Complex regional pain syndrome (CRPS) is the result of changes to the somatosensory systems that process noxious, tactile, and thermal information; to the sympathetic systems that innervate skin (blood vessels, sweat glands); and to the somatomotor systems. The changes suggest that the CNS representations of the systems have been altered. Patients with CRPS also have peripheral changes (e.g., oedema, signs of inflammation, sympathetic-afferent coupling [the basis for sympathetically maintained pain], and trophic changes) that cannot be explained by central changes. On the basis of clinical observation and research in human beings and animals, we hypothesise that CRPS is a systemic disease involving the CNS and peripheral nervous system. The most important question for future research is: what causes CRPS? In this article, we suggest a change to the focus of research efforts and treatment. We also suggest that there be diagnostic reclassification and redefinition of CRPS.

Lancet Neurol 2003; 2: 687–97

Complex regional pain syndromes (CRPSs) are painful disorders that develop as a disproportionate consequence of traumas. These disorders are most common in the limbs and are characterised by pain (spontaneous pain, hyperalgesia, allodynia), active and passive movement disorders (including an increased physiological tremor), abnormal regulation of blood flow and sweating, oedema of skin and subcutaneous tissues, and trophic changes to skin, organs of the skin, and subcutaneous tissues.1–6

CRPS I (previously known as reflex sympathetic dystrophy) typically develops after minor trauma with no obvious or a small nerve lesion (e.g., bone fracture, sprains, bruises, skin lesions, or surgery). CRPS I can also develop after remote trauma in the visceral domain or even after a CNS lesion (e.g., stroke). Important features of CRPS I are that the severity of symptoms is disproportionate to the severity of trauma and pain has a tendency to spread distally in the affected limb. The symptoms are not confined to the innervation zone of an individual nerve. Thus, all symptoms of CRPS I may be present irrespective of the type of the preceding lesion. Furthermore, the site of the lesion at the limb does not determine the location of symptoms. CRPS II (previously known as causalgia) develops after a large nerve lesion.

This classification of CRPS is based on a consensus between clinicians and basic scientists and is practice-based, not mechanism-based.1–4 Although both CRPS I and CRPS II are categorised under neuropathic pain they seem to be mechanistically rather different syndromes. CRPS II (nerve lesion present) is by definition a neuropathic pain syndrome. However, the more common CRPS I is unlikely to be a neuropathic pain syndrome. Patients with CRPS I do not have an obvious nerve lesion, but the neuropathic pain results from injuries or diseases that affect the peripheral nervous system or the CNS.7

CRPS I is a fascinating syndrome for basic and clinical scientists. Various traumas can trigger combinations of clinical phenomena in which the somatosensory system, the sympathetic nervous system, the somatomotor system, and peripheral (vascular, inflammatory) systems are involved. Also, intensity and combination of clinical symptoms are out of proportion with the causal lesion. This situation has been extensively described since Silas Weir (causalgia/CRPS I),10–12 Paul Sudeck (CRPS I),13,14 René Leriche,15,16 John Bonica,17 and others. The work has created the present jungle of names, theories about the mechanisms that underlie this syndrome,18–20 and recommended treatment options.

By use of an integrative approach with basic and clinical research we argue that the mechanisms that underlie this syndrome can be explained.21 In this review we primarily focus on CRPS I because this syndrome is much more prevalent than CRPS II. However, mechanisms that underlie CRPS II are included in so far as patients with CRPS II may have all the symptoms seen in patients with CRPS I.

Observations in patients and mechanisms

Results of experiments in patients with CRPS and quantitative clinical data clearly set the stage to formulate hypotheses that can be tested experimentally with various in vivo or in vitro animal models, or in human beings. Any model is an approximation of the clinical situation and research on mechanisms should focus on quantifiable symptoms seen in patients (e.g., mechanical allodynia, spontaneous pain, tremor, changes of blood flow, swelling, etc). Each symptom can be generated by more than one mechanism depending on the patient. Experimental models used to study the underlying mechanisms of CRPS cannot represent CRPS I or CRPS II as such, at least not in the first approach. For this purpose patients are the best.

WJ is at the Department of Physiology and RB is at the Neurological Clinic, Christian-Albrechts-University of Kiel, Kiel, Germany.

Correspondence: Prof Wilfrid Jänig, Physiologisches Institut, Christian-Albrechts-Universität zu Kiel, Olshausenstrasse 40, 24098 Kiel, Germany, Tel +431 880 2036; fax +431 880 5256; email w.janig@physiologie.uni-kiel.de
Somatosensory abnormalities and pain

Until recently, experimental investigations of CRPS have mainly concentrated on pain, sympathetically maintained pain (SMP), and abnormalities at the skin. This led to a rather limited view with the tendency to put the nociceptive system and its peripheral (and maybe central) coupling to the sympathetic nervous system into the foreground. Yet clinical observations of CRPS I show that the pain is commonly projected into the deep somatic tissues, that many patients do not have SMP (as judged by clinical criteria; eg, significant decrease in pain following sympathetic blocks), and that 5% of the patients do not even have spontaneous pain but have evoked pathological pains.

Sensory systems

Most patients with CRPS I have a burning spontaneous pain felt mostly deep in the distal part of the affected limb. Characteristically, the pain is disproportionate in intensity to the initial event. The pain usually increases when the limb is in a dependent position. Stimulus-evoked pains include mechanical, cold and heat allodynia, and hyperalgesia. These sensory abnormalities appear early in many patients, are most pronounced distally, and have no consistent spatial relation to individual nerve territories or to the site of the trauma. Pain is typically elicited by movements and pressure at the joints (deep somatic allodynia), even if the joints are not the site of the causal lesion, which indicates that the deep somatic tissues are involved. On the basis of experimental findings in animals, spontaneous pain and various forms of allodynia/hyperalgesia in the distal portion of the limb are thought to be generated by processes of peripheral and central sensitisation.

50% of patients with chronic CRPS I develop hypoaesthesia and hypalgesia on the whole half of the body or in the associated quadrant on the same side as the affected arm. In these patients quantitative sensory testing has shown that thresholds to mechanical, cold, warmth, and noxious heat stimuli are higher on the affected side than on the healthy body side (figure 1). Patients with these extended sensory deficits have a longer illness, greater pain intensity, a higher frequency of mechanical allodynia, and a higher tendency to develop changes in the somatomotor system than do patients with spatially restricted sensory deficits. The anatomical distribution suggests that these deficits are due to CNS changes that may cause widespread alterations in the perception of painful and non-painful sensations.

The central representation of somatosensory sensations is changed, probably in the thalamus and cortex. This theory has been supported by two recent studies of patients with CRPS by use of PET or magnetoencephalography. If generalised sensory deficits in patients with chronic CRPS I are permanent and irreversible, it would be the first documented case of such irreversible changes in the brain that are triggered by trauma with minor or no nerve lesion.

These findings lead to several important questions. Are the generalised sensory changes correlated with neglect-like phenomena in these patients also present in patients with disuse syndrome? And, therefore, is one common denominator of CRPS, neglect-syndrome, and disuse syndrome an absent input from deep somatic tissues (skeletal muscles, joints, fascia) to the central representations? Most patients with CRPS I have deep somatic spontaneous pain and mechanical

50% of patients with chronic CRPS I develop hypoaesthesia and hypalgesia on the whole half of the body or in the associated quadrant on the same side as the affected arm. In these patients quantitative sensory testing has shown that thresholds to mechanical, cold, warmth, and noxious heat stimuli are higher on the affected side than on the healthy body side (figure 1). Patients with these extended sensory deficits have a longer illness, greater pain intensity, a higher frequency of mechanical allodynia, and a higher tendency to develop changes in the somatomotor system than do patients with spatially restricted sensory deficits.

The anatomical distribution suggests that these deficits are due to CNS changes that may cause widespread alterations in the perception of painful and non-painful sensations.
hyperalgesia/allodynia. Are the non-painful sensations elicited from muscle and joints changed too? Finally, do the generalised sensory changes depend on a continuous nociceptive input from the affected region and disappear after successful treatment of the pain? After all, the continuous nociceptive afferent input could be subthreshold for the conscious perception of pain, but high enough to maintain the central changes.

**Sympathetically maintained pain (SMP)**

On the basis of experience and clinical studies the term SMP was redefined. Patients who present with similar clinical signs and symptoms can clearly be divided into two groups by the positive or negative effect of selective blockade of the sympathetic nervous system or blockade of α-adrenoceptors into those with SMP and those with sympathetically independent pain. SMP is now defined as a symptom in a subset of patients with neuropathic disorders and not a clinical entity and not essential for the diagnosis of CRPS I.

**Influence of sympathetic activity and catecholamines on primary afferents in patients with CRPS**

Clinical studies support the idea that cutaneous nociceptors develop catecholamine sensitivity after partial nerve lesions (CRPS II). Intracutaneous application of norepinephrine into a symptomatic skin area rekindles spontaneous pain and dynamic mechanical hyperalgesia or allodynia that had been relieved by sympathetic blockade. Intracutaneous injection of norepinephrine in control individuals does not elicit pain.

The question arises whether the mechanisms of SMP are similar in CRPS I, even though there is no major nerve lesion present. We used physiological stimuli to excite sympathetic neurons in patients with CRPS I. Cutaneous sympathetic vasoconstrictor outflow to the painful area was experimentally activated to the highest possible physiological degree by whole body cooling. This experimental intervention selectively alters sympathetic cutaneous vasoconstrictor activity without influencing other sympathetic systems innervating the deep somatic tissues (eg, muscle vasoconstrictor neurons). During the thermal challenge the affected region was kept at 35°C in order to avoid thermal effects at the nociceptor level. The intensity of spontaneous pain and mechanical hyperalgesia or allodynia (dynamic and punctate) and the area of dynamic mechanical hyperalgesia or allodynia increased significantly in patients that had been classified as having SMP by positive sympathetic blocks but not in patients with sympathetically independent pain (figure 2).

In these patients, the relief of spontaneous and evoked pain after sympathetic blockade was more pronounced than changes in spontaneous and evoked pain that could be induced experimentally by sympathetic activation. One explanation for this discrepancy might be that a complete sympathetic block affects all sympathetic outflow channels projecting to the affected region. It is very likely that in addition to a coupling in the skin, a sympathetic-afferent interaction may also occur in other tissues, in particular
Complex regional pain syndrome

Animal models lend support for peripheral mechanisms being involved in SMP in CRPS II (figure 3). It should be kept in mind that coupling of sympathetic neurons not only to nociceptive afferent neurons but also to non-nociceptive ones (e.g., mechanosensitive, cold) may turn out to be important. Sympathetic activation of these afferent neurons may excite sensitised or hyperexcitable central neurons of the somatosensory system (e.g., in the dorsal horn) and contribute to mechanical or cold allodynia in patients with CRPS II.

The mechanisms of SMP in CRPS II (i.e., after trauma with nerve lesion) are unlikely to be the same as those in CRPS I, in which only a small part of the coupling occurs in the skin. We suggest that an important sympathetic afferent coupling occurs in the deep somatic tissues and that the mechanism of this coupling is indirect and involves the vascular bed and possibly other non-neural components (figure 4). This way of coupling has been repeatedly postulated but has never been explored experimentally in animal models.

Other potential ways of coupling between sympathetic neurons and afferent nociceptive neurons have been identified in animal experiments, but have not been explored in patients (figure 3). These modes of coupling do not involve activity in the sympathetic nerve fibres, but the sympathetic fibres may mediate the effects of inflammatory factor (e.g., bradykinin) or other compounds (e.g., nerve growth factor) to nociceptive fibres in the peripheral tissue. This sympathetic afferent coupling may turn out to be important in inflammatory pain and in CRPS I.

Finally, the sympathetic nervous system may be coupled with nociceptive neurons via the adrenal medulla (figure 3). This mechanism has been inferred on the basis of behavioural experiments in rats that suggests that epinephrine released by the adrenal medulla (during its activation by preganglionic neurons) causes sensitisation of nociceptors for mechanical stimulation. The process of sensitisation has a slow time course of days to weeks to develop fully.

**Pain relief from sympathetic blockade**

Pain relief outlasts the conduction block of sympathetic neurons by at least one order of magnitude. Sometimes only a few (in extreme cases, only one) temporary sympathetic blockades produce permanent pain relief. The long-lasting pain-relieving effects of sympathetic blockade suggest that activity in sympathetic neurons, which is of central origin, maintains a positive feedback circuit via the primary afferent neurons. Animal models for positive feedback circuits are absent. We postulate that activity in sympathetic neurons maintains a central state of hyperexcitability (e.g., of neurons in the spinal dorsal horn), via excitation of afferent neurons initiated by an intense noxious event. The persistent afferent activity needed to maintain such a central state of hyperexcitability is probably low. This central state of hyperexcitability is switched off during a temporary block of conduction in the sympathetic chain lasting only a few hours and cannot be switched on again when the block wears off and the sympathetic activity (and therefore also the sympathetically-induced activity in afferent neurons) returns.
Finally, unanimous assumption made is that cutaneous (sympathetic and afferent) systems are mainly involved. However, sympathetic systems and afferent systems innervating deep somatic tissues may be more important in this hypothetical positive feedback circuit and need to be investigated experimentally (figure 2).21

**Sympathetic systems and regulation in skin and deep somatic tissues**

In CRPS, abnormalities related to the sympathetic nervous system include changes of sweating and skin blood flow.41,53–59 In the acute stages of CRPS I the affected limb is commonly warmer than the contralateral limb.60 Hypohidrosis or, commonly in acute stages, hyperhidrosis are present in many patients with CRPS I.

**Evidence for a central autonomic dysregulation**

Sympathetic denervation and mechanisms of denervation hypersensitivity cannot account for vasomotor and sudomotor abnormalities in CRPS I because there is no visible nerve lesion.61 In fact, there is direct evidence for a reorganisation of central autonomic control in these syndromes.

Resting sweat output, as well as thermoregulatory and axon reflex sweating, are increased in patients with CRPS I.41,55,60 Increased sweat production cannot be caused by a peripheral mechanism because, unlike blood vessels, sweat glands do not develop denervation supersensitivity.62 We have analysed central sympathetic reflexes in cutaneous sympathetic vasoconstrictor innervation induced by thermoregulatory (whole-body warming, cooling) and respiratory stimuli41,54,55,60 by the measuring of skin temperature and skin blood flow in the limbs. In normal conditions these reflexes do not show differences between the two sides of the body (figure 5). In patients with CRPS three distinct vascular regulation patterns were identified related to the duration of the disorder.

In the warm regulation type (acute stage, <6 months), the affected limb was warmer and skin perfusion values were higher than in the contralateral limb. Even massive body cooling or respiratory stimuli did not activate sympathetic vasoconstrictor neurons.64 Norepinephrine concentrations in the venous effluent above the area of pain were low in the affected region.51,52,53 In the intermediate type, temperature and perfusion were either high or low depending on the degree of sympathetic activity. In the cold type (chronic stage), temperature and perfusion were low while norepinephrine concentration remained low on the affected side.51

---

**Figure 4. The microenvironment of primary afferents is thought to affect the properties of the receptive endings of myelinated and unmyelinated afferent fibres. Top: the micromilieu depends on several interacting components: Neural activity in postganglionic noradrenergic fibres (1) supplying blood vessels (2) causes release of noradrenaline (NA) and possibly other substances and vasoconstriction. Excitation of primary afferents (A/H9254 fibres and C-fibres; 3) causes vasodilation in precapillary arterioles and plasma extravasation in postcapillary venules (C-fibres only) by the release of substance P (SP) and other vasoactive compounds. Some of these effects may be mediated by non-neuronal cells such as mast cells and macrophages (4). Other factors that affect the control of the microcirculation are the myogenic properties of arterioles (2) and more global environmental influences such as a change of the temperature and the metabolic state of the tissue. Reproduced with permission from John Wiley and Sons Ltd. Bottom: hypothetical relation between sympathetic noradrenergic nerve fibres, peptidergic afferent nerve fibres, macrophages (5), and blood vessels (6). The activated and sensitised afferent nerve fibres activate macrophages (via substance P release). The immune cells start to release cytokines, such as tumour necrosis factor α (TNF α) and interleukin 1 (IL 1) which further activate afferent fibres by enhancing sodium influx into the cells. Vasoactive compounds, released from the afferent nerve fibres, react with neurokinin 1 receptors in the blood vessels (arteriolar vasodilation, venular plasma extravasation; neurogenic inflammation).**
Mechanisms of autonomic dysregulation

The few microneurographic studies of small sympathetic nerve fascicles in patients with CRPS do not confirm the presence of sympathetic reflex abnormalities. However, recordings were not done selectively from vasoconstrictor and sudomotor neurons. The analysis of skin sympathetic activity might conceal subtle changes in selective sympathetic channels.

Mechanisms involved in motor abnormalities

The motor changes are unlikely to be related to a peripheral process (eg, influence of sympathetic nervous system on neuromuscular transmission or contractility of skeletal muscle). Because they are lateralised, these changes are possibly related to changes in spinal reflex circuits linked to the motor neurons (ie, they have a central origin). Motor changes may be induced by the continuous nociceptive input. However, why these motor changes may disappear after sympathetic blocks are given is unclear. There are no animal models in which these motor changes can be studied systematically.

The results of kinematic analyses of target reaching as well as grip force analysis to quantitatively assess motor deficits point to a cerebral abnormality in patients with CRPS. A pathological sensorimotor integration in the parietal cortex may induce abnormal central programming and processing of motor tasks. Interestingly, the motor ability was also slightly impaired on the contralateral unaffected side. A recent controlled study also supports a discrepancy between central motor output and sensory input as underlying mechanism in CRPS. By use of a mirror, the visual input from a moving unaffected limb to the brain was able to re-establish the pain-free relationship between sensory feedback and motor execution. After 6 weeks of therapy, pain and function were improved as compared with the control group.

Inflammation and oedema: role of the sympathetic nervous system

The role of oedema and inflammation and their underlying mechanisms in CRPS (in particular CRPS I) are controversial. Swelling is a very common symptom in patients with acute CRPS and mostly extends far beyond the territory of the trauma. The extent of swelling depends very crucially on the aggravating stimuli and may decrease after sympathetic blocks. These findings indicate that activity in
sympathetic neurons maintains swelling, but the underlying mechanism is unknown.

Capillary filtration pressure might be high owing to an imbalance of the activity or pattern of activity between vasoconstrictor neurons innervating precapillary blood vessels and vasoconstrictor neurons innervating postcapillary blood vessels (veins). Venous congestion plethysmography showed that the hydrostatic pressure to achieve net capillary filtration was high on the affected side in patients with CRPS. However, venules and small deep veins are not or only sparsely innervated by sympathetic noradrenergic fibres (figure 4). Thus, the sympathetic fibres do not form close contacts with the smooth muscle cells of the venules as they do with the precapillary resistance vessels.

Sympathetic fibres may be coupled to peptidergic unmyelinated fibres that lead to release of peptides with subsequent precapillary vasodilation and postcapillary (venular) plasma extravasation (neurogenic inflammation; figure 4).

The idea that patients with CRPS I have inflammatory processes in the affected region, in particular in the deep somatic tissues including bones, goes back to Sudeck who believed that this syndrome is an inflammatory bone atrophy ("entzündliche Knochenatrophie").

Accordingly, bone scintigraphy revealed periarticular tracer uptake in 
acute CRPS and synovia biopsies and scintigraphic investigations with radiolabelled immunoglobulins showed protein extravasation, hypervascularity and neutrophil infiltration. Microdialysis through the skin revealed that evoked neurogenic inflammation produced by activation of peptidergic unmyelinated afferents is increased, and that lactate production is increased in the skin, which suggests that hypoxia increases the rate of anaerobic glycolysis. In the fluid of artificially produced skin blisters significantly higher concentrations of interleukin 6 and tumour necrosis factor α were observed in the involved region. Furthermore, on the basis of animal experiments it has been proposed that oxygen-derived free radicals cause increases in vascular permeability, soft tissue damage, and pain.

Although there is some evidence that inflammatory processes are involved in the pathogenesis of early CRPS, the exact mechanisms of initiation and maintenance of these reactions are unclear. Animal studies have shown that the sympathetic nervous system can influence the intensity of an inflammatory process and clinical studies indicate that sympathectomy can ameliorate pain, inflammation, and oedema in human beings. However, this concept has yet to be proven in patients with CRPS.

Conclusions

We have put forward the hypothesis that CRPS is a disease of the CNS as well as the peripheral nervous system (panel 1; figure 6). This indicates that the central representations of these systems are changed. The central changes are reflected

 reviewer
in changes of somatic sensations (including pain), of the motor system and of peripheral autonomically regulated effector systems (vasculature, sweat glands, inflammatory cells, etc) and argue that CRPS, particularly type I, is a systemic disease of these neuronal systems. The peripheral changes cannot be seen independently of the central ones. Both systems interact with each other via the afferent and efferent signals. This view of CRPS indicates that the disorder is not caused by just one system or just one mechanism (eg, sympathetic afferent coupling, adrenoceptor disease, peripheral inflammation, psycho-

genicity). We should also begin to understand how CRPS type I might develop after a trivial trauma, after a trauma remote from the affected region, and possibly after immobilisation of a limb. The multifactorial model of the disease will explain why, in CRPS patients with SMP, a few temporary blocks of the sympathetic supply to the affected region sometimes lead to a long-lasting (even permanent) pain relief and to resolution of the other changes present in CRPS. Finally, it may help us to understand why some patients with CRPS I develop neglect-like symptoms.

Future research and diagnostic classification

Integration of the clinics and basic research

As stated by Woolf and coauthors in 1998, “In creating a mechanism-based classification (of pain) care must be exercised in extrapolating from animal models to clinical mechanisms. Animal models are only approximations. Ultimately, it is advisable to align clinical and human models with animal models to be certain of dissecting a particular mechanism. Caution also needs to be exercised when grouping people based on symptomatology and then testing these people with a drug irrespective of their underlying disease. Once we identify mechanisms (of pain), this should help the evolution of more uniform descriptors for symptoms. A real challenge is to establish operational criteria for distinct mechanisms.”

This type of integrative research is a necessity if we are to unravel the mechanisms that operate in CRPS and if we are to find the organising pathophysiological principles that orchestrate the different changes. It is essential that basic research in animal models (panel 2) and human beings and clinical investigations of CRPS should be closely aligned (figure 7). Even research in human beings is only an approximation to the clinical situation. Research on mechanisms in the models should concentrate on symptoms but not on syndromes.
**The long path approaching the CNS**

In recent years, researchers concentrated on the investigation of peripheral mechanisms that underlie CRPS. We are now at a turning point after recognising that important parts of the CRPS pathophysiology obviously involve the CNS. In the future we will fully understand the neurological components of CRPS and the effects they have on several functional systems that are closely integrated, including the processing of cognitive and affective information.

**Do genes predispose to CRPS?**

One of the unsolved features in human pain diseases is that in patients with the same injury only a few patients develop chronic pain. Similarly, in some nerve-lesion animal models, differences in pain susceptibility were caused by genetic factors. To address this question in patients with CRPS, gene technology has been used to characterise the genetic pattern of patients at risk of CRPS. In 52 patients with CRPS, class I and II major histocompatibility antigens were typed; the frequency of HLA-DQ1 was significantly high in patients. In patients with CRPS who progressed towards multifocal or generalised tonic dystonia, an association with HLA-DR13 was reported. Furthermore, a different locus, centromeric in HLA-class I, was found to be associated with spontaneous development of CRPS, suggesting an interaction between trauma severity and genetic factors that describe CRPS susceptibility.

**Diagnostic classification**

The definition of standardised diagnostic criteria for CRPS in 1994 was a major advance in the classification of regional pain disorders associated with vasomotor or sudomotor abnormalities. On the basis of these criteria, clinical research on mechanisms was done on much more homogeneous groups of patients and studies were, for the first time, comparable. However, continuous improvement of the criteria based on results of systematic validation research is needed. The diagnostic criteria for CRPS are adequately sensitive (ie, they rarely miss a case of actual CRPS). However, both internal and external validation research suggests that CRPS is overdiagnosed. The inclusion of motor and trophic signs and symptoms improves specificity without losing much sensitivity. The establishment of such modified diagnostic criteria will have a huge effect on the quality of studies on pathophysiological mechanisms and therapy. Such a diversified research strategy on CRPS including diagnosis, mechanisms, and therapy provides hope that we will ultimately be able to intervene successfully against this disease.

The variability in symptoms among patients with CRPS I/II makes it difficult to draw conclusions about mechanisms of the disorders based on clinical profiles and could contribute to unclear findings in clinical trials. Strict patient selection based on defined clinical criteria could help to resolve this problem. Epidemiological studies may also help to elucidate the reasons for the variable incidence rates of CRPS in general, the different incidence rates between women and men, and the differences between the disease in children compared with adults. Furthermore, epidemiological studies may serve to work out prospective studies in order to find predictors for the development of CRPS I/II.

Finally, whether clinical staging of patients is a valid concept is unclear. Individual patients probably do not pass through the three stages as is still reported. At the time the new taxonomy was developed, it was felt that staging was no longer a useful concept for a diagnosis of the syndrome.

**Future therapies**

The poor understanding of the underlying pathophysiological abnormalities and the lack of objective diagnostic criteria result in inherent difficulties of doing clinical trials of therapy. Therefore, only a few evidence-based treatment regimens for CRPS are available so far and outcome studies find little consistent information regarding the pharmacological agents and methods for treatment of CRPS. Thus, treatment of CRPS is still largely empirical. It should be immediate, pain free, and directed toward restoration of full function of the region and include neurologists, anaesthesiologists, orthopaedic surgeons, physiotherapists, and psychologists.

**Authors’ contributions**

We both contributed equally to this review

**Conflict of interest**

We have no conflicts of interest

**Role of the funding source**

Our work is supported by the Deutsche Forschungsgemeinschaft and by the Bundesministerium für Bildung und Forschung. No funding source had a role in the preparation of this review or the decision to submit it for publication.

**Search strategy and selection criteria**

Data for this review were identified by searches of MEDLINE and the authors’ own files.


References

For personal use. Only reproduce with permission from The Lancet.
complex regional pain syndrome

Review

76 Bhatia KP, Bhat MH, Manden CD. The causalgia-