential diagnoses

Temperature measurement
- Normal result makes CRPS unlikely
- Thermography, infra-red thermometer, thermal imaging camera
- Repeated or long-term measurements in particular reveal temperature differences in comparison with the contralateral side, as well as asynchronous fluctuations and oscillations between left and right side

Quantitative sensory testing (QST)
- Normal result makes CRPS unlikely
- Thermal hypoesthesia, mechanical and thermal hyperalgesia support the diagnosis of CRPS
- Does not reliably distinguish from normal fracture healing, however

Electrophysiology
- Normal result militates against CRPS 2
- In CRPS 2, reduced amplitude and/or reduced nerve conduction velocity in motor/sensory nerve conduction studies; signs and symptoms, however, do not correspond to a definite nerve distribution
- Occasionally nonspecific abnormalities in CRPS 1
- Caution: strict indication essential for needle electromyography

Laboratory tests (blood, skin biopsy, and the like)
- No reliable CRPS marker available to date
- Normal result militates in favor of CRPS
- Elevated serum osteoprotegerin (osteoblast activity marker) may reveal increased bone turnover during the first six months just as well as a bone scan.

*Given the wide-ranging differential diagnosis, only the most important procedures are presented here.
CRPS, complex regional pain syndrome

eTABLE 1

Pharmacotherapy of complex regional pain syndrome (CRPS)

Substance class	Mode of application and primary mode of action	Comments	CRPS-LL [*1]
Bisphosphonates	PO, IV, IM Osteoclast inhibitory, anti-inflammatory, immuno-modulatory effects	• seven RCTs • in the acute phase, when duration of illness <12 months • poor oral absorption, tolerability and risk profile unfavorable with IV administration (caution: osteonecrosis of the jaw) • no potential for addiction	+
Glucocorticoids	PO Anti-inflammatory, as well as immunomodulatory and analgesic	• two RCTs • in the acute phase, as early as possible within the first six months • extracorporeal shock wave therapy for two weeks, not for maintenance therapy • effects evident possibly within three weeks • relatively few side effects, no potential for addiction	+
Gabapentinoids	PO Central, probably also peripheral, pain modulation	• one RCT on gabapentin: poor effect; better effect on disturbances of sensory function than on pain • effective against neuropathic (in some cases of CRPS 2), possibly also against nociplastic pain • only case report to date on pregabalin in children, no RCT; nevertheless, surprisingly uncritical prescription • gabapentin and pregabalin approved, and first-choice drug, for neuropathic pain[*2] • caution: potential for addiction to pregabalin; guideline warning regarding use for neuropathic pain in patients with comorbid addiction[*2]	(+)/(-)
Tri-/tetracyclic antidepressants	PO Central pain modulation	• evening dose utilizes sedative effect; otherwise, relatively unfavorable side effects • low dose is usually adequate but is usually insufficient for the treatment of comorbid depression • no potential for addiction • first choice for neuropathic pain[*2] • amitriptyline is approved for neuropathic pain • caution: combination of amitriptyline with a CYP2D6 inhibitor (especially duloxetine)[*1]	NM
Serotonin noradrenalin reuptake inhibitors	PO Central pain modulation	• possible synergistic improvement of pain, motivational drive, and mood in cases of comorbid anxiety disorder/depression • drive-enhancing effect, usually to be taken in the morning • no potential for addiction • SSRI: negative recommendation for neuropathic pain[*2] • SNRI: only duloxetine (approved for diabetic polyneuropathy) is recommended as drug of first choice, weak recommendation for venlafaxine[*2] • caution: combination of a CYP2D6 inhibitor (especially duloxetine) with amitriptyline[*1]	NM
Ketamine	IV Central neuroplastic, neuro- and pain modulation	• two RCTs • good, rapid, but only short-lasting analgesia • many risks; caution: addiction, intoxication, angina pectoris, increased heart rate and blood pressure, organ toxicity • individually titrated, single continuous infusion under inpatient conditions in intractable cases • requires strict indication, including thorough evaluation of mental comorbidities and continuous monitoring in specialist centers • negative recommendation for neuropathic pain[*2]	(+)
Opioids	PO Central analgesic	• mainly preventive and in the acute phase • longer-term therapeutic use only in case of positive effect and few or tolerable side effects[*3] • are viewed with increasing skepticism; caution: addiction, opioid-induced hyperalgesia, sedation, sleep disturbances • third choice treatment for neuropathic pain[*1] • possible advantage of tramadol (proven for neuropathic pain)/tapentadol (assumed): μ-opioid receptor agonism and noradrenergic/ serotonergic reuptake inhibition	NM
Non-steroidal anti-inflammatory drugs, COX-2 inhibitors	PO Peripheral analgesic, anti-inflammatory	• two RCTs • preventative measure after injuries/surgery, in particular, possibly also in the acute phase • efficacy in CRPS not proven • negative recommendation for neuropathic pain[*1]	NM
Botulinum toxin A	IM/SC Reduces muscle contraction/ sweating; probably also has a local analgesic effect	• third choice (SC) for focal neuropathic pain[*1] • according to CRPS guideline, option (IM) for treatment-limiting focal dystonia, but with no clear recommendation	(+)

Cannabinoids	PO/SL Central pain modulation	• off-label third-line treatment attempt with oral cannabis extracts when other pain treatments have failed • after submitting an application pursuant to section 31 subsection 6 German Social Security Code (SGB) Part V • caution: sedation/adynamia, enhanced anxiety, psychoses • considering its minimal effect and high side-effect rate, no recommendation for neuropathic pain*1	NM
N-acetylcysteine (NAC)	PO Free radical scavenger	• one RCT • treatment attempt for cold CRPS	(+)
Dimethyl sulfoxide (DMSO) – ointment	Topical Free radical scavenger	• one RCT • standard therapy in the Netherlands	(-)
5% lidocaine patch	Topical Local analgesic	• second choice for neuropathic pain*2, especially recommended for focal nerve injury due to its lower side effects rate*2	NM
20% ambroxol cream	Topical Local analgesic	• initial data encouraging	NM
8% capsaicin patch	Topical Local analgesic	• early use recommended • must be applied and removed by qualified medical staff • duration of action around 12 weeks after single application for one hour • for neuropathic pain/allodynia in particular • approved for neuropathic pain secondary to CRPS • second choice for neuropathic pain*2, but preferably used for focal nerve injury because of its lower side effects rate*2	NM
10% ketamine cream	Topical Local analgesic	• initial data encouraging	NM

*1 according to CRPS guideline weak recommendation +; recommendation with restrictions (+); no recommendation -; data too unclear: (-); NM not mentioned
*2 according to S2k guideline "Diagnosis and Non-Interventional Treatment of Neuropathic Pain"
*3 according to S3 guideline "Long-term Administration of Opioids for Non-tumor Pain (LONTS)"
CRPS, complex regional pain syndrome; CRPS-LL, S1 guideline "Diagnostic and Treatment Guidelines for Complex Regional Pain Syndrome"; IM: intramuscular; IV: intravenous; PO, oral; RCT, randomized controlled trial; SL: sublingual; SNRI, serotonin noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor;

eTABLE 2

Technical or invasive interventions for complex regional pain syndrome (CRPS)

Procedure	Mode of application	Comments	CRPS-LL*[1]
Dorsal root ganglion (DRG) stimulation	Not local, invasive	• one controlled study • possible alternative to SCS: longer pain relief and fewer side effects • only in patients with no significant mental comorbidity • after successful test stimulation	(+)
Spinal cord stimulation (SCS)	Not local, invasive	• one RCT • in CRPS of the lower limb without mechanical allodynia and without significant mental comorbidity • after successful test stimulation • S3 guideline on spinal cord stimulation: weak recommendation for CRPS 1, "open" recommendation for CRPS 2*[2]	(+)
Intrathecal baclofen	Not local, invasive	• one small RCT, one controlled study • high complication rate, e.g. infection, low cerebrospinal fluid pressure syndrome, urinary retention • painful and treatment-limiting dystonia not manageable by conservative treatment • only in patients with no significant mental comorbidity; consider an underlying functional cause in intractable cases (or with an immediate effect) • reserved for specialist enters • test injection prior to maintenance therapy	(+)
Sympathetic trunk block	Not local, invasive	• three RCTs • for intractable confirmed sympathetically maintained pain (SMP) 10(–15) blocks (SMP clinically, difficult to differentiate) • reserved for specialist centers • caution: risks, above all: infection, neurovascular injury – no serial injections without significant improvement	(+)
Repetitive transcranial magnetic stimulation	Not local, not invasive	• one RCT • reduces pain possibly for some days by modifying central pain processing • caution: epilepsy is a contraindication • may be tried in individual intractable cases	(+)
Plasmapheresis	Not local, invasive	• no RCT • caution: risks, above all infections, clotting abnormalities	(-)
Sympathectomy/sympathetic nerve ablation	Not local, destructive	• caution: high risk of deafferentation pain/neuralgia and motor function deterioration	(-)
Various pain catheters	Not local, invasive	• no RCT, only case reports using various substances, e.g. local anesthetics, clonidine • caution: risks, above all infections, neurovascular injury	NM
Hyperbaric (100%) oxygen therapy	Not local, invasive	• one RCT • uncertain benefit-risk ratio	NM
Various surgical procedures for findings worthy of surgery	Local invasive	• e.g. joint stabilization or nerve decompression • dilemma: local procedures (and hence renewed traumatic injury) usually aggravate signs and symptoms. However, symptomatic recovery is sometimes achieved in isolated cases by surgical removal of local painful/inflammatory stimuli or by improved perfusion/innervation, above all when nerve compression has resulted in CRPS 2.	NM
Amputation	Local destructive	• last resort in rare individual cases • caution: high risk of clinical (e.g. deafferentation pain) and functional deterioration • caution: mental comorbidity, above all factitious and body integrity identity disorders	NM

*[1] According to S1 guideline "Diagnostics and Treatment of complex regional pain syndrome (CRPS)": recommendation with restrictions: (+); available data too uncertain: (-); not mentioned: NM
*[2] According to S3 guideline "Epidural Spinal Cord Stimulation for Treatment of Chronic Pain"
CRPS, complex regional pain syndrome; CRPS-LL, S1 guideline "Diagnostics and Therapy of Complex Regional Pain Syndrome"; DRG, dorsal root ganglion; RCT, randomized controlled trial; SCS, spinal cord stimulation

Questions on the article in issue 51–52/2022:

Modern Principles of Diagnosis and Treatment in Complex Regional Pain Syndrome

cme plus

The submission deadline is 26 December 2023. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

What are risk factors for developing CRPS?

a) prolonged immobilization, high initial pain intensity, female sex
b) mobilization encouraged too early, depression, male sex
c) infectious diseases, reduced general condition, advanced age
d) history of addiction, heavy physical work, migration background
e) ADHD, unemployment, adolescence

Question 2

What is meant in the article by the term nociplastic pain?

a) potentially reversible pain after plastic surgery
b) pain due to potentially reversible central hypersensitivity to stimuli without tissue or nerve damage
c) pain due to irreversible central hyposensitivity to stimuli with tissue damage
d) potentially reversible delusional pain associated with neoplasm
e) irreversible pain due to toxic nociceptive stimulation

Question 3

A 63-year-old worried female patient presents for follow-up to confirm maintained reduction of a distal radius fracture managed conservatively. What do you discuss with her?

a) That complications during the course of healing are likely due to her age
b) That she must expect continuing pain
c) That she does not need to consult a doctor again, even if she notices unusual signs and symptoms such as changes in skin color, in nail or hair growth
d) That she should touch the fingers of the affected hand as normally as possible and carefully move them
e) That she should take medication to treat her anxiety

Question 4

Which symptoms commonly occur with CRPS but are not yet included in the diagnostic criteria?

a) lack of appetite, weight loss, night sweats
b) body perception disturbance, e.g., experiencing the affected limb as alienated
c) mood fluctuations, self-harm tendencies, ligature marks
d) crepitations or air inclusions in tissue
e) exhaustion, abscess formation, fever

Question 5

How is the diagnosis of CRPS confirmed or excluded?

a) The diagnosis of CRPS is excluded by normal findings on X-ray in comparison with the healthy side.
b) A bone scan is required to confirm the diagnosis of CRPS.
c) CRPS is a clinical-interdisciplinary diagnosis confirmed according to the Budapest criteria.
d) Evidence of nerve damage is required for the diagnosis of CRPS.
e) The diagnose of CRPS is confirmed by quantitative sensory testing.

Question 6

What is the treatment of CRPS?

a) A predominantly surgical approach by joint release, tenolysis and/or neurolysis
b) A predominantly passive-analgesic approach using the WHO Analgesic Ladder
c) A predominantly interdisciplinary approach using rehabilitation and pain medication
d) A predominantly psychotherapeutic approach applying the principles of depth psychology
e) As time-saving and cost-reducing as possible because treatment is usually unsuccessful

Question 7

What is "graded exposure" in physiotherapy and occupational therapy of CRPS?

a) Gradual stepwise approach to the accident location with psychological support
b) Passive mobilization of the affected limb several times a day
c) Gradual, stepwise, motor and sensory exercises with psychological support
d) Exposure to the pain without psychological support
e) Staged dosing of analgesics

Question 8

What are the core elements of graded motor imagery?

a) Massage, manual lymph drainage, continuous passive motion machine
b) Adequate immobilization, then mobilization under anesthesia
c) Opioid titration, passive physiotherapy, then opioid withdrawal
d) Confrontation with images of severe CRPS cases on the computer or using VR eyeglasses.
e) Left-right discrimination training, explicit motor imagery, mirror therapy

Question 9

How can the typical signs of inflammation in patients with early CPRS (swelling, redness, increased warmth) be alleviated?

a) Bisphosphonates or steroids, manual lymph drainage
b) Steroid injection into the affected joints, strict immobilization
c) Shock wave therapy under sedation, possibly under hypnosis
d) Lidocaine patch, if ineffective then fentanyl or buprenorphine patches
e) Antibiotic treatment based on antibiogram

Question 10

Which groups of substances are suitable for symptomatic medical management of the neuropathic pain components of CRPS?

a) Steroids
b) Antidepressants and antiepileptic drugs/gabapentinoids
c) Bisphosphonates
d) NSAR
e) Ketamine