# Review

# The therapeutic approach to complex regional pain syndrome: light and shade

R. Casale[1], F. Atzeni[2], P. Sarzi-Puttini[3]

[1]*Department of Clinical Neurophysiology and Pain Rehabilitation Unit (RC), Foundation Salvatore Maugeri IRCCS, Montescano, Italy;*
[2]*IRCCS Galeazzi Orthopaedic Institute, Milan, Italy;*
[3]*Rheumatology Unit, L. Sacco University Hospital, Milan, Italy.*

*Roberto Casale, MD*
*Fabiola Atzeni, MD, PhD*
*Piercarlo Sarzi-Puttini, MD*

*Please address correspondence to:*
*Roberto Casale, MD,*
*Department of Clinical Neurophysiology and Pain Rehabilitation Unit,*
*Foundation Salvatore Maugeri IRCCS,*
*Via Per Montescano,*
*27040 Montescano, Italy.*
*E-mail: roberto.casale@fsm.it*

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**ABSTRACT**

*Complex regional pain syndrome (CRPS) is a highly painful, limb-confined condition that usually arises after a trauma although its causes remain unknown. It is associated with a particularly poor quality of life, and considerable healthcare and societal costs. Its distinct combination of abnormalities includes limb-confined inflammation and tissue hypoxia, sympathetic dysregulation, small fibre damage, serum autoantibodies, central sensitisation and cortical reorganisation, which place it at the crossroads of disciplines including rheumatology, pain medicine and neurology. The significant scientific and clinical advances made over the past 10 years promise an improved understanding of the causes of CRPS, and for more effective treatments. This review summarises the currently available treatments. The therapeutic approach is multidisciplinary, and involves educating patients about the condition, sustaining or restoring limb function, reducing pain, and providing psychological support. This paper describes the systemic drug treatments, grouped on the basis of their real or presumed antinociceptive mechanisms and reported actions without making any formal distinction between CRPS types I and II.*

## Introduction

Patients with complex and transient clinical pictures in which pain is associated with motor disorders, trophic changes of the skin and adnexae, vasomotor and sudomotor alterations may be frequently seen in everyday clinical practice, and the pieces of this complex clinical puzzle (1) have been given the apparently clarifying definition of complex regional pain syndrome (CPRS) types I and II (2).

CRPS has had many names reflecting contemporary understanding of the condition over the years (1, 2). It was first described over 100 years ago as 'causalgia', subsequently became known as 'reflex sympathetic dystrophy', 'Sudeck's atrophy', 'algodystrophy' or 'neurodystrophy' and, in 1994, was called 'complex regional pain syndrome' by the International Association for the Study of Pain (IASP) in recognition of the fact that its pathophysiology and diagnosis were much more complicated than previously acknowledged.

Pain is the pivotal symptom for a diagnosis of CPRS, but it is also necessary to have severe and disabling trophic disorders of the skin, muscle and adnexae. CPRS has been classified as type I idiopathic or secondary to another disorder or event, but without any objective sign of a nervous system lesion, and type II, which is always secondary to a lesion of the nervous system. According to IASP definition, reflex sympathetic dystrophies (RSDs) are now included in CRPS type I, whereas causalgia is included in CRPS type II.

The distinction of CRPS types I and II seemingly indicates a precise clinical, pathophysiological and therapeutic distinction, but recent evidence of minor nerve lesions (3, 4) and substantially shared clinical features indicate that this classification is empirical rather than evidence-based (5). This is also reflected in the myriad of pharmacological, invasive, rehabilitative and alternative treatments for CRPS used in general clinical practice. At the time this paper was written, PubMed had more than 90 meta-analyses and systematic reviews of the literature relating to all forms of CRPS therapy. This tells us that many of the treatments recommended in the guidelines

(invasive therapies such as sympathetic ganglion block, sympathectomy, and spinal cord stimulation) are only minimally if at all, or have been inadequately researched, used indifferently for both types of CRPS, and mainly inferred from treatments used for neuropathic pain (6-13). All of these treatments are far from what can be done in a clinical outpatient setting.

The aim of this review is to describe the systemic drug treatments for CRPS grouped on the basis of their real or presumed antinociceptive mechanisms and reported actions without making any formal distinction between CRPS types I and II. Three tables show the claimed causes of CRPS (Table I), its clinical picture (Table II) and the current diagnostic criteria (Table III). The antinociceptive mechanisms used to group the different drugs are briefly described at the beginning of each section.

## Clinical picture

CRPS have been associated with a large number of etiopathogenetic factors ranging from trivial injuries such as joint sprains, to pharmacologically-related forms (14-16), and particular cases due to burns (17) and even a snake bite (18) (Table I).

The best clinical description of the evolution of CRPS regardless of the presence of a defined nervous system lesion remains that given by Bonica (19, 20), who identified three stages (Table II). This clinical picture is shared by CRPS types I and II, with minor and clinically irrelevant variations. The main differences in the diagnostic criteria between type I and II is the demonstration of the presence or absence of a nervous system lesion, and so the algorithm for defining a CPRS should include the history and evolution of the symptoms, and the presence, distribution and quality of positive and negative sensory and motor abnormalities. The diagnostic criteria depend on a meticulous physical examination because no gold standard has been established, and instrumental and laboratory findings (x-ray, scintigraphy, thermography, electromyography and standard assessments of nerve conduction velocity) can only help to confirm the clinical diagnosis (22). Table III shows the diagnostic criteria and a possible diagnostic algorithm.

## Systemic treatments

Over the last few decades, a large number of drugs have been proposed for the systemic therapy of CRPS, some of which were rapidly abandoned but others have shown partial and even promising results. However, the fact that many of these studies did not evolve from phase I to a randomised, controlled trials (RCTs) underlies the still empirical approach to treatment.

### *Drugs acting on the inflammatory cascade*

#### *– Corticosteroids*

Corticosteroids (CS) were the first agents to be studied, but the rationale underlying their use (*i.e.* the presence of an inflammatory component in CRPS) remains controversial (26, 27). CS can act on inflammatory responses by inhibiting the cycloxygenase enzymes (28) mediating pain, swelling and functional impairment. Their anti-inflammatory effects can also antagonise increased capillary permeability, the chronic presence of a perivascular infiltrate in the sinovium (29) and, partially, the development of bone atrophy in CPRS type I (27, 30). They also inhibit ectopic neuron discharges (31) in CRPS II and CRPS I, which may be associated with minor nerve lesions (32).

The most frequently used CS is prednisone, which is usually administered at high oral doses (60-80 mg), followed by a slow and gradual reduction. Therapeutic response rates have generally been 75-82% in patients at an early pseudo-inflammatory stage (33, 34). Prolonged low doses of predisone (10 mg three times a day) have been used for a maximum of twelve weeks until a clear response is achieved (34). Good results in terms of pain and other parameters have also been obtained using dexamethasone 8 mg/day for one week in combination with 10% mannitol 2 x 250 mL/day (35).

Unfortunately, CS have well known systemic side effects (36), can modify mood and memory (37), and can worsen osteopenia in patients with Sudeck's disease or osteoporotic fractures (38-40). Moreover, one case of CRPS type I has been reported following steroid injection (16).

The recent hypothesis that inflammation of a nerve proximal to the symptoms can lead to neural changes consistent with clinical CRPS has led to the use of CS being suggested once again (41, 42), at least in the early phase [7] when there are clear signs of inflammation (Table II).

*Various doses of CS can be favourably used in the early stage of CRPS when an inflammatory over-reaction can be seen. However, their long-term use or high doses are not recommended because of the high risk/benefit ratio. There is a need for a re-evaluation of their use in the early phase in double-blind, controlled clinical trials.*

#### *– NSAIDs and COX-2 selective inhibitors*

Prostanoids are involved in the spinal facilitatory effects of "wind up" induced by peripheral nerve lesions. In

**Table I.** CRPS and the etiopathogenetic factors.

| Peripheral tissue damages | Peripheral nervous lesions | Central nervous lesions | Deep visceral lesions | Drugs |
|---|---|---|---|---|
| Bone fractures | Nerve trunk | Spinal cord | Myocardial infarct | Anticonvulsants (phenytoin, |
| Sprains | Plexus | Traumatic head injury | Pacemaker implantation | Phenobarbital, carbamazepine) |
| Soft tissue damages (traumas) | Dorsal root | Acute cerebrovascular | Abdominal pathologies | Corticosteroids |
| Arthritis | | diseases (hemiplegia) | | Isoniazid |
| Immobilisation | | | | |
| Deep venous thrombosis | | | | |

**Table II.** Phases of CRPS (modified from Bonica and Scadding).

| | Pain | Skin and adnexa | Evolution |
|---|---|---|---|
| Phase 1 | Pain: constant, irritating, moderate and localised to the affected parts. Hyperaesthesia, muscle spasms and pain can lead to severe limitation of ROM | The skin is normally dry, pink and warm, with or without rare signs of vasoconstriction | This stage persists for some weeks, responds very well to the therapy. It rarely persists for about six months. |
| Phase 2 | Pain spontaneous or evoked: burning, aching, throbbing. Hyperalgesia or allodynia evoked by mechanical and thermal (*e.g.* cold) factors or joint movement | Increased oedema and joint stiffness. The skin is damp, cyanotic, cold and hairless. The nails are jagged. | The pathological process persists for about 3–6 months, but if it is properly treated, it can regress. |
| Phase 3 | The pain can be moderate or intense, and may get worse with cold exposure. The distribution of the pain can be diffused to any anatomical innervation areas. | Trophic lesions often irreversible. The skin becomes smooth, without folds, pearl-like at low temperatures. The subcutaneous tissue can be atrophic (particularly the interosseous muscles). The limbs become extremely weak, with limitation of movements associated with ankylosis of joints of the feet and hands. Widespread osteoporosis. Cold skin with reduction of oscillometric traces. | Chronic phase. This stage is unresponsive to the drugs. |

**Table III.** Diagnostic criteria of CPRS (modified from: Stanton-Hicks M).

| | |
|---|---|
| 1 | Continuous and remarkable pain unexplainable by the level of the injury |
| 2 | At least one symptom from three of the following categories:<br>Sensory: hyperesthesia and/or allodynia<br>Vasomotor: asymmetric temperature and/or change of the skin colour and/or asymmetric skin colour<br>Sudomotor /Oedema: oedema and/or changes of the sweating and/or asymmetric sweating<br>Motor/Trophic: decreased of the motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin). |
| 3 | A least one sign at the physical examination from two or more of the following categories:<br>Sensory: hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)<br>Vasomotor: asymmetric temperature (>1°C) and/or changes of the skin colour and/or asymmetric skin colour<br>Sudomotor/Oedema: Oedema and/or sweating changes and/or sweating asymmetry<br>Motor/Trophic: decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin). |
| 4<br>Note: | Absence of other diagnosis able to explain the signs and symptoms.<br>Absence of the "major nerve damage"= CRPS I<br>Presence of the "major nerve damage"= CRPS II<br>The diagnostic criteria are fulfilled in presence of one symptom from any category and one sign from two or more categories. Criteria number one is required to make the diagnosis; these criteria are missing in 5–10% of patients . |

animals, the spinal administration of COX inhibitors can inhibit the hyperalgesia induced by a tissue lesion (43, 44). Since the recognition of the role of cycloxygenase in the spinal cord and its role in the development of hyperalgesia and allodynia, paracetamol/acetaminophen and selective and non-selective COX-2 inhibitors have been used to treat both nociceptive and neuropathic pain (43, 45, 46). Like CS, NSAIDs and selective COX-2 inhibitors have been used because of the inflammatory symptoms associated with some stages of CRPS (Table II) and their capacity to reduce inflammation and nociceptive pain (47). However, their systematic use is not common and sometimes considered negative (48), being present only in complex multi-pharmacological treatments in which their efficacy cannot be distinguished from that of the other drugs (49-51).

*NSAIDs and selective COX-2 inhibitors are not specifically indicated for CRPS. However, the WHO suggests the use of paracetamol and NSAIDs as a first step in the treatment of pain. In clinical practice, they are currently used in any phase of CRPS, but always in combination with other more specific drugs. In the future, the peripheral and central actions of these drugs deserve more attention from researchers.*

*Drugs for bone metabolism*

• *Calcitonin*

Calcitonin is still considered one of the first-line treatments for CRPS (52, 53) because the use of an anti-osteoclastic agent is favoured by the rapid development of secondary osteoporosis associated with marked osteolysis in certain forms of CRPS (known as Sudeck's disease), and it has central serotoninergic anti-nociceptive activity (53).

The original porcine calcitonin was initially used at very high doses, but it has been replaced by eel, salmon or human calcitonin administered at different doses and by various routes. A meta-analysis has remarked upon the heterogeneity of experimental conditions and related variable responses to calcitonin treatment (7) but, regardless of type, calcitonin appears to have a better effect on pain than sympathetic suppressors,

guanethidine and intravenous regional blocks (8), although it is less effective than β-blockers (54-56). A comparative study of intranasal and injected salmon calcitonin has shown that intranasal leads to more rapid and powerful analgesia with fewer side effects (57-59).
Calcitonin has also been also used in the prevention of CRPS, with conflicting results (60, 62), but highly positive results have been obtained in preventing its recurrence in patients requiring surgery in a previously algodystrophic arm or limb (63).
*Despite its side effects, which are mainly related to intramuscular administration (20-30% of cases, mainly gastroenterological problems) (59), calcitonin has been one of the most widely used drugs for CRPS. Its efficacy in acute pain control has always been clinically reported in the early phase, but the recent meta-analysis and review articles indicate conflicting results (7, 8, 64, 65).*

• *Bisphosphonates*
A number of mechanisms have been proposed to explain the anti-nociceptive effects of bisphosponates. The may have a direct effect on pain mechanisms because of their inhibitory action on the synthesis of interleukin-6 (IL-6), TNF-α, bradykinin and prostaglandin $E_2$ (66), and it has also been postulated that they may have a direct effect on nociceptors (67). Their capacity to modulate bone microcirculation, secondary tissue acidosis and increased intramedullary pressure may explain an indirect action on pain. These actions are of pivotal importance in the early phases of CRPS, when the disease has inflammatory characteristics (Table II).
Various bisphosphontes have been used. Pamidronate was introduced in 1988 and led to striking pain relief within three days of treatment (68), and when injected intravenously (67-70). Almost all of the bisphosphonates used in CRPS (alendronate (71-73), clodronate (74, 75), neridronate (76), etidronate (73), risedronate (73) and ibandronate (77)) offer a certain amount of pain relief, but its duration is less clear. Alendronate, etidronate and risedronate have also been compared in terms of pain relief at lower doses than those usually used in osteoporosis and CRPS, but for a longer period (seven months) (73).
The recent publication of the results of an RCT of neridronate (78) provides fairly convincing evidence that bisphosphonates have an acceptable safety profile and can significantly relieve spontaneous and stimulus-evoked pain and improve functional status in patients with early disease (<6 months) and an abnormal uptake during 3-phase bone scintigraphy (68). Moreover, the most recent and largest study of neridronate showed that the improvement was sustained or even enhanced over a follow-up of at least one year (78). There are indications that the doses necessary to achieve long-term remission are quite high: neridronate 100 mg or pamidronate 90 mg, each given intravenously four times over a period of 10 days (78). Recruitment in all but one of these studies (68) was restricted to patients in whom the generation and maintenance of pain was most probably associated with osteoclastic overactivity (79). Bisphosphonates have analgesic properties that go beyond their effect on bone metabolism, and preclinical data suggest that they have anti-nociceptive effects in animal models of neuropathic pain (79). Their efficacy may therefore not be limited to CRPS patients with bone-related pain, but no relevant clinical data are available.
In general, bisphosphonates are administered intravenously and at higher doses than those usually used to counteract lost bone mass lost, and transient flu-like symptoms and asymptomatic hypocalcemia may be experienced with the intravenous route (80-82).
*Only a few randomised controlled trials of bisphosphonates have the characteristics required for a systematic review. Differences in protocols, compounds, doses and routes of administration do not allow any definite conclusions, but improved function, quality of life and pain relief have been observed and indicate their possible use in CRPS. Their analgesic mechanism is not fully understood and should be clarified in order to help design effective new analgesic bisphosphonates. The differences in pain control between bishosphonates, and the reasons for the differences in the doses required to increase bone mass density and induce analgesic effects also need clarification. In this respect, the most powerful analgesic bisphosponate (etidronate) is the least used, and others (such as zoledronic acid) have not even been tried. Caution is required when administering high bisphosphonate doses in order to alterations in bone metabolism.*

*Drugs acting or influencing N-methyl-D-aspartate receptors*
The activation of N-methyl D-aspartate (NMDA) receptors as a result of the release of the voltage- dependent magnesium blockade induced by calcium influx is central to the genesis and maintenance of peripheral and central sensitisation. NMDA plays a role in the development of chronic neuropathic pain, including CRPS (83-85), and NMDA blockers or compounds modulating NMDA receptor activity have been proposed for its treatment. However, the ubiquity of these receptors means that their clinical targeting has been limited by their significant side effects.

• *NMDA receptor antagonists*
In humans, the clinically relevant NMDA-blocking agents are ketamine, amantadine, memantine, dextromethorphan (DM), and methadone.
Ketamine, a potent NMDA antagonist, has been used intravenously at coma-inducing (85) and lower doses (86) with effective results (86, 87), whereas its oral use has a limited place as adjunctive therapy and only when other therapeutic options have failed (88). Ketamine has also been used topically without the side effects of the oral and parenteral formulations (89-93).
Memantine, amantadine and DM are weaker NMDA receptor blockers than ketamine and also have fewer central nervous system side effects. Antitussive DM is a non-competitive NMDA receptor antagonist that is capable of preventing neuronal damage and modulating the sensation of pain via the non-competitive antagonism of excitatory amino acids in the CNS (94). It is effective in controlling the pain of painful diabetic neuropathy but not other neuropathic pains (95). Amantadine

is the most widely used oral NMDA receptor antagonist as it is an antiviral and anti-parkinson drug at a maximum daily dose of up to 400 mg (96). It has been used efficiently at 1000 mg/day and in combination with clonidine in two reported cases of neuropathic pain (97). No data are available concerning the systemic use of DM or amantadine in CRPS.

It has been shown that memantine, a recently introduced drug for Alzheimer's disease at a dose of 20 mg/day, controlled CRPS symptoms and modified cortical reorganisation at a daily dose of 30 mg for eight weeks in a six-case study (98), but not when used at lower doses of 1.8-6 mg /day (99).

*The concept of NMDA antagonism as a therapeutic target in neuropathic pain remains theoretically proved but more clinical trials are needed to establish the NMDA blockers that have the most clinically useful cost/benefit ratio in terms of side effects and analgesic action. In the case of amantadine and memantine, concerns have been raised about the poor tolerability of high doses (99).*

• *Magnesium*

Oral magnesium is a physiologically competitive calcium antagonist that has always been anecdotally reported to have some general efficacy as a complementary supplement in myofascial pain. Intravenous magnesium has been used with promising results in small placebo-controlled trials involving patients suffering from neuropathic pain (100, 101). Good clinical results on pain were obtained in eight CRPS patients who received magnesium sulphate 70 mg/kg by means of a 4-hour intravenous infusion at 25 mL/hour/day for five days (102). However, although no serious adverse events were reported, 50% of the subjects reported infusion site pain, flushing, nausea, fatigue, headache, burning eyes, dizziness and light-headedness. A transient increase in plasma magnesium plasma levels was recorded in four subjects on the first day of treatment (102).

*Only a few, almost exclusively anecdotal data are available concerning the use of oral Mg++ in myofascial pain. However, data concerning its use in CRPS show that intravenous Mg++ can be considered a potential non-pharmacological supplement, not least because of it has fewer side effects than other treatments. Further studies are necessary to identify the best route of administration.*

• *Free radical scavengers and anti-oxidants*

It has been suggested that reactive oxygen species (ROS) may be involved in the pathogenesis of reflex sympathetic dystrophy (103) on the assumption that CRPS type 1 is caused by an exaggerated inflammatory response to trauma mediated by an overproduction of ROS (26, 104-106). Moreover, as ROS are important contributors to capsaicin-induced mechanical secondary hyperalgesia, this treatment may help reduce hyperalgesia in patients with CRPS (107).

A number of ROS scavengers have been used in CRPS, including topical dimethyl-sulphoxide (DMSO), N-acetylcysteine, mannitol and vitamin C, all of which can neutralise toxic free radicals. DMSO has been used in CRPS with better results than guanethidine (108) and placebo (109). A comparison of topical DMSO 50% and N-acetylcysteine 600 mg three times daily showed similar results (110). Interestingly, the results of DMSO were better in "warm" CRPS I, whereas treatment with N-acetylcysteine seemed to be more effective in the case of "cold" CRPS I (Table II). Intravenous mannitol 10% did not improve pain in patients with CRPS I (107), whereas the combination of mannitol 10% twice a day for seven days and dexamethasone was effective in reducing pain and disability (35).

Recent research papers have reported that vitamin C prevents CRPS due to foot and ankle surgery and fractures. Studies of a remarkable number of patients have shown that it is effective in preventing CRPS secondary to a wrist fracture at a daily dose of 500 mg for 50 days (112, 113). No data are available concerning vitamin C as a treatment for CRPS, but it has been suggested that other dietary compounds such as omega-3 fatty acid play a role (114): however, although there are some clinical data for RA (115), only the findings of a pilot study are available for CRPS (115).

*Because of their efficacy and the substantial absence of side effects, free radical scavengers have been proposed as a first-line treatment in some national CRPS treatment guidelines (116). Although no convincing clinical evidence is available for CRPS, a dietary regimen rich in anti-oxidant agents and omega-3 can always be recommended (115).*

*Sympathetic blockers*

The importance of sympathetic activity in inducing/maintaining some form of pain has been assumed since the first successful sympathectomy by Leriche *et al*. the beginning of the last century, and has apparently more recently been confirmed (117, 118). On the basis of these premises, sympathetic blockade and systemic sympatholytic drugs have been tested in CRPS (20). However, the few clinical results and new research data (119, 120) challenge the assumption that the pain in CRPS is always maintained by sympathetic over-activity and suggest the possibility that only a sub-group of CPRS of both types is associated with sympathetically maintained pain, and that the sympathetic nervous system is primarily involved in generating appropriate responses to noxious inputs but not pain in most forms of CRPS (121, 122).

• *Alpha-adrenoceptor blockers: phenoxybenzamine, phentolamine, yohimbine, prazosin, terazosin, clonidine*

Many α-adrenoceptor blockers have been used with the aim of blocking or at least reducing sympathetic activity and therefore pain.

Phenoxybenzamine has been used in the treatment of CRPS (123) and causalgia, and led to a striking 100% response rate in two weeks (124). In a small group of patients, phenoxybenzamine led to results depending on the doses used: 20 mg daily for four months, 10 mg every three days, or pulsed treatments for three weeks (125). Minimal and transient side effects, mainly consisting of orthostatic

hypotension and ejaculatory problems, have been reported (126, 127).

Two studies of systemic phentolamine, a non-specific α-adrenoreceptor blocker, used 30–40 minute intravenous infusions of 25–35 mg with partially conflicting results: no responses in one trial (121), and only partial responses in the other, in which phentolamine was compared with a sympathetic ganglion blockade (122). These negative or partially negative findings were probably due to an incomplete blockade of the α-adrenoreceptor because the same group subsequently proposed a phentolamine dose of 1 mg/kg over 10 min (123). Phentolamine has also been compared with yohimbine, a selective α2 blocker used for erectile dysfunction with positive results (124). The reported side effects of phentolamine are tachycardia, nausea, vomiting, headache, dizziness, nasal stuffiness, and transient hypotension (124).

Clonidine, an α2-adrenergic agonist used in various clinical settings, decreases the NMDA-evoked responses of neurons in the medulla and spinal cord (129, 130). Clonidine has considerable anti-nociceptive activity when administered epidurally (131), its intravenous administration to normal volunteers did not reduce experimental thermal- or capsaicin-induced pain and hyperalgesia (132). In CRPS, a clonidine topical patch has been used with positive but limited effects mainly due to the small area covered by the patch (133), and oral clonidine at a dose of 1 mg twice a day was used in one case in association with intrathecal ziconotide (134).

Oral clonidine has never been systematically used in CRPS. Other α-adrenoceptor blockers such as prazosin and terazosin have been used in animal experiments with negative results (131).

• *β-adrenoceptor blockers: propanolol*

The β-blocker propanolol has been successfully used in causalgia (137) and CRPS (138, 139). Progressively increasing doses (from 40 mg to 80 mg t.i.d.) are usually used until the heart rate decreases to 60 beats a minute, and the pain relieving success rate in the early studies ranged from 77% to 100% (64, 140); however, these first positive results were not confirmed. The use of propanolol for post-traumatic neuralgia has been openly criticised, and its use in CRPS has been gradually abandoned (141).

*In CRPS, sympathetic blockers are generally only relatively useful in the forms of pain maintained by an overactive sympathetic nervous system. The only drug that is clinically effective in blocking α-adrenoceptors is phentolamine at a dose of 1 mg/kg/day. It is used in some advanced pain centres to assess the presence of sympathetically maintained pain, but not as a pain treatment. A clonidine patch may be a means of obtaining a substantial reduction in pain arising from a neuroma, when it can be appropriately positioned. The use of the β-adrenoceptor blocker, propanolol, has now been abandoned. At possible therapeutic doses, they all have side effects.*

*Calcium channel blockers*

• *Gabapentin, pregabalin, nifedipine, conotoxins*

Calcium ions are ubiquitous signalling elements and their influx in a neuron can directly modify membrane excitability by facilitating membrane potentials, thus leading to abnormal electrical activity and transmission. Calcium ions enter a cell through voltage-gated or ligand-gated calcium channels. The $alpha_1$ subunits of N and T type channels are those most involved in nociception (142). Gabapentin, pregabalin, zonisamide and a number of conotoxins (ziconotide) are calcium channel blockers that have been used to control neuropathic pain and CRPS, although gabapentin and pregabalin are otherwise classified as anti-epileptic drugs. Gabapentin is one of the first-line drugs for neuropathic pain (143), and its use has been suggested mainly in early-stage CRPS (144). The results range from positive in a small cohort of patients (doses ranging from 900 mg/ to 2400 in six cases) (145) to doubtful slight pain relief in a controlled, double-blind cross-over study in which the final daily dose of 1800 mg relieved pain only in the first period and had no significant long-term effect (146). Gabapentin has also been used to prevent relapses in a patient with recurrent CRPS (147), and in children (148).

Pregabalin has been used to prevent and treat post-surgical CRPS (149, 150). It has been demonstrated that the efficacy of pregabalin (average dose 190 mg/day) and tramadol (average dose 90 mg/day) is comparable, with both leading to a statistically significant improvement in pain (150). A prospective study found that pregabalin at flexible doses of 150-600mg/day twice daily for six weeks controlled pain and improved sleep following orthopedic surgery (151).

The hypothesised mechanism of the calcium channel blockers nifedipine and verapamil in CRPS is related to their blockade (at different speeds and intensities) of the influx of extra-cellular calcium into the smooth muscle cells of the vascular wall, thus clinically producing a vasodilatory effect (152). This suggests their use in the case of "cold" CRPS (19, 20) (Table II). The oral calcium antagonist nifepidine was successfully used in a pilot study of 13 patients (153). The use of nifedipine 10–20 mg/day and phenoxybenzamine up to 120 mg/day has been proposed with an original therapeutic regimen: nifedipine for 5–7 days after which, if no results are obtained, switch to phenoxybenzamine (118). As far as we know, verapamil (which is currently used in the prophylaxis and treatment of headache) has never been used in CRPS.

The newly marketed calcium antagonist ziconotide does not cross the blood-brain barrier and can only be administered intrathecally to block N-type calcium channels. Ziconotide is mentioned here because of its apparently promising results on difficult pain. It has been used in CRPS in combination with other drugs at full dose of 24 mg/day (130).

Gabapentin and pregabalin are the most widely used systemic drugs in pain medicine. No clear data from double-blind controlled studies are available concerning their usefulness in CRPS, and so they cannot be highly recommended. Nevertheless, they seem to be the most useful and are easy to handle

in the management of neuropathic pain and CRPS II. Nifedipine and phenoxybenzamine have given encouraging results that have not been confirmed. They can currently only be suggested in cases of "cold" CRPS with clear vasoconstriction.

*Sodium channel blockers*

• *Carbamazepine, oxcarbamazepine, phenytoin and lamotrigine*

Tetrodotoxin-resistant, voltage-gated sodium channel subtypes are involved in the development of pain after a nerve injury when an accumulation of sodium channels at the site of injury leads to hyperexcitability and spontaneous firing (154).

Like gabapentin and pregabalin, carbamazepine, oxcarbamazepine, phenytoin and lamotrigine are classified as anti-epileptic drugs. However, unlike gabapentin and pregabalin, their main action is to block sodium channels. Tricyclic antidepressants such as amitriptylin also act by inhibiting sodium channels at less than therapeutic doses, and this seems to be more than other actions in controlling pain (155). All of these drugs have been used as adjuvants in various pain conditions and are generally suggested for CRPS type II in the presence of a nerve lesion (156). In a single case report, phenytoin led to positive results at a dose of 300 mg/day (157). In general, there are few double-blind, controlled studies of the use of anti-epileptic agents in CRPS I, one of which showed that carbamazepine was significantly better than morphine (158). However, it is worth mentioning that both carbamazepine and phenytoin have been related to the development of a CRPS (14, 15).

• *Lidocaine and mexiletine*

Other sodium channel blockers are the local anesthetic lidocaine and the so-called local anesthetic-type drug mexiletine, both are which are used intravenouslyv to treat ventricular arrhythmias. Following peripheral nerve injury, the tetrodotoxin-resistant sodium channels on primary nociceptive afferent fibres and small dorsal root ganglia pain transmission neurons are up-regulated and undergo significant physiological changes (159). They are also responsible for some more centrally located activity at suprasegmental level (160). In animals, intravenous lidocaine dose-dependently reduces the ectopic barrages originating from a damaged nerve (161). Both lidocaine and mexiletine have been mainly studied in painful diabetic neuropathy, although with no clear-cut results (162) and different procedures (163). It has been shown that lidocaine reduces neuropathic pain in humans for only a short time (164), which is why periodic, continuous intravenous or subcutaneous infusions have been proposed in CRPS (165) at different blood concentrations, with some efficacy on strong cold-evoked pain (166). Intravenous lidocaine has also been proposed as a means of predicting the clinical efficacy of oral mexiletine (167). Local anesthetics have also been used in the form of creams and patches (see the dedicated paragraph) .

*Systemic lidocaine is only therapeutically efficacious in the case of cold-induced allodynia. However, its sodium channel blocking activity is quite unspecific and effective doses may be difficult to achieve because of the development of cardiovascular adverse effects. Its interesting application as a diagnostic tool at a lower dose of 1.5 mg/kg should be retested on a larger scale*

*Tricyclic, tetracyclic and selective serotonin and noradrenalin re-uptake inhibitors*

The possible mechanisms underlying the rationale for using antidepressants in CRPS have been inferred from the results of studies of neuropathic pain, and range from a direct antidepressant effect on the psychological and behavioural components almost always presents in CRPS (168), to their potentiation of the anti-nociceptive serotoninergic and noradrenergic inhibitory descending pathways (169). It has also been suggested that their sodium channel blocking activity may be involved in their analgesic efficacy (170). Lower than therapeutic doses of amitriptylin are more effective in inhibiting sodium channels than selective serotoninergic reuptake inhibitors (150).

Tricyclic (*i.e.* amitriptyline nortriptyline), tetracyclic (mianserin, trazodon, maprotinin) and the newly introduced selective inhibitors of serotonin (sertralin, paroxetin, citalopram), noradrenalin (reboxetin) or both (venlafaxin) have been widely recommended and used in neuropathic pain (171), and occasionally in the treatment of CRPS. Positive results have been obtained using very different doses of amitriptyline ranging from 10–75 mg/day (22) to 240–720 mg/day (172), and in very different clinical settings also as second-line treatment after sympathetic blockade (173).

*Serotonin and noradrenalin-specific reuptake inhibitors have been put on the list of first-line treatments for neuropathic pain by the special neuropathic pain interest group of the International Association for the Study of Pain (171), and approved by the American FDA and the EMA for some forms of neuropathic pain. However, older antidepressants such as amitriptyline or nortriptyline, which are not indicated by the FDA or EMA have been proposed as first-line treatment by others (174). No drug of this category has been authorised for CRPS as no positive double-blind controlled trial of the efficacy of old and new antidepressants has been published.*

*Given the presence of signs of psychological and cognitive involvement in almost all patients with CRPS, support therapy with antidepressants can always be used when reactive depression is suspected.*

*Anti TNF-α drugs: infliximab, thalidomide, lenalidomide*

Pro-inflammatory cytokines play a fundamental role in generating and maintaining joint pain in various rheumatological diseases (175). High levels of IL-6 and TNF-α have been found in the affected arm of patients with CRPS, thus suggesting that anti-TNF-α agents can be used in the early stages of the disease (176, 177) when the clinical signs of an inflammatory process are predominant (178). Two case reports describe the successful use of intravenous infliximab in the USA and Europe (179). In general, anti-TNF agents can also be administered subcutaneously

with some advantages (180), but this has never been tried in CRPS.
It has been shown that various doses of thalidomide have analgesic activity by inhibiting TNF-α and interfering with TNF mRNA and IL-10 production via macrophage recruitment (181). Thalidomide has been used in CRPS patients with Behçet's disease (182) and multiple myeloma (183), and an open study found that high doses had some effect in 31% of cases (184). It has also been demonstrated that low doses of lenalidomide, a less toxic thalidomide derivate, lead to broad symptom relief in subjects with chronic CRPS I after prolonged treatment (more than 104 weeks in some patients) (185). In addition to their teratogenic effects, thalidomide and lenalidomide may also induce sedation, constipation, rash and peripheral neuropathy.
*The apparently positive effects of anti-TNF drugs need to be confirmed by double-blind, controlled trials. No clinical trial of thalidomide in CRPS has yet been published, and only the cases mentioned above demonstrated some efficacy.*

*Griseofulvin*
Griseofulvin is an anti-fungal agent that alters fungal cell mitosis. Its hypothesised mechanism of action in CRPS is vasculotrophic activity, but that has not been clearly defined at microcirculatory level (186). Its therapeutic use in CRPS and other rheumatological conditions dates back to the 1960s, and is mainly supported by the French literature (64, 187).
Controlled clinical studies include a comparative study of griseofulvin and calcitonin, beta-blocking agents and guanethidine (135), and have shown that griseofulvin is generally less effective than beta-blockers (135, 188). Griseofulvin must be used at particularly high doses (1.5-3 g/day) in order to guarantee its pharmacological activity, but such doses often lead to gastric intolerance.

*Naftidrofuryl*
Like nifedipine and verapamil, naftidrofuryl hydrogen oxalate (NH) is used as a vasodilator but it has a different mechanism of action. It selectively inhibits the 5-HT2 receptor expressed on human endothelial cells and the TNF-alpha-triggered increase in intercellular adhesion molecules, and considerably increases the synthesis of nitric oxide (NO), all of which account for its ability to reduce the vasospasm associated with stroke and its potent inhibition of platelet aggregation (189). The impaired microcirculation that leads to increased vasoconstriction, tissue hypoxia and metabolic tissue acidosis during the third stage of CRPS (Tab II) could theoretically be opposed by the induced increase in NO (190). NH has been positively used in Sudeck's disease (CRPS I) at a daily oral dose of 400 mg/day (200 mg twice a day) (191).

*Opioids*
The use of opioids to treat neuropathic pain is still widely debated because nerve injury alters the activity of opioid systems or opioid specific signalling, and this reduces the anti-nociceptive potency of morphine (192). It is generally recognised that opioids have little or no effect on chronic neuropathic pain conditions (192), but it has been found that oxicodone (193) and tramadol (194, 195) can reduce pain and improve the quality of life even in patients with neuropathic pain of various origins. However, no controlled studies have yet demonstrated any real improvement in patients with CRPS. These conflicting findings and the frequent side effects of particularly high doses (nausea, vomiting, constipation, cognitive impairment and somnolence) do not suggest opioids as a first-line treatment for CRPS. Moreover, their long-term use may lead to hyperalgesia (196) and immune suppression (197), both of which may worsen CRPS .
Naltrexone, an antagonist of μ-opioid receptors, is clinically used as an adjuvant in the treatment of alcohol addiction (198). There have been recent reports of positive outcomes, including the remission of dystonic spasms or fixed dystonia, in two CRPS patients treated with low-dose naltrexone (LDN, a glial attenuator) in combination with other CRPS therapies. It is known that LDN antagonises the Toll-like receptor 4 pathway and attenuates activated microglia, and it was used in these patients after conventional CRPS pharmacotherapy failed to suppress their recalcitrant CRPS symptoms (199).
Recent reviews do not recommend opioids in the treatment of CRPS (200-203).

• *Baclofen*
Spinal cord stimulation (SCS) is a widely used procedure for the treatment of CRPS. However, it rarely leads to complete pain relief and its effect diminishes over time. It has recently been suggested that intrathecal baclofen (ITB) can be used to treat CRPS-related fixed dystonia, and other reports have suggested that ITB therapy can enhance the effect of SCS in patients with neuropathic pain. One retrospective study evaluated the effectiveness of adding ITB therapy to SCS in order to control the symptoms of advanced CRPS in five affected extremities of four patients (two males; mean age 32.5 years) refractory to conservative treatment. Three patients underwent SCS implantation and then had ITB pumps implanted a few years later; the fourth received a bolus ITB injection during temporary percutaneous SCS. Pain intensity was evaluated before and after ITB administration using a visual analogue scale (VAS), which showed >50% relief in the upper extremity of one patient, and >30% relief in two patients. The mean pain reduction in all four patients was 28.9% before and 43.8% after treatment. All of the patients, including the one without any improvement in the VAS score, experienced an improvement in postural abnormalities (fixed dystonia or paroxysmal tremor-like movements) and a reduction in pain fluctuations (204).

*Topical and transdermal drugs*
A very large number of compounds have been applied to the skin in an attempt to alleviate pain in CRPS, including lidocaine, ketamine, various NSAIDs, corticosteroids, DSMO, clonidine, NO donors (the use of DMSO (104-106) or clonidine patches (125) has been described above). The possible therapeutic targets for the use of topical agents

can vary not only in terms of the active drug, but also in terms of their formulations, which range from creams and ointments to sophisticated transdermal drug delivery systems. However, their possible usefulness depends on the extent to which peripheral mechanisms are involved in initiating and maintaining pain (205).

Capsaicin has been used to treat neuropathic pain and CRPS, but offers very limited benefits (206); furthermore, the compliance of CRPS patients is poor even in the case of a euteric mixture with lidocaine (207). In non-neuropathic pain conditions such as CRPS I, capsaicin has also been used in a mixture with glyceryl trinitrate with good results (208). A mixture of the NO donor isosorbide dinitrate (ISDN), a vasodilator, capsaicin and lidocaine has recently been used to treat a case of painful diabetic polyneuropathy (209). There have also been positive reports in relation to other mixtures of ketamine and different TCAs (210, 211), but these have not been confirmed and must be still considered anecdotal (196). The use of such formulations in CRPS has only been suggested (205), and no controlled trials have been carried out (152). The use of ISDN ointment to treat "cold" CRPS has led to conflicting results even in studies conducted by the same group (212, 213). Only lidocaine patches are approved by the FDA for the treatment of postherpetic neuralgia, and are increasingly being used for CRPS (214, 215).

Nanotechnologies have greatly improved the passive delivery of drugs in the form of patches, including fentanyl and clonidine transdermal drug delivery systems (transdermal clonidine and the fentanyl patch). The new device-based technique used to overcome the skin barrier include iontophoresis, electroporation, ultrasound, magnetophoresis, radiofrequencies and laser (216). Iontophoresis has been used to carry lidocaine, sodium salicylate and fentanyl for post-surgery pain control. No data are available concerning CRPS.

*Topical treatments are a new and rapidly growing field as a result of the use of new technologies. There are currently no data concerning their use in CRPS, but the substantial absence of side effects and relatively low systemic drug doses make such treatments potentially very interesting.*

*Placebo*

The presence of a brief note concerning placebo should not surprise readers because it has been shown that the incidence of placebo responders is high among patients with chronic neuropathic pain and those affected by CRPS (causalgia) (217, 218). The placebo effect has recently been explained in biological terms and, in a certain manner, reassigned to the category of real treatment (219). Moreover, the presence of side effects in the placebo groups of pain trials shows that placebo is not the same as nothing (220). In a pathology with such a large psychological component (164) and possibly high level of placebo responses as CRPS, it is necessary to study new and retest old treatments using rigorous treatment protocols (221). No data are available concerning the entity of the placebo effect in patients with CRPS.

**Discussion**

In conclusion, this review shows that there are no validated treatments for CRPS. Moreover, evidence concerning the use of common pain therapies in CRPS is scarce, and systematic reviews and meta-analyses of trials of medications for CRPS only partially agree (222).

One of the greatest limitations of the experience gained with agents proposed for CRPS is the poor methodological quality of the various clinical studies. Measures such as the number needed to treat (NTT) or number needed to harm (NNH) have not usually been considered, thus making it impossible to compare different experimental sets. Even the relatively few "head-to-head" studies (in which a gold standard treatment is compared with a new drug) have been disappointing because most of the drugs so far proposed are only slightly better than an inert compound. In other words, using harmful drugs is sometimes only slightly better than nothing

All of the consulted review articles agree on this point. In particular, the greatest criticisms are the retrospective nature of most clinical trials and the lack of an adequate control group, which is particularly important in the case of an illness that is undoubtedly susceptible to a placebo response and frequently has a natural tendency to improve (see Table II). The scarce emphasis given to the standardisation of patient admission and evaluation criteria is an even more critical point. The presence of a complex and variable clinical picture, and sometimes the lack of a clear etiopathogenesis, are normally exclusion criteria in randomised, double-blind controlled studies. This inevitably leads to scepticism in the case of studies with fabulous 100% positive results, and means that there is a lack of support from pharmaceutical companies that need to fulfil FDA criteria in order to obtain a labelled indication (197) and a consequent difficulty in organising double-blind controlled studies involving large numbers of patients. Moreover, even in the case of large-scale clinical trials, there are no subgroup analyses of CRPS patients and only individual cases can be described.

It can therefore be concluded that, for the time being, the use of different agents to treat CRPS will remain largely empirical, and that the lack of prospective, randomised and double-blind studies carried out using appropriate methodologies and involving a sufficiently large number of patients will continue to prevent the definition of their role in CRPS therapy .

Drugs are not always considered the first choice for treating CRPS, and some authors consider physical therapy as the cornerstone of treatment (22). As far as systemic pharmacological treatments are concerned, there is a substantial (if incomplete) overlap between the treatments for peripheral neuropathic pain and those for both types of CRPS. Furthermore, CRPS I and II have both been treated with essentially the same drugs, and no data are available comparing the results of a given drug between the two types.

However, although these statements are substantially true and sound like a death knell for our patients, there are reasons for optimism. Over the last

few decades, a greater understanding of the pathophysiological components of CRPS has been acquired, such as the presence of an excessive inflammatory reaction in peripheral tissues; the presence of minor nerve damage also in CRPS I; neural sensitisation in the primary somatosensory afferents, and at segmental and supra-segmental level; and the presence of psychological and behavioural changes. In other words, a number of pathogenetic factors concur to form the multifaceted clinical picture of CRPS, which is sometimes more "sympathetic", sometimes more "inflammatory", and sometimes openly neuropathic. It follows that a single treatment can control the pain if it affects the appropriate pathophysiological mechanism in the lucky case of a single or predominant mechanism but, in all of the other cases, the presence of multiple pain mechanisms means that the only solution is cautious, low-dose polytherapy (223) bearing in mind what the clinical picture tells us about the symptoms and underlying causes (224). Unfortunately, many of these patients are seen by specialists only months after the onset of pain and several treatments. This is crucial because the clinical picture of CRPS changes over time and a treatment that is correct in a certain phase of its natural history may be completely wrong in another phase. In conclusion, the mystery of CRPS remains and is confirmed by the large number of systemic treatments used to treat it (225).

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