Current Concepts in adult CRPS

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CRPS diagnosis, epidemiology, recovery, health economics and rare presentations

CRPS is a painful condition which usually develops after trauma to a limb. It is characterized by limb-confined sensory, autonomic, motor, skin and bone changes, but the lead symptom is pain. Earlier names for the condition are given in appendix A. The CRPS diagnostic criteria have recently been updated ('Budapest Criteria', appendix B), because earlier criteria were not specific. These new criteria, although widely used have not yet been formally adopted by the International Association for the Study of Pain (1). Over the past 10 years many investigators, scientists and clinicians alike have jointly achieved remarkable progress in understanding and treating CRPS. These efforts have been enhanced by the success of the 'TRENDS' consortium led by Prof. J.J. van Hilten from Leiden and Prof. van der Helm from Delft, who secured in the early 2000’s over 20 million Euro in research support from the Dutch Ministry of Economic Affairs to study CRPS and related conditions.

As a result of the first ever, population based European epidemiological study, we now understand that CRPS is more common (incidence: 26/100,000 population) than previously thought (for comparison, the incidence of Multiple Sclerosis in the UK is estimated at 4/100,000). It has its peak in people aged 55-75 years, but may take a more benign course in this group, than in younger patients (2). CRPS is associated with migraines, osteoporosis and asthma (3). Overall 85% of patients will have substantial pain reduction within the first 2-3 years after disease onset. However only 30% of patients consider themselves fully recovered even 6 years after disease onset, and only 40% of people who worked before will return to their prior work. CRPS which has not improved early is less likely to improve later (4).

A definition of recovery from CRPS has not yet been achieved. Autonomic signs usually reduce with time, even where pain persists (5). Without autonomic signs, a diagnosis of CRPS can often not be made (Appendix B), so that patients may lose their initial diagnosis after some years, but continue to suffer from pain (6). It is likely that we will in the future define a ‘post-CRPS syndrome’ for patients who have fulfilled the Budapest criteria in the past. Similar as postherpetic neuralgia, but unlike lower back pain and fibromyalgia almost all CRPS is monophasic (once truly disappeared it won’t come back), with only 2% relapsing-remitting cases (6).

Because most cases of CRPS get better early on, for clinical trial purposes it can make sense to separately consider the difficult-to-treat longstanding CRPS (with > 6 months disease duration). This concept has received more attention over the last 10 years. Almost all clinical studies in longstanding CRPS have been conducted after 2000. For health economic calculations, the National Institute for Clinical Excellence (NICE) has assumed a 15 year estimated average CRPS duration for those cases of CRPS which require spinal cord stimulation (http://www.nice.org.uk/nicemedia/live/12082/42367/42367.pdf, page 21).

Similar as many other chronic pains (7), CRPS is expensive. Average annual health-care costs (excluding physiotherapy) in the Netherlands were €5700 in 1998. Because patients with longstanding CRPS almost never work (8) overall costs are higher. Return to work rates may remain low even in patients who successfully received spinal cord stimulation (SCS) treatment (Prof. Kemler, personal communication). That is in spite of the fact that SCS treatment improves patients’ quality of life (9). The average quality of life of patients with longstanding CRPS is very low, with an Euroqol score of 0.2 to 1 (8). For comparison the average scores in multiple sclerosis are 0.4-0.5-1 (10).

We all know that patients with CRPS can present in many different ways. For example, limbs can be hot or cold, shiny, swollen or thin, red or blue, with scaling or with clammy skin. However there are some rare presentations/complications, which even pain specialists may only encounter every few years. These include CRPS with spontaneous onset (no trauma), with a painful shoulder and autonomic signs (but not pain) only in the ipsilateral hand (formerly termed ‘shoulder-hand syndrome’), the spreading of symptoms to another limb, chronic lymphedema, skin ulcerations (often with secondary infections, Figure 1), blister formation, dystonia, severe atrophy and myodolorus; the complications are more common in young women (11).
In the right upper extremity in a mechanistic sense, travelling immune cells (IYG) were contributed while autonomic regulation (CRPS) also explain the effect, driving formal models for clinical response to the application of tourniquet which conveys that pain.

Causes and treatments of CRPS

There are currently seven major concepts about the CRPS etiology. These concepts can also explain the rationale for most clinical treatments:

1) CRPS as a sympathetically mediated disorder

Sweating and colour/temperature changes in the CRPS-affected extremity are in part mediated by sympathetic dysregulation, however the permanent cold temperature in some cases of late CRPS may be due to endothelial dysfunction (13). Evans had introduced the, now superseded term 'Reflex Sympathetic Dystrophy' (RSD, appendix A) to indicate that the autonomic dysregulation causes the patients' pain (14). Hannington-Kiff later suggested that agents which deplete the limb autonomic nerve endings of noradrenaline, such as regional guanethidine (intravenous regional sympathetic block, IVRSB) should be effective (15). Unfortunately all four RCT's conducted to assess this treatment have been negative (12), Given the experience shared by most clinicians that this method actually does reduce pain in some patients, one wonders whether it is perhaps the application of tourniquet which conveys that effect. Of note, one study has shown that IVRSB with saline is more effective than IVRSB with guanethidine (16). Local anaesthetic application to the sympathetic ganglia can relief pain short term in selected patients (17), but repeat application does not prolong that effect (18). These trial results have contributed to prompting CRPS experts to de-emphasize the importance of sympathetic dysregulation for CRPS pain.

2) Central sensitisation as the driving factor for CRPS

Central sensitisation is the molecular process that corresponds to the clinical observation that after a period of intense or repeated noxious stimulation, innocuous (non-noxious) stimuli become painful and remain painful (for a while at least) even if the initial noxious stimulation has subsided. This mechanism is important in most chronic pain (19). Because N-methyl D-aspartate (NMDA) receptors play a critical role in central sensitisation, the recent observation in two randomized controlled trials that low-dose intravenous ketamine (an NMDA-antagonist) can dramatically reduce CRPS pain indicates an important role for such central sensitisation (20). There is currently no RCT evidence for high-dose 'ketamine-coma' under intensive care conditions, which has sometimes been discussed in the media (21). In the two published low-dose RCT's, ketamine strongly reduced average pain intensity for several weeks, independent of the CRPS disease duration. It is uncertain whether these research findings will translate into clinical practice. Side effects from repeated ketamine infusions are poorly understood, with some experts expressing concern about potential neurotoxicity (22). Current protocols for Ketamine treatment are expensive and cumbersome. In the published protocols either a 5-day hospital inpatient stay, or 10 consecutive working-days outpatient treatments are required to achieve pain relief lasting several weeks. Recently a small pilot trial suggested efficacy of intravenous magnesium which, similar to Ketamine may work to reduce central sensitisation (23).

3) Autoimmunity may cause CRPS

This is a novel concept which has recently been suggested both by our and Frans Blaa's group. Both groups found evidence for anti-neuronal autoantibodies in CRPS (24-26). We have shown in a recent RCT that low-dose intravenous immunoglobulin (IVIG) is effective in longstanding CRPS (27). Pain relief in responders lasted for five weeks on average. Most medical conditions which respond to IVIG treatment are autoimmune in nature, and associated with functionally important autoantibodies. In our trial, patients typically responded within 2 days, which is atypical. If autoantibodies are indeed responsible, then the mechanism of their interaction with the nervous system should be different from that described in other conditions.

4) CRPS as a result of limb ischemia or ischemia-reperfusion injury

A recent pilot-trial showed that Tadalafil a phosphodiesterase inhibitor, reduces pain in some patients with CRPS who have cold limbs (28). Tadalafil is a vasodilator and it may be that the vasodilatory property of this drug is responsible for pain relief, however the affected limbs did not get warmer with treatment (limb temperature was the primary outcome). No other trial has to date demonstrated the success of a treatment which improves limb blood flow (the working mechanism of sympathetic blocks could of course be explained that way). In animal models, transient application of limb ischemia produces a syndrome which resembles CRPS (29). A possible prophylactic efficacy of Vitamin C in CRPS after dorsal

Figure 1. Lymphedema of the right upper extremity in a 35 year old man. This patient had an undisplaced right sided fracture of the fifth metacarpal. He developed Complex Regional Pain Syndrome complicated by lymphedema and recurrent episodes of cellulitis, which were treated with antibiotics. Amputation of the affected limb was later considered necessary. Chronic lymphedema with cellulitis is a rare complication in CRPS (from NEnglMed 2008; 359(5):508, with permission).

III The clinical trial evidence cited in this section is derived from at least one randomized controlled trial in each case, and with no conflicting results, unless specifically noted. These trials have been identified in systematic reviews by Tonnenfors et al. (12), until 06.2000, and the UK CRPS guideline group (email from 06.2000-04.2010; Consilus, in preparation)
radius fracture has been explained by the production of free radicals after such injury (30).

5) Cortical reorganisation is responsible for the CRPS pain

This is another exciting clinical and research development. Functional MRI studies over the last 10 years have clearly shown that the sensory representation of the CRPS affected limb is altered (shrunk and shifted), that the degree of the alteration corresponds to the pain intensity, and that pain reduction is associated with normalisation (31,32). There are also important changes in the motor cortex. We don’t know whether these changes are secondary, or whether they relate to the CRPS pathophysiology. Clinically we have learned that patients often feel alienation with their affected limb, which can feel strange and disfigured and out of place (33); these feelings are often not communicated to avoid the suspected danger of not being believed. Some patients can’t stop thinking about amputating that limb. These feelings may be associated with the altered cortical limb representation, although this has yet to be confirmed. Computer-based ‘graded motor imagery’ (GMI), which involves an exercise to train the brain in better recognizing the affected limb can reduce (34) pain and swelling (35). Mirror therapy\(^V\) was first applied to the treatment of CRPS by Candy McCabe’s group (36). It has been shown to reduce pain in CRPS (both early and late) after stroke (37).

These therapeutic advances appear particularly exciting since these treatments have few adverse events (2). Unfortunately we and others were recently unable to reproduce the published GMI findings in a 2-hospital audit setting (Johnson et al., under review). GMI and mirror treatment are now widely practiced, and clinicians should be aware that many patients with longstanding CRPS will not respond. But even if no pain relief can be achieved, the clinician’s anticipation and reflection of his/her patient’s ‘strange’ limb feelings may well support a better understanding and acceptance of the condition. Physiotherapy and occupational therapy (PT/OT) constitute one pillar of CRPS treatment (Figure 2). There are many reported PT/OT treatment methods. We recently found that therapists in our Liverpool region use over 20 different methods, with patterns greatly varying between individual therapists. Important methods include desensitisation (rubbing the affected limb gently with cloth or similar), gradual weight bearing, stretching and simple functional exercises.

6) CRPS may be due to nerve damage

This concept states that persistent dysfunction of small-diameter primary afferent nociceptor axons distal to the trauma is causal to CRPS. Studies in CRPS amputated limbs and skin biopsies have shown small fibre loss (38-40). Thus it is postulated that CRPS-I may represent a neuropathic pain syndrome\(^V\), a small-fibre-

\(^V\) Mirror therapy requires that the patient hides the affected limb behind a mirror which is positioned perpendicular to his body-midline. When looking into the mirror and performing bilateral synkinetic gentle movements, the visual affected limb (the reflection of the unseen limb in the mirror) has a normal appearance and also moves normally. It remains unknown why this treatment works.

\(^V\) Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system (41).

predominant mono- or oligoneuropathy (SFN), initiated by limb trauma (42). The concept shares some arguments with that of a ‘neurogenic inflammation’ (see next section) and demands that CRPS signs, symptoms and associated tissue inflammation are caused by the consequences of end-organ (including sweat glands and small vessels) partial denervation, by malfunctioning of neighbouring survivors to the dead small fibres (‘irritable nociceptors’), and by resulting central changes (42). The cause for the first step in the proposed cascade of events, the posttraumatic death of small fibres is currently unknown. Of the recommended first or second line treatments for neuropathic pain (43), only Gabapentin at a submaximal dose of 1800mg/day has yet been assessed, with negative result (44).

7) Inflammation can explain clinical CRPS signs

This was originally proposed by Peter Sudeck (‘Sudeck’s atrophy’) (45). The painful CRPS-affected limb is often red, hot and swollen, with reduced function: the five cardinal signs of inflammation (46). And indeed recent research found that inflammatory markers are elevated in blister fluid from CRPS-affected limbs (47). However the titre of these markers is not related to the pain intensity and markers can remain high even if the pain disappears (48). One small randomized control trial has suggested that steroid treatment is effective in very early CRPS and some clinicians find this observation confirmed by their clinical experience (49). In longstanding CRPS intraheal steroids are not effective (50). TNF-alpha treatment has been proposed, but no RCT has been conducted. Lenalidomide, a highly toxic anti-inflammatory thalidomide derivative was tested in one of the largest ever trials in CRPS, but unfortunately the company (Celgene) has not published the results.

It remains unclear which cells initiate CRPS inflammation. One possibility is that neuropeptides, antidromically released from...
sensory neurons cause skin reddening and swelling thus producing CRPS signs (‘neurogenic inflammation’); immune mediator release may follow. In detailed experiments, Frank Birkele’s team has indeed confirmed an abnormality of the neuropeptide handling in CRPS and termed what they found ‘facilitated neurogenic inflammation’ (51). They showed that when c-fibres in affected (and to a lesser degree also unaffected) limbs are stimulated, CRPS patients respond with much stronger (neuropeptide-mediated) skin reddening and swelling than control patients. The cause is unclear. It is possible that in CRPS these neuropeptides, once released are not properly metabolized. The importance of neuropeptides for the CRPS pathophysiology has gained further credence by the recent finding that CRPS is associated with intake of angiotension converting enzyme (ACE)-inhibitor medication (53). ACE metabolises the neuropeptides substance P and bradykinin to inactive forms, thus ACE-inhibitors may lead to higher tissue levels of both neuropeptides. Up until now, these interesting findings have not translated into clinical treatments.

Alternative concepts on the CRPS pathophysiology

Some authors have placed CRPS broadly into the context of somatoform disorders or malingering. A few authors have also taken the fact that CRPS’s 1st is not associated with structural lesions as evidence that this problem should be, at least in part of psychological origin (54). Recent more systematic investigations were not corroborative (3,55). Stressful life events may be more common in patients before development of the condition (55). Some people self-induce injuries to resemble CRPS (56).

Although this has not been systematically assessed, it is my clinical impression that patients can feel stigmatised by health professionals who did not believe that their condition is ‘real’. The scientific evidence in support of somatisation and malingering as causes for CRPS is meagre at best. Interestingly, almost hidden from most clinicians there can be intense arguments in the medico-legal contexts about the causes of CRPS. Stakes in the context of work-related injuries can be high, and ‘psychogenic’ concepts about the CRPS pathophysiology may be cited more frequently than would be in clinical situations.

In common with other chronic pains, CRPS should best be seen as a biopsychosocial condition. Randomised controlled trials of cognitive behavioural therapy in CRPS are still missing. The UK guideline group will recommend cognitive behavioural therapy as one of the four pillars of treatment (Figure 2).

Genetic predisposition is important in a wide range of medical disorders. Several groups have examined genetic associations in CRPS, but to date no robust association has been found (57). Genome-wide association studies have not yet been accomplished.

Recommendations for the treatment of CRPS

(i) patients should be educated about CRPS and be given simple information on self-management such as advice to direct attention to the limb and to stroke and use it frequently and gently.

(ii) most patients require specialised physiotherapy delivered by physiotherapists or occupational therapists experienced in the treatment of patients with chronic pain (Figure 2). This should be initiated as early as possible, recognizing that advice to gently move the frequently red, swollen and painful limb of early CRPS can sometimes appear counterintuitive to patients and practitioners. Important methods include desensitisation (rubbing the affected limb gently with cloth), gradual weight bearing, stretching and functional and fine motor exercises. Since the required expertise to deliver these treatments is not universally available, the development of a network approach appears useful, where stakeholders in a region know to locate the regional expert centre(s) and/or experienced practitioner(s). More research is needed to better understand the relation between early physiotherapy treatment and prevention of late complications (such as ankylosis and contracture).

(iii) multidisciplinary pain management treatment, guided by principles of cognitive behavioural therapy should be considered early for those patients who do not improve, and who show signs of distress. Here again stakeholders should know of the nearest centre which offers such service.

(iv) a number of novel drug or interventional treatments, which may provide pain relief have been described, however confirmatory trials are required for most before recommendations can be given. It is reasonable to initially treat patients with drugs developed for neuropathic pain, although there is no CRPS-specific evidence for any of these treatments (35). In addition, a one off pamidronate 60mg iv infusion treatment should be considered for those with less than 6 months duration. Intravenous regional sympathetic blocks (IVRSB) should not routinely be used in the treatment of CRPS since four randomised controlled trials have not demonstrated any benefit. Pragmatically, in those rare patients with early CRPS, for whom local anaesthetic injection to sympathetic ganglia provides days or weeks of pain relief, this treatment may bridge the time until the disorder gets better by itself, however more research is needed before a recommendation can be made – importantly repeat blocks will not prolong the analgesic effect. In the UK, spinal cord stimulator (SCS) treatment is the only NICE approved method to treat CRPS. With time, the SCS effect does slowly diminish, so that in the RCT the SCS results did not exceed those in the ‘physical therapy’ control group from 3 years after implantation (58). The authors of the seminal RCT conclude that, although patient satisfaction was generally high, ‘the unknown working mechanisms of the (SCS) treatment apparently do not function indefinitely’ (59). Spinal cord stimulator treatment may be appropriate where these other treatments do not provide benefit. Unfortunately, even with best

VI CRPS II/2 is defined as with/without damage to a major nerve. VII 1800mg gabapentinol/day is not effective (44).
current treatment approaches some patients may not experience sufficient pain relief.

(v) perioperative care and prevention after trauma: The risk of surgery causing a severe new CRPS episode in someone who had CRPS in the past is probably neither high nor zero (60). It seems common sense to defer operating in an early case of CRPS until acute symptoms have subsided, if at all possible, to reduce the risk of aggravating the condition, though even for such recommendation no RCT-derived evidence exists. There is no evidence for the superiority of any anaesthetic technique to prevent re-igniting or aggravating CRPS. There is preliminary evidence in favour of giving oral vitamin C after dorsal radius fracture (500mg x 50 days), but more evidence is needed before this can be recommended (30).

(vi) long-term care: Not a single publication to date has described how we should care for those who have trialled available physical, behavioural and pain relief treatments, but who still have ongoing pain and a reduced quality of life. Any long-term approach should be patient-centred and include facilitated ways for the patient to request top-up support (e.g. by way of occasional on-demand consultation with a named specialist physiotherapist, psychologist or doctor), attendance of self-support groups under the umbrella of, or with some link to the medical treatment centre, and access to information about available support for developing adapted work, leisure and social activities. In a recent series of CRPS focus group discussions at our centre, patients named the education of healthcare professionals, particularly their GPs, about CRPS a top priority (in preparation).

Initiatives in the UK to enhance the care of patients with CRPS and research into this condition

Late diagnosis of CRPS may lead to unnecessary suffering from not knowing what is going on and, in some cases, inappropriate treatment. In addition, where patients never reach pain management specialists, research is not so easy to conduct. When we looked at enrolling patients to our, now completed randomised controlled trial in central London, we saw only two suitable patients with longstanding CRPS within a 2.5 year period, in a busy pain clinic with a direct catchment area of 600,000 population plus tertiary referrals, suggesting that patients in this area are not referred to specialist care. You could check this for your own region: Assuming the published incidence- and recovery rates, you should see every year 4 new patients with un-resolving CRPS of >1 year duration/100,000 of your catchment population; further, supposing an average 15 year duration, you should have 60 CRPS patients/100,000 catchment area population on your books. Is this number anywhere remotely close to the number of patient you see? At least in some UK regions it is not. Where are these patients? We suspect that they may either remain undiagnosed, or that they do not reach pain services.

In order to address these issues, Chris Barker (Specialist in pain medicine, Selston community pain services) and I initiated in 2008 a multidisciplinary UK guidance workshop series with an aim to support the diagnosis and appropriate management of patients with CRPS across the wide range of those health professionals who see them (Figure 3). The guidance development process has now been adopted by the Royal College of Physician ‘Concise Guidance series’, and this process (but not yet the product) has been supported by 3 Royal Colleges and 8 UK professional organisations including the Faculty of Pain Medicine within the Royal Colleges of Anaesthetists and the British Orthopaedic Association. We hope to complete this process and distribute the guidance by summer 2011. Chris Barker has also led efforts to revise the GP ‘read codes’ for CRPS. Read codes appear when a GP enters a certain medical term into the electronic records database. Up until last year the term ‘CRPS’ or ‘Complex Regional Pain Syndrome’ was not recognized, but this has now been changed and GP’s are given the option to link to a short explanatory leaflet about the condition.

Candy McCabe has previously reported in ‘BPS’s newsletter on the foundation of the ‘CRPS Network UK’, a multidisciplinary group of currently 10 clinicians and researchers with a special interest in CRPS (61). This group aims to enhance clinical care for and research into CRPS in the UK, and liaise with other European investigators. We welcome interested clinicians to join the network. Should you be interested (membership is informal and open), please do contact our administrator, Mrs. Yvette Hibbert for further information and upcoming meeting dates (appendix C). As a first joint project we have (in 2008) established the UK CRPS registry, supported by the cancer services information technology unit at the University Southampton. Participating investigators enter, after taking informed consent contact data for CRPS patients on this web-based database. By giving consent, patients agree that they can later be contacted by researchers for ethics-approved projects. Database access will be
managed by a steering committee, which will be happy to receive proposals for access from late 2011. The management lead for the registry is Dr. Nick Shenker (appendix C). The registry currently holds 140 entries of patients with longstanding CRPS, and recruitment is going strong.

Future developments: One never knows what is around the next corner, however for my special area of autoimmunity and immune modulation, I suspect that clinicians will eventually be offered a serum test for CRPS diagnosis, and that novel applications of immunoglobulin (such as low-dose home application) will be assessed\textsuperscript{10}.

Summary
We have learned a lot about CRPS in the past 10 years, and we have even been given a glimpse upon some treatments which, for the first time promise effective pain reduction for those with longstanding disease. To date all evidence is preliminary, with the exception of that for Spinal Cord Stimulator treatment and, potentially, the treatment with bisphosphonates (12)\textsuperscript{3}. The quality of clinical trials has much improved and the quantity of research into the condition has skyrocketed. While we still don't know what causes CRPS, one has the sense that efforts to tackle this fascinating, debilitating condition are exemplary for the progress of the new field of Pain Medicine to come into its own.

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Conflict of interest
Dr. Goebel has received grant support from Talecris, SC, USA and CSL-Behring, Bern, Ch, and a speaker honorarium from Baxter, USA. These companies produce polyvalent immunoglobulins.

References


APPENDIX

A) Now superseded old terms for CRPS:

- Algodystrophy
- Shoulder-Hand Syndrome
- Reflex Sympathetic Dystrophy
- Algodystrophy
- Causalgia
- Sudeck’s atrophy

B) Budapest Diagnostic Criteria for CRPS

All of the following statements must be met:

- The patient has continuing pain which is disproportionate to the inciting event
- The patient has at least one sign in two or more of the categories below
- The patient reports at least one symptom in three or more of the categories below
- No other diagnosis can better explain the signs and symptoms

<table>
<thead>
<tr>
<th>Category</th>
<th>Sign/Symptom</th>
</tr>
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<tbody>
<tr>
<td>1 ‘sensory’</td>
<td>Allodynia (pain to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement) and/or hyperalgesia (to pin-prick)</td>
</tr>
<tr>
<td>2 ‘sensomotor’</td>
<td>Temperature asymmetry (&gt;1°C if counted as a sign) and/or skin colour changes and/or skin colour asymmetry</td>
</tr>
<tr>
<td>3 ‘sudomotor/oedema’</td>
<td>Oedema and/or sweating changes and/or sweating asymmetry</td>
</tr>
<tr>
<td>4 ‘motor/trophic’</td>
<td>Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair/nail/skin)</td>
</tr>
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</table>

C) Contact details and links

- CRPS Network UK: Mrs. Yvette Hibberd Yvette.Hibberd@mhnd.nhs.uk
- UK CRPS Registry: Dr. Nick Shenker nicholas.shenker@addenbrookes.nhs.uk
- Liverpool Centre for Immune Studies in Pain: http://www.liv.ac.uk/prl/cisp/

X The here reflected understanding of ‘allodynia’ as painful sensation to a number of non-painful stimuli is currently under review by the IASP taxonomy group. Some experts suggest that the term allodynia should be reserved only for brush-stroke evoked pain (dynamic mechanical allodynia).