UPDATED GUIDELINES

COMPLEX REGIONAL PAIN SYNDROME TYPE 1

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Initiative:

- Netherlands Society of Anaesthesiologists
- Netherlands Society of Rehabilitation Specialists

Organisation:
CBO a TNO Company

Authorising Associations / Institutions:

- Dutch Pain Society
- Royal Dutch Society for Physical Therapy
- Dutch Professional Association of Psychologists
- Dutch Orthopaedic Association
- Netherlands Society of Neurosurgeons
- Netherlands Association for Occupational and Industrial Medicine
- Dutch Association of Occupational Therapy
- Netherlands Society of Surgery
- Netherlands Society of Paediatric Medicine
- Netherlands Society of Neurology
- Netherlands Society for Plastic Surgery
- Netherlands Society of Rheumatology
- Netherlands Society for Insurance Medicine
- Netherlands Association of Posttraumatic Dystrophy Patients

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Imprint

Updated Guidelines for Complex Regional Pain Syndrome type 1

Netherlands Society of Rehabilitation Specialists
PO Box 9696
3506 GR UTRECHT
Tel.: +31 (0)30-2739696
Fax: +31 (0)30-2739406
www.revalidatiegeneeskunde.nl/

Netherlands Society of Anaesthesiologists
PO Box 20063
3502 LB UTRECHT
Tel.: +31 (0)30-2823387
Fax: +31 (0)30-2881853
www.anesthesiologie.nl

The Netherlands Society of Rehabilitation Specialists (VRA) is the national society for doctors specialising in rehabilitation medicine. The core activities of a rehabilitation specialist are: providing diagnosis, treatment, advice and consultation for patients who have experienced a loss of function following illness, accident or a congenital condition. The aim of rehabilitation treatment is to help patients play a more active part in society and reduce the impact on their social life.

The Netherlands Society of Anaesthesiologists (SA) is a society made up of and working on behalf of anaesthesiologists. It promotes its members' interests and helps create a positive image for anaesthesiology and anaesthesiologists in the Netherlands. It supports high-quality and appropriate performance of anaesthesiology by developing and implementing policies in the field of scientific research, medical technology, quality assurance and inspections.

The Utrecht-based Institute for Healthcare Improvement (CBO) works to support individual healthcare practitioners, their professional associations and healthcare institutions in improving patient care. The CBO runs programmes and projects to support and assist with the systematic and structured assessment, improvement and assurance of high-quality patient care.

COMPOSITION OF THE PROJECT GROUP

Core editors

- R.S.G.M. MSc PhD, Perez, Associate Professor, Pain, pain control & palliative care research, VU University Medical Centre, Amsterdam, chair
- Prof. J.H.B. Geertzen MD PhD, Rehabilitation Specialist, Groningen University Medical Centre, Groningen, Vice-chair
- Prof. P.U. Dijkstra MSc PhD, Physiotherapist/Epidemiologist, Groningen University Medical Centre, Groningen
- M. Dirckx, MD, Anaesthesiologist, Erasmus Medical Centre, Rotterdam
- F. van Eijs MD PhD, Anaesthesiologist, St. Elisabeth Hospital, Tilburg
- J.P. Frölke MD PhD, Trauma Surgeon, Radboud University Medical Centre, Nijmegen
- J. Patijn, MD PhD, Neurologist, Maastricht University Medical Centre, Maastricht
- C.J.G.M. Rosenbrand, MD, Physician, Institute for Healthcare Improvement CBO, Utrecht, senior adviser, Utrecht
- I.L. Thomassen-Hilgersom MSc, Chair of the Dutch Association of CRPS Patients, Nijmegen
- G.J. Versteegen MSc PhD, Clinical Psychologist, Groningen University Medical Centre, Groningen
- P.E. Zollinger MD PhD, Orthopaedetic Surgeon, Rivierenland Hospital, Tiel

Advisory group

- H.R. Van den Brink MD PhD, Rheumatologist, Alkmaar Medical Centre, Alkmaar
- W.A.J.J.M. Haagh MD PhD, Trauma Surgeon, St. Anna Hospital, Helmond
- Prof. J.J. Van Hilten MD PhD, Neurologist, Leiden University Medical Centre, Leiden
- Prof. F.J.P.M. Huygen MD PhD, Anaesthesiologist, Erasmus Medical Centre, Rotterdam
- M.A. Kemler MD PhD, Plastic Surgeon, Martini Hospital, Groningen
- Prof. M. Van Kleef MD PhD, Anaesthesiologist, Maastricht University Hospital, Maastricht
- Prof. W. Kuis MD PhD, Paediatrician, University Medical Centre – Wilhelmina Children's Hospital, Utrecht
- L. Van der Laan MD PhD, Surgeon, Amphia Hospital, Breda
- J.M. Ruijgrok MD PhD, Rehabilitation Specialist, Maastricht University Hospital, Maastricht
- F.G. Slebus MD PhD, Insurance Company Medical Adviser, Employee Insurance Agency - East Region, Arnhem

- S.D. Strackee MD PhD, Plastic Surgeon, University Medical Centre, Amsterdam
- P.J.M. Veldman MD PhD, Surgeon, Tjongerschans Hospital, Heerenveen
- L.A.W. Van de Ven-Stevens MSc, Occupational Therapist, Radboud University Medical Centre and Occupational therapy, Nijmegen
- I.T.H.J. Verhagen MD PhD, Neurosurgeon, St. Elisabeth Hospital, Tilburg
- A.C.L.P.J. Verhoeven MD PhD, Company Doctor and Insurance Company Medical Adviser, SMZ UWV, Zwolle
- Prof. W.W.A. Zuurmond MD PhD, Anaesthesiologist, VU University Medical Centre, Amsterdam

The Dutch Pain Society is represented by members participating in the development of these guidelines.

CRPS-I GENERAL INTRODUCTION

Background

In the Guidelines for Complex Regional Pain Syndrome type I (CRPS-I) from 2006, the intention was expressed to determine by no later than 2010 whether a complete revision or (partial) update of the guidelines from 2006 would be needed.
At the initiative of the Netherlands Society of Rehabilitation Specialists (VRA) and the Netherlands Society of Anaesthesiologists (NVA), a core group was assembled to examine whether essential developments from published studies on the diagnostics and treatment of CRPS-I required changes to be made to the current recommendations. The core group also consulted a broad advisory group regarding whether there are new problem areas in the field that could form the basis for formulating new fundamental questions which the revision could answer.

In light of the evolving insights into the diagnostics and treatment of CRPS-I, the core group found it desirable to update the guidelines from 2006. In this update, the patient perspective was once again a key focus. The new guidelines will give care providers an up-to-date overview of the areas in which recent research has led to a change in recommendations and in which areas recommendations have remained unchanged, with a view to guaranteeing the best care for patients with CRPS-I.
The update also devoted attention to implementation aspects.

Funding for the update was made available by the TREND consortium (www.trendconsortium.nl). The Dutch Institute for Healthcare Improvement CBO was asked to provide methodological support in the revision of these guidelines.

The update to the guidelines from 2006 was developed based on the Evidence-Based Guideline Development method. A core group prepared the draft of this update, while an advisory group provided input on the problem-area analysis during the preparatory phase and feedback on the draft at a later stage. Nearly all core group members and advisory group members had also participated in the project group responsible for the CRPS-I guidelines from 2006, once again representing all the associations that were involved then.

Since 2006, a lot of new knowledge has become available regarding the epidemiology and pathophysiology of CRPS-I. Diagnostic criteria were also further developed. A lot of new literature on medical and paramedical treatment which evaluates the value of (new) treatment for CRPS-I has also been published since 2006.

Table 1. Classification of the methodological quality of individual studies

	Intervention	Diagnostic accuracy of study	Damage or side effect, aetiology, prognosis*
A1	Systematic review of at least two independently conducted A2-level trials		
A2	Randomised, double-blind comparative clinical trial of good quality and sufficient size	Research relating to a benchmark test (a 'gold standard') with predefined cut-off values and an independent assessment of the results of the test and gold standard, encompassing a sufficiently large series of consecutive patients who have all been administered the index and benchmark test	Prospective cohort study of sufficient size and follow-up, with proper control for 'confounding' and sufficient exclusion of selective follow-up.
B	Comparative trial, but without all features listed under A2 (this also includes patient-control studies, cohort studies)	Research relating to a benchmark test, but without all features listed under A2	Prospective cohort study, but without all features listed under A2 or retrospective cohort study or patient-control study
C	Non-comparative trial		
D	Opinion of experts		

*** This classification only applies to situations in which controlled trials are not possible for ethical reasons or otherwise. If, however, they are possible, the classification for interventions applies.**

Level of conclusions

	Conclusion based on
1	A1-level research or two A2-level studies conducted independently of each other, with consistent results
2	One A2-level study or two B-level studies conducted independently of each other
3	One B-level or C-level study
4	Opinion of experts

These guidelines employ the definition from the most recent version of the Classification of Chronic Pain (Merskey and Bogduk 2011) of the IASP:

"CRPS-I is a syndrome characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of pain after trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor/oedema and/or trophic findings. The syndrome shows variable progression over time. CRPS-I occurs after any form of trauma, particularly a fracture or soft tissue lesion. CRPS-II occurs after nerve damage."

CHAPTER 1: DIAGNOSTICS - PATHOPHYSIOLOGY AND ADDITIONAL DIAGNOSTICS - EPIDEMIOLOGY AND PREDISPOSING FACTORS

1.1 Diagnostics of the Complex Regional Pain Syndrome type I

CRPS-I is characterised by sensory, vasomotor and autonomic disorders of a limb, usually following a trauma or operation. Clinical evaluation and diagnosis of CRPS-I is based on evaluation of observable phenomena and symptoms reported by the patient based on defined sets of diagnostic criteria. Establishing a clinical diagnosis of a case of CRPS-I that is typical and acute in all its facets is often quite straightforward. However, in most cases CRPS-I does not present itself in the classic form with all the symptoms. A diagnosis may not be made at all, or it may be inaccurate or delayed.

The "Budapest" criteria" (2005)

The aforementioned criteria as per Bruehl et al. were evaluated and amended by the IASP-sponsored symposium that was held in Budapest in 2005. In these "Budapest" criteria (see Appendix 1, Table 4), a distinction was made between diagnostic criteria for clinical use and diagnostic criteria for research. The criteria were then revalidated in an international study which also involved Dutch centres (Harden et al. 2010). The study found the clinical criteria to have a diagnostic sensitivity of 0.99 and a specificity of 0.68 in 113 CRPS-I patients when compared with a control group of non-CRPS neuropathic pain patients (n=47). The Budapest research criteria resulted in a higher specificity (0.79), though this was accompanied by a lower sensitivity (0.78).

Conclusions

Level 2	It is likely that the diagnosis of CRPS-I can be made by means of anamnesis and findings from physical examination. *B Bruehl 1999, Harden 2010* *C Atkins 2003, Perez 2002* *D Brunner 2008*

Level 2	The discriminatory capacity in relation to a control group has only been studied with respect to the Bruehl and Budapest criteria. *B Bruehl 1999, Harden 2010*

Level 2	There is evidence that a reliable diagnosis can be made based on criteria drawn up by Veldman. The results are conflicting with respect to a diagnosis made using the Bruehl criteria. *B Vusse van den 2003, Perez 2005* *C De Mos 2007*

Other considerations

The lack of a clear pathophysiological mechanism, as well as the absence of a good benchmark test, let alone a gold standard, necessitates the use of clinical diagnostic criteria. For example, a recent Japanese study (Sumitani et al. 2010) involving 195 patients attempted to replicate the factor solution that was used as the basis for the Budapest criteria set. The study found a different factor solution, which resulted in a different set of criteria. This fact calls for the further development and study of this criteria, analogous to the development of other clinical diagnostic criteria (such as the DSM-IV) (Harden 2012). In doing so, it should be kept in mind that the simultaneous use of various diagnostic criteria is undesirable, given that this may lead to randomness in the diagnostics of this condition. There is evidence that the various diagnosis sets lead to differences in the number of diagnosed patients and differences in clinical profiles between patients diagnosed with CRPS-I (Perez et al. 2007; De Boer et al. 2011). What is more, it is desirable for the criteria to be attuned to international guidelines in this field so that (future) scientific findings based on internationally accepted criteria can be related to the way in which diagnosis takes place in Dutch clinics.
The diagnostic criteria of the IASP-Orlando, Veldman et al. and the clinical Budapest criteria seem to be sufficiently sensitive. The latter has sufficient discriminatory capacity with respect to patients who have neuropathic pain.
Stricter criteria such as those proposed by Bruehl et al. and the Budapest research criteria could lead to underdiagnosis. The Budapest criteria were recently formally approved by the taxonomy committee of the IASP as diagnosis criteria for CRPS-I (Merskey and Bogduk 2012).
It should also be taken into consideration that a definitive diagnosis of CRPS-I can only be made once the usual recovery period for the original trauma is assumed to have passed. Nonetheless, doctors are asked to be on the alert if hyperalgesia and allodynia, temperature asymmetry, colour difference and oedema are observed in a patient (Perez et al. 2007). An online diagnostic aid for doctors can be found at http://www.trendconsortium.nl/diagnose/.

Recommendations

- The Budapest criteria are recommended for the clinical diagnosis of CRPS-I.
- Due to the heterogeneity of the syndrome, the patient's clinical symptoms should be described in detail.
- The Budapest research criteria can be used if a more specific patient population is desired for scientific research.

1.2 Pathophysiology and additional diagnostics

As there is not yet a clear and all-encompassing pathophysiology for CRPS-I, there are still no diagnostics tests that can be used as a gold standard for CRPS-I (Harden 2012). It is believed that the pathophysiology of CRPS-I can be divided into three major "biological pathways": 1. Aberrant inflammatory mechanisms, 2. Vasomotor dysfunction and 3. Maladaptive neuroplasticity (Marinus et al. 2011; Bruehl 2010; Nickel & Maihöfner 2010; Jänig 2010; De Mos, Sturkenboom, & Huygen 2009). The heterogeneity within the CRPS-I population can thus be explained on the basis of the between-individual variability in the activation of mechanisms within these three biological pathways (Marinus et al. 2011).

Any additional diagnostics in CRPS-I patients pertain to and/or are derived from experimental evaluation within the three biological pathways: aberrant inflammatory mechanisms, vasomotor dysfunction and maladaptive neuroplasticity. Different clinical diagnostic testing in CRPS-I patients can pertain to quantification and objectification of symptomatology, but have no diagnostic value as such. Various predisposing factors will also be discussed because these may provide evidence of pathophysiological mechanisms in CRPS-I.

Inflammation plays a very prominent role in CRPS-I. This inflammation has no systemic character or signs of an allergic reaction. Examination of inflammatory mediators in the serum of CRPS-I in the affected and/or unaffected limb produces contradictory results, particularly with respect to the difference between the affected and unaffected limb. The examination of inflammatory mediators in blister fluid suggests that the inflammatory response is local in nature, given the fact that inflammatory mediators such as cytokines, chemokines, neuropeptides, vascular endothelial function mediators and other inflammatory mediators are most abnormal in the affected limb. The inflammatory response in CRPS-I is not found in cerebrospinal fluid.
It is unclear as to why the inflammatory response derails. One of the causes may be inadequate inactivation of released inflammatory mediators and/or increased receptor availability, with neuropeptides possibly playing a major role. The clinical significance of these inflammatory mediators is limited, in light of the substantial lack of a mutual relationship between the clinical symptomatology of CRPS-I and observed increased concentrations of inflammatory mediators in serum, blister fluid and cerebrospinal fluid. The conclusions in many studies are often interpretations of observations in the context of explaining inflammatory mechanisms in CRPS-I. The conclusions of these studies should be considered with the appropriate caution, in part due to the fact that the CRPS-I criteria used in the studies vary greatly.

Conclusion General serum inflammation parameters

Level 3	The additional diagnostic value of general inflammation parameters in serum has not been demonstrated in CRPS-I patients. *C Ribbers 1998, Veldman 1993, Schinkel 2006, 2009, Uçeyler 2007*

Recommendation

The project group is of the opinion that blood testing to determine general inflammation parameters should not be used as a diagnostic tool on patients with suspected CRPS-I, unless another diagnosis is suspected that can be demonstrated by means of this technique.

Conclusion Specific serum, blister fluid and cerebrospinal fluid inflammation parameters

Level 3	The additional diagnostic value of specific inflammation parameters in serum, blister fluid (in affected and unaffected limb) and cerebrospinal fluid in CRPS-I patients has not been demonstrated. *C Drummond 1994, Blair 1998, Birklein 2000, 2001, Van de Beek 2001, Figuerola 2002, Huygen 2002, 2004, Eisenberg 2004, Munnikes 2005, Alexander 2005, 2007, 2012, Heijmans-Antonissen 2006, Groeneweg 2006, Schinkel 2006, 2009, Uçeyler 2007, Wesseldijk 2008a, 2008b, 2008, 2009, Munts 2008, Ritz 2011, Krämer 2011*

Recommendation

The project group is of the opinion that the testing of serum, blister fluid and cerebrospinal fluid for specific inflammation parameters should not be used as a diagnostic tool on patients with suspected CRPS-I, unless another diagnosis is suspected that can be demonstrated by means of these techniques.

Conclusion Skin tests

Level 3	The additional diagnostic value of skin tests in CRPS-I patients has not been demonstrated. *C Birklein 2000, Calder 1998, Drummond 1996, Koban 2003, Leis, 2003, Krämer 2012*

Recommendation

The project group is of the opinion that skin tests should not be used a diagnostic tool on patients with suspected CRPS-I.

Conclusion

Level 3	Volumetry and measurement of finger diameter as indirect indicators of hand and ankle oedema can be used to objectify CRPS-I criteria. *C Atkins 1990, Iwata 2002, Harden 2000, Oerlemans 1999*

Recommendation

The project group is of the opinion that measurement of limb oedema using volumetry and finger diameter should not be used as a unique diagnostic tool on patients with suspected CRPS-I. However, these methods can be used to objectify oedema.

Diagnostics Inflammatory response: Skin temperature

Conclusion Infrared thermometer and infrared thermography

Level 3	Absolute skin temperature measurements using infrared thermometers or infrared thermography (with or without stimuli) offer limited additional diagnostic value in CRPS-I patients. These techniques can be important in objectifying skin temperatures in the context of CRPS-I criteria. A difference of 1.5 ℃ is recommended as a way of differentiating between normal posttraumatic syndromes and patients with CRPS-I. C *Karstetter & Sherman 1991, Cooke 1989, 1993, Sherman 1994, Low 1994, Chelimsky 1995, Gulevich 1997, Oerlemans 1999a, Oerlemans 1999b, Oerlemans 1999c, Birklein 2000, 2001, Wasner 2002, Huygen 2002, 2004, Alexander 2012, Perez 2005, Singh & Davis 2006, Schürmann 2007, Goris 2007, Groeneweg 2008, Wesseldijk 2008b, 2008, Krumova 2008, Eberle 2009, Koike 2010, Campero 2010, Huge 2011b, 2008*

Recommendation

The project group is of the opinion that skin temperature measurements using infrared thermometers or infrared thermography should not be used as a unique diagnostic tool on patients with suspected CRPS-I. However, these methods can be used to objectify temperature differences.

Diagnostics Inflammatory response: pain

Conclusion Quantitative Sensory Testing (QST)

Level 3	The additional diagnostic value of QST in CRPS-I patients has not been demonstrated. However, this method can be important in quantifying sensory abnormalities in the context of the CRPS-I criteria and research. *C Price 1992, Thimineur 1998, Sieweke 1999, Birklein 2000, 2001, Kemler 2000,Tahmoush 2000, Vaneker 2005. Drummond & Finch, 2006, Eisenberg 2006, Seifert 2009, Sethna 2007, Huge 2008, Ebeler 2009, Maier 2010, Van Eijs 2010, Knudsen 2011, Ritz 2011, Terkelsen 2012, Gierthmühlen 2012, Kolb 2012, Kharkar 2012*

Recommendation

The project group is of the opinion that Quantitative Sensory Testing (QST) should not be used as a unique diagnostic tool on patients with suspected CRPS-I. However, this method can be used to objectify sensory disorders.

Conclusion

Level 3	Some evidence has been found for the benefits of using the VAS (severity of the pain), the McGill and the NPS (nature of the pain) to diagnose CRPS-I patients. *C Forouzanfar 2002, Galer & Jensen 1997, Perez 2005*

Recommendation

The project group is of the opinion that the McGill Pain Questionnaire, the Neuropathic Pain Scale (NPS) (nature of the pain) and the Visual Analogue Scale (VAS) should not be used as a diagnostic tool on patients with suspected CRPS-I. However, these methods can be used to quantify the severity of the pain.

Limb motor function impairment

Conclusion

Level 3	It is doubtful whether any benefit accrues from measuring loss of strength by means of a sphygmomanometer or dynamometer in patients with CRPS-I. This method is therefore as yet unsuitable for quantifying loss of strength in CRPS-I patients that has been observed from physical diagnosis. *C Atkins 1990, Oerlemans 2000, Schasfoort 2003, 2004, Veldman 1993*

Recommendation

The project group is of the opinion that loss of strength measurement by means of a sphygmomanometer or dynamometer should not be used as a diagnostic tool on patients with suspected CRPS-I. However, these methods can be used to quantify loss of strength.

Conclusion

Level 3	The lack of clear data as to the reproducibility of movement impairment using a goniometer means that this method is as yet unsuitable for quantifying impaired movement in CRPS-I patients that has been observed from physical diagnosis. *C Dijkstra & Geertzen 2001, Horger 1990, Oerlemans 1999*

Recommendation

The project group is of the opinion that measurement of impaired movement by means of a goniometer should not be used as a diagnostic tool on patients with suspected CRPS-I. However, this method can be used to quantify impaired movement.

Compound scores

Conclusion

Level 3	Little research has been carried out to date on the value of the Impairment level SumScore (ISS) as an indicator of the severity of impairment. The ISS can be used to describe impairments related to CRPS-I in the context of research. *C Oerlemans 1998, Perez 2003*

Recommendation

The project group is of the opinion that the day-to-day treatment of CRPS-I patients does not need to involve objectifying the severity of impairment by means of the Impairment level SumScore (ISS).

Diagnostics of inflammatory response: functional imaging techniques

Conclusion Diagnostics of inflammatory response: functional imaging techniques

Level 3	The additional diagnostic value of MRI, white blood cell scan, NMR spectroscopy and scintigraphy with radioactive-labelled substances in the context of the inflammatory response of the affected limb in CRPS-I patients has not been demonstrated. *C Koch 1991, Schweitzer 1995, Graif 1998, Schimmerl 1991, Tan 2005, Heerschap 1993, Schurmann 2007*

Recommendation

The project group is of the opinion that MRI, white blood cell scan, NMR spectroscopy and scintigraphy with radioactive-labelled substances in the context of the inflammatory response of the affected limb should not be used as a diagnostic tool on patients with suspected

CRPS-I, unless another diagnosis is suspected that can be demonstrated by means of these techniques.

Inflammatory response diagnostics: bone pathology

Conclusion Inflammatory response diagnostics: bone pathology, imaging techniques Three-phase bone scan

Level 3	The additional diagnostic value of three-phase bone scans in CRPS-I patients has not been demonstrated. *C* *Atkins 1993, Holder & Mackinnon 1984, Intenzo 1989, Kozin 1981, Werner 1989, Lee & Weeks 1995, Todorović-Tirnanić 1995, Steinert & Hahn 1996, Moriwaki 1997, Intenzo 2005, Lin 2010, Moon 2012, Nitzsche 2011, O'Donoghue 1993, Okudan 2005, Pankaj 2006, Park 2007, Pennekamp 2011, Schürmann 2007, Wüppenhorst 2010, Ringer 2012*

Recommendation

The project group is of the opinion that three-phase bone scans should not be used as a diagnostic tool on patients with suspected CRPS-I, unless another diagnosis is suspected that can be demonstrated by means of this technique.

Conclusion Inflammatory response diagnostics: bone pathology, imaging techniques X-ray

Level 3	The additional diagnostic value of the qualitative assessment of x-rays of CRPS-I patients for bone abnormalities could not be demonstrated. *C* *Plewes 1956, Kozin 1981, Holder & Mackinnon 1984, Bickerstaff 1991-1993, Sarangi 1993, Todorović-Tirnanić 1995, Rommel 1995, Moriwaki 1997, Gradl 2003, Schürmann 2007*

Recommendation

The project group is of the opinion that x-ray diagnostics for bone abnormalities in the affected limb should not be used as a diagnostic tool on patients with suspected CRPS-I, unless another diagnosis is suspected that can be demonstrated by means of this technique.

Conclusion Inflammatory response diagnostics: bone pathology, imaging techniques Bone density

Level 3	The additional diagnostic value of bone density measurements in CRPS-I patients has not been demonstrated. *C* *Sarangi 1993, Chapurlat 1996, Otake 1998, Müller 2000, Kumar 2001, Karacan 2004, Simm 2010*

Recommendation

The project group is of the opinion that bone density measurements should not be used as a diagnostic tool on patients with suspected CRPS-I, unless another diagnosis is suspected that can be demonstrated by means of this technique.

Vasomotor dysfunction

Vasomotor dysfunction diagnostics: sympathetic function testing

Conclusion Vasomotor dysfunction diagnostics: Sympathetic function testing

Level 3	The additional diagnostic value of Laser Doppler Flowmetry and Computer-Assisted Venous Occlusion Plethysmography in CRPS-I patients has not been demonstrated. *C* *Low 1983, 1994, Bej & Schwartzman 1991, Cooke 1993, Kurvers 1994, 1995a, 1995b, 1996, Schürmann 1999, 2000, Drummond 2001, Wasner 2001, Weber 2001, Birklein 2004, Eberle 2010, Schulz & Troeger 2010, Smith 2011, Terkelsen 2012, Meier 2006, Schattschneider 2006, Brunnekreef 2009*

Recommendation

The project group is of the opinion that Laser Doppler Flowmetry and Computer-Assisted Venous Occlusion Plethysmography should not be used as a diagnostic tool on patients with suspected CRPS-I, unless another diagnosis is suspected that can be demonstrated by means of these techniques.

Conclusion Vasomotor dysfunction diagnostics: Sudomotor function testing

Level 3	The additional diagnostic value of Resting Sweat Output, Thermoregulatory Sweat Test and Quantitative Sudomotor Axon Reflex Test in CRPS-I patients has not been demonstrated. However, these methods can be important in quantifying sympathetic dysregulation in the context of CRPS-I criteria. *C* *Birklein 2001, 1999, 1998, 1997, Sandroni 1998, Low 1994, Arunodaya & Taly 1995, Chelimsky 1995, Cronin 1982, Knezevic & Bajada 1985*

Recommendation

The project group is of the opinion that Resting Sweat Output, Thermoregulatory Sweat Test and Quantitative Sudomotor Axon Reflex Test should not be used as a diagnostic tool on patients with suspected CRPS-I, unless another diagnosis is suspected that can be demonstrated by means of these techniques.

Conclusion Vasomotor dysfunction diagnostics: Sympathetic skin response

Level 3	The additional value of routine sympathetic skin response measurement in CRPS-I patients has not been demonstrated. However, this method can be important in quantifying peripheral nerve injury in the context of the CRPS-I criteria. *C Knezevic & Bajada 1985, Arunodaya & Taly 1995, Figuerola 2002, Mailis 1997, Bolel 2006, Pankaj 2006, Clinchot & Lorch 1996, Rommel 1995, Chan 2000, Selçuk 2006*

Recommendation

The project group is of the opinion that sympathetic skin response measurement should not be used as a diagnostic tool on patients with suspected CRPS-I. However, this method can be used to quantify peripheral nerve injury if this is suspected.

Maladaptive neuroplasticity

Conclusion Maladaptive neuroplasticity diagnostics: functional imaging techniques

Level 3	The additional diagnostic value of sMRI, fMRI, PET scan and SPECT in CRPS-I patients has not been demonstrated. *C Shiraishi 2006, Ladarola 1995, Klega 2010, Baliki 2011, Geha 2008, Fukumoto 1999, Ushida 2010, Wu 2006, Apkarian 2001, Gravech 2002, Becerra 2009, Freund 2011, 2010, Gieteling 2008, Gustin 2010, Lebel 2008, Maihöfner 2010, 2007, 2006, 2005, Pleger 2006, 2005, Schwenkreis 2009, Vartiainen 2008*

Recommendation

The project group is of the opinion that sMRI, fMRI, PET scan and SPECT should not be used as a diagnostic tool on patients with suspected CRPS-I, unless another diagnosis is suspected that can be demonstrated by means of these techniques.

Maladaptive neuroplasticity diagnostics: neurophysiology

Conclusion: Maladaptive neuroplasticity diagnostics: neurophysiology

Level 3	Electromyography (EMG), nerve conduction study and Somatosensory Evoked Potentials (SSEP) can be of additional value in demonstrating nerve lesion and/or CNS dysfunction. The diagnostic value of EMG, nerve conduction study, SSEP, transcranial magnetic stimulation (TMS), magnetoencephalography (MEG), H-reflex and polysomnography (PSG) in CRPS-I patients has not been demonstrated. *C Drory & Korczyn 1995, Bruehl 1999, Rommel 2001, Verdugo &*

	Ochoa 2000, Van de Beek 2002, Munts 2008, Van Rijn 2009, Procacci 1979, McCabe 2003, Hyman 1991, Lenz 2011, Schwenkreis 2003, Eisenberg 2005, Krause 2005, 2006a, 2006b, Avanzino 2008, Maihofner 2003, Larbig 2006, Kirveskari 2010, Walton 2010

Other considerations:

If there is doubt concerning the diagnosis of CRPS type I or CRPS type 2, it is advisable to consult with a neurologist.

Recommendation

The project group is of the opinion that electromyography (EMG), nerve conduction study, SSEP, transcranial magnetic stimulation (TMS), magnetoencephalography (MEG), H-reflex and polysomnography (PSG) should not be used as a diagnostic tool on patients with suspected CRPS-I. However, electromyography (EMG), nerve conduction study and Somatosensory Evoked Potentials (SSEP) can be used to diagnose a nerve lesion (when CRPS-II is suspected) or central nervous system dysfunction, if these conditions are suspected.

Summarising conclusion Pathophysiology and Additional Diagnostics in CRPS-I

While a lot of research has been conducted into the three different aspects of pathophysiological mechanisms in CRPS-I (aberrant inflammatory response, vasomotor dysfunction and maladaptive neuroplasticity), CRPS-I is a purely clinical diagnosis and additional diagnostic methods should primarily be used to rule out other causes. None of the diagnostic tests that assess aberrant inflammatory response, vasomotor dysfunction and maladaptive neuroplasticity have additional diagnostic value with respect to CRPS-I. However, some of these diagnostic procedures, such as temperature measurement, oedema measurement and QST, can be used to quantify clinical symptomatology in CRPS-I. In research on inflammatory mediators, a trend has emerged that indicates that the derailed inflammation response is a local process. This conclusion must be treated with caution because studies on these inflammatory mediators cannot be compared due to the highly diverse inclusion criteria used and it is not always clear why studies chose to evaluate a particular combination of pro-inflammatory and anti-inflammatory mediators and neuropeptides in different bodily fluids. The relationship of early symptoms during the immobilisation of the fracture with a plaster cast and the chance of developing CRPS-I and the increased pressures found in the cast (using oedema as a measurement for inflammatory response) suggest that the derailed inflammatory response is caused by the immobilisation of the fracture. The resulting release of large concentrations of inflammatory mediators leads in the second place to the vasomotor dysfunction and maladaptive neuroplasticity. Peripheral and central sensitisation, together with the disinhibitory descending pathways and/or facilitating ascending pathways, play a large role in maladaptive neuroplasticity. Why neurological symptoms such as dystonia and body schema disorders occur is as yet unclear.

1.3 Epidemiology and predisposing factors

Introduction

There are varying descriptions of the incidence of CRPS-I in the literature. This is partly due to the criteria used to diagnose the condition.

CRPS-I often develops following wrist fractures, though the incidence varies widely from 1% (Dijkstra et al. 2003) to 37% (Atkins et al. 1989). Other groups of conditions that can lead to CRPS-I are other fractures (such as to the foot and lower leg), soft tissue injuries or contusions, CVA (either in isolation or in association with hemiplegia) and myocardial infarction CRPS-I can also occur as a complication following surgery (CTS, peripheral vascular surgery, hand and/or foot surgery).

CRPS-I in children needs to be considered as a separate issue.

Conclusion

Level 2	It is not likely that the use of an external fixator in patients with a severe distal radius fracture increases the likelihood of developing CRPS-I. *B Howard 1989, Roumen 1991, Diaz-Garcia 2011* *C Van Raay 1990, Gradl 2003, Suso 1993, Hegeman 2005, Grala 2008, Zollinger 2010*

Recommendation

The use of an external fixator for a distal radius fracture does not increase the chance of developing CRPS-I.

Conclusions

Level 3	Most cases of CRPS-I affect Caucasians. CRPS-I affects two to three times more women than men. *C Veldman 1993, Allen 1999, Birklein 1999, Galer & Jensen 2000, De Mos 2006, 2007, De Boer 2011, Birklein 2000, Sandroni 2003, Beerthuizen 2012*

Level 3	The incidence of CRPS-I varies depending on the original injury. The incidence following wrist fractures is relatively high. *C Atkins 1990, Daviet 2002, Mansat 2000, Myerson 1994, Sarangil 1993, Sennwald 1995, Webb 1999, Zollinger 1999, 2007, De Mos 2007, Arora 2011*

Level 2	When a distal radius fracture is immobilised with a plaster cast, early symptoms in plaster can be seen as a predictive factor for the occurrence of CRPS-I. *A2 Zollinger 1999, 2007* *C Field 1994*

Level 3	There is evidence that the use of ACE inhibitors is associated with the occurrence of CRPS-I. *C De Mos 2009*

Level 3	There is evidence that the overall risk for family members of a CRPS-I patient of developing CRPS-I themselves is not increased. *C De Rooij 2009, Mos 2009a*

Level 3	It is unclear as to what extent genetics are a risk factor for the occurrence of CRPS-I with respect to the HLA immune system. *C Mailis & Wade 1994, van de Beek 2000, 2003, Kemler 1999, De Rooij 2009, Gosso, 2009b*

Level 3	It is unclear as to what extent genetics are a risk factor for the occurrence of CRPS-I with respect to genes for neuropeptides (NEP, TNF□, ACE, CGRP, NPY, TGFb, TAC) and interleukins (IL), which are involved in the inflammatory process. *C Vaneker 2002, Herlyn 2010, Birklein 2001, Huehne 2010*

Level 3	There is very limited evidence that other inflammatory autoimmune processes can play a role in the pathophysiology of CRPS-I. *C Ostrov 1993, Neustadt 1994, Tsutsumi 1999, Das & Puvanendran 1999, Bodur 1999, Bordin 2006, Moroz 2001, Wysenbeek 1981, Blaes 2004, 2007, Goebel 2005, Kohr 2009, 2011, Beerthuizen 2012*

Level 3	There is insufficient evidence that viral and bacterial infections play a role in the pathophysiology of CRPS-I. *C Muneshige 2003, Goebel 2005b, Bruckbauer 1997, Sibanc & Lesnicar 2002, Neumann 1989, Genc 2005, Jastaniah 2003,*

	Kwun 2012, van de Vusse 2001, Gross 2007

Level 3	There is evidence that migraine, asthma and osteoporosis are associated with CRPS-I, with the common factor being neurogenic inflammation, nuclear factor kappa B and mast cells. The relationship of CRPS-I with other forms of comorbidity is based exclusively on case reports. *C Ray & Singhi 2011, Lehmann 1996, Merello 1991, Karacan 2004, Huygen 2004, Hettne 2007, , Barnes 2006, Peterlin 2010, de Mos 2008, 2009, Toda 2006, Faillace & de Carvalho 2012, Roig-Vilaseca 2000, Neri 1997, Bouvier 1997 Karras 1993, Ku 1996, Mekhail & Kapural 2000, West 2001, Kennedy 2010, de Carvalho 1999, Shibata 2003, Stoler & Oaklander 2006*

Level 3	There is evidence that in women with CRPS-I hormonal factors play a role in the pathophysiology with respect to the severity of the symptomatology of CRPS-I. *C Straub 2007, Chakrabarti & Davidge 2013, Park & Ahn 2012, de Mos 2008, 2009*

CHAPTER 2: MEDICINAL AND INVASIVE TREATMENT

2.1 Medicinal treatment

2.1.1 Analgesics in CRPS-I

General introduction

Although analgesics are often used in clinical practice when treating patients with CRPS-I, and their use is described in various treatment protocols and guidelines (Stanton-Hicks et al. 1998; Raja & Grabow 2002; Kirkpatrick 2003; Stanton-Hicks et al. 2002), the scientific support for their administration to patients with CRPS-I is very limited.

Administration of standard analgesics appears to be based on experience in other fields. The administration sequence in Dutch practices is based on the WHO ladder (see Appendix 2) (Perez et al. 2003). In addition to oral administration, analgesics are also administered intravenously (Conelly et al. 1995) and by means of peripheral blockade techniques (Azad et al. 2000; Price et al. 1998) .

Paracetamol

Conclusion

Level 4	There is no evidence that paracetamol is effective in treating pain in CRPS-I patients. *D Opinion of project group members*

Other considerations

Administration of paracetamol in pain control is generally accepted, partly thanks to the low threshold of administration and the minor side-effect profile.

NSAIDs

Conclusion

Level 3	There is insufficient evidence of the degree of pain control achieved by NSAIDs in CRPS-I patients. *C Rico 1987*

Other considerations

NSAIDs are often associated with side effects. These involve, among other things, the gastrointestinal system, renal function, blood clotting and blood pressure, the central nervous system and cardiac function (College voor Zorgverzekeringen, 2012). Although the new generation of COX2 inhibitors is thought to cause milder gastrointestinal side effects, these drugs are associated with a higher incidence of cardiac side effects (Bombardier et al. 2000).

Conflicting data has been published with regard to the use of NSAIDs in patients with neuropathic pain (Namaka et al. 2004).

Opioids

Conclusions

Level 2	There is insufficient evidence of whether pain control is achieved by oral opioids in CRPS-I patients. *B Gustin 2010, Harke 2001*

Level 3	There is insufficient evidence of whether continuous infusion of morphine to the axillary plexus is an effective method of pain control for CRPS-I patients. *C Azad 2000*

Other considerations

Many side effects have been described for the various weak and strong-acting opioids (College voor Zorgverzekeringen 2012).

Although we have little specific information on weak and strong-acting opioids in patients with CRPS-I, systematic reviews on their use for neuropathic pain have found tramadol to be effective (Duhmke et al. 2004). Positive short-term effects have also been reported for strong-acting opioids administered for neuropathic and muscular-skeletal pain (Kalso et al. 2004; Eisenberg et al. 2006). Given the long-term effects of opioids, as well as problems with opioid-induced hyperalgesia, tolerance and addiction, one should exercise restraint with respect to prescribing opioids for CRPS-I, especially during the chronic phase (Kalso et al. 2004; Manchikanti et al. 2010, Crofford et al. 2010).

Recommendation

The project group is of the opinion that pain medication should be administered in accordance with the WHO pain ladder up to and including step 2. Strong opioids should not be administered to this patient group.

Anaesthetics

N-methyl-D-aspartic acid (NMDA) receptor antagonists can counteract the effects of central sensitisation in pain syndromes. In the group of the NMDA antagonists, the effect of ketamine on CRPS-I was the primary focus.

Conclusions

	It is likely that the intravenous administration of a sub-anaesthetic dose of ketamine has a temporary pain-lowering effect in CRPS-I patients.

Level 2	*A2 Sigtermans 2009* *B Schwartzman 2009*

Level 2	It is likely that the topical administration of ketamine can reduce pain in CRPS-I patients. *A2 Finch 2009*

Level 3	There is evidence that the addition of oral memantine to morphine can reduce pain in CRPS-I patients. *B Gustin 2010*

Other considerations

Ketamine must only be considered in the case of severe, therapy-resistant pain: ≥ 7 on the numeric rating scale (NRS). The effect on the pain is limited in duration. Ketamine can cause psychotomimetic effects and nausea. The simultaneous administration of midazolam and ondansetron must be considered. Administering ketamine in anaesthetic doses is not advised, as there is no convincing evidence for this and it requires an intensive care setting.

The effect of oral memantine has only been studied in combination with other interventions. The side-effect profile of memantine is described as mild.

Recommendations

- For CRPS-I with severe therapy-resistant pain (NRS ≥ 7), the administration of an intravenous sub-anaesthetic dose of ketamine can be considered. The patient must be told prior to administration that the effect is temporary. Ketamine in an intravenous sub-anaesthetic dose should be administered in a clinical setting.
- Further research is needed to determine the right dose and duration for ketamine administration. When administering ketamine intravenously, liver function should be checked regularly. The ketamine should be discontinued at the first sign of liver function disorders.
- The use of topical ketamine in the treatment of CRPS-I must only be considered in the context of a trial.
- The use of oral memantine in the treatment of CRPS-I can be considered in the context of a trial.

2.1.3 Co-analgesics

Gabapentin

General introduction

Gabapentin is an anticonvulsant that is an analogue of the neurotransmitter GABA. It does not bind to GABA receptors and is not converted into a GABA agonist. Though the exact mechanism of action is unclear, it reduces the neuronal sensitivity by binding to an auxiliary sub-unit (α_2-δ) of voltage-gated calcium channels on central neurons. It also reduces the release of various neurotransmitters, including glutamate, norepinephrine and substance P.

Conclusion

Level 2	It is likely that gabapentin reduces sensory abnormalities with respect to hyperaesthesia and allodynia. The longer-term effect of gabapentin in patients with CRPS-I is not known. *A2 Van de Vusse 2004*

Other considerations

Dizziness, sleepiness and fatigue occurred significantly more often in patients taking gabapentin than in patients taking placebo.

Recommendation

Administration of gabapentin should be considered for patients with CRPS-I.

Other anticonvulsants

Scientific support

In addition to gabapentin, there are three other anticonvulsants that can be used to treat neuropathic pain. Carbamazepine is used mainly to combat trigeminal neuralgia. There are no known studies that involve testing carbamazepine in patients with CRPS-I.

The other frequently used anticonvulsant that is used for neuropathic pain is phenytoin. This medication has been tested most often in cases of diabetic polyneuropathy (Saudek et al. 1977; Jensen 2002).

The more recently introduced pregabalin is a molecule with a similar mechanism of action to gabapentin. The efficacy of pregabalin has been demonstrated with respect to diabetic polyneuropathy and postherpetic neuralgia, but no trials have been conducted for CRPS-I.

Conclusion

Level 4	There is no evidence that anticonvulsants such as carbamazepine, pregabalin and phenytoin are effective in reducing pain in CRPS-I patients. *D Opinion of project group members*

Other considerations

Strictly speaking, CRPS-I does not satisfy the current definition of neuropathic pain (Treede et al. 2008). By definition, (some of the) pain in CRPS-II is neuropathic in nature. In view of experience from the aforementioned trials, the use of anticonvulsants to treat neuropathic pain in CRPS-II should be considered.

Recommendation

A trial course of carbamazepine, pregabalin or other anticonvulsants can be considered for CRPS-I patients in whom sensitisation symptoms are present.

Antidepressants

Scientific support

Tricyclic antidepressants affect noradrenergic neurotransmission and are widely used in patients suffering from constant neuropathic pain. They are currently regarded as the best drugs to treat neuropathic pain. It is thought that tricyclic antidepressants act against neuropathic pain by a variety of mechanisms. The mechanism of action potentiates serotonergic and noradrenergic descending inhibiting pathways, which as a result reduce posterior horn hyperactivity (Jensen 2002).

Conclusion

Level 4	There is no evidence that antidepressants are effective in reducing pain in CRPS-I patients. *D Opinion of project group members*

Other considerations

Strictly speaking, CRPS-I does not satisfy the current definition of neuropathic pain (Treede et al. 2008). By definition, (some of the) pain in CRPS-II is neuropathic in nature (see distinction on page 18). In view of experience from the aforementioned trials, the use of antidepressants to treat neuropathic pain in CRPS-II should be considered.

Recommendation

A trial course of amitriptyline or nortriptyline can be considered for CRPS-I patients in whom sensitisation symptoms are present.

2.1.4 Capsaicin

Capsaicin (8-methyl-N-vanillyl-6-noneamide) is obtained from chilli peppers. In recent years, there has been an increase of interest in this substance as a treatment for neuropathic pain. The mechanism of action is unclear, but it is assumed that capsaicin may have a selective effect on the nociceptors bound to the C fibres.

Conclusion

Level 3	There is insufficient evidence that capsaicin is effective in CRPS-I patients. *C Robbins 1998*

Recommendation

There is as of yet no place for capsaicin in the treatment of CRPS-I.

Free radical scavengers

Scientific support

The use of oxygen radical inhibitors, or free radical scavengers, to treat CRPS-I has primarily been evaluated scientifically in the Netherlands.

Conclusions

Level 2	DMSO (dimethyl sulphoxide) cream (50%) reduces the symptoms in CRPS-I patients. *A2 Perez 2003* *B Geertzen 1994, Goris 1987, Zuurmond 1996*

Level 2	There is evidence that 600 mg of N-acetylcysteine administered three times a day reduces the symptoms of CRPS-I. *A2 Perez 2003*

Level 3	There is evidence that 50% DMSO (dimethyl sulphoxide) cream is more effective on primary warm CRPS-I while N-acetylcysteine is more effective on primary cold CRPS-I. *C Perez 2003*

Level 2	It is likely that mannitol is not effective in the treatment of CRPS-I. *A2 Perez 2008* *C Tan 2010, Zyluk 2008*

Other considerations

In general, DMSO generates lower (direct and indirect) costs than N-acetylcysteine. However, sub-group analysis indicates that N-acetylcysteine generates lower costs and is more effective for patients with a cold form of CRPS-I. DMSO generates lower costs and is more effective for warm forms of CRPS-I (Van Dieten et al. 2003).

Recommendations

- The application of 50% DMSO (dimethyl sulphoxide) cream 5 times a day (applied locally to the skin) for three months is recommended for patients with prominent inflammation symptoms who have had CRPS-I for less than a year.

- A one-month trial course of DMSO cream applied 5 times a day locally can be considered for patients who have had CRPS-I for more than a year. If the results are favourable, the treatment can be continued for three months.
- A three-month course of 600 mg of N-acetylcysteine 3 times a day can be considered for patients with CRPS-I who do not have prominent inflammation symptoms.
- The DMSO should be left on the skin for 10 minutes before removing it.
- Mannitol is not recommended as a treatment for CRPS-I.

Muscle relaxants

Oral administration

Scientific support

Motor symptoms are a relatively underexplored category of the clinical spectrum of CRPS-I. They can include paresis, dystonia, myoclonias and/or tremor. Some literature refers to spasms, though it is not always clear whether this term also covers intermittent dystonia or myoclonias.

No controlled drug trials have been carried out on orally administered muscle relaxants to treat the aforementioned motor symptoms.

Conclusion

Level 3	There is insufficient evidence of the efficacy of muscle relaxants in treating movement disorders associated with CRPS-I, such as dystonia and muscle spasms. *C* *Bhatia 1993, Van Hilten 2001, Jankovic 1988, Marsden 1984, Schwartzman 1990*

Other considerations

Although anticholinergics and carbamazepine are also used in treating dystonia in CRPS-I patients, these forms of medication do not strictly speaking belong to the muscle relaxant group. No controlled studies have been carried out into the treatment of dystonia in patients with CRPS-I Two of the aforementioned descriptive studies report that anticholinergics have never produced (lasting) effects (Bathia et al. 1993; Van Hilten et al. 2001).

Prescribers using diazepam or clonazepam must be alert to the possible risk of addiction.

Recommendation

In the case of dystonia or myoclonias in CRPS-I patients, the following treatment can be considered:
- oral baclofen according to the standard dose-increase pattern;
- diazepam or clonazepam, titrated slowly in the light of the effect and side-effects.

Intravenous administration

Scientific support

Conclusion

Level 3	There is evidence that intravenous magnesium leads to an improvement of pain, restriction and quality of life in CRPS-I patients. *B Collins 2009*

Recommendation

The intravenous administration of magnesium salts can be considered in patients who have had CRPS-I for less than six months. This should be conducted in the context of a trial.

Botulin toxin

Conclusion

Level 3	There is insufficient evidence that botulin toxin A is effective in treating dystonia or allodynia in CRPS-I patients. *C Safarpour 2010, Cordivari 2001, Van Hilten 2001, Jankovic 1985*

Recommendation

The project group is of the opinion that botulin toxin has no place in the treatment of CRPS-I-patients with dystonia or allodynia.

Intrathecal administration

Baclofen

Conclusion

Level 2	While it is likely that intrathecal baclofen (ITB) has a positive effect on dystonia in CRPS-I patients, it is often accompanied by side effects. *A2 Van der Plas 2011* *B Van Rijn 2009* *C Van Hilten 2000, Zuniga 2002*

Recommendation

Intrathecal baclofen (ITB) can be considered for CRPS-I patients who have more than one affected limb if dystonia is prominent and conventional therapy has proven to be ineffective. This treatment should be conducted in the context of a trial.

Glycine

Conclusion

Level 2	It is likely that intrathecal glycine is not effective for treating pain or dystonia in CRPS-I patients. *A2 Munts 2009*

Recommendation

There is no place for intrathecal glycine in the treatment of CRPS-I patients with dystonia.

Treatment with immunomodulators

Anti-inflammatory medication inhibits the inflammatory response, while immunomodulators reduce the inflammation by means of mediators, such as cytokines.

Corticosteroids

Corticosteroids are anti-inflammatory. Interaction between the nervous system, the hypothalamus-pituitary-adrenal axis and components of the immune system play an important role in the regulation of inflammation and immunity.

Conclusion

Level 3	Oral corticosteroids may have an effect on CRPS-I. Little is known as to the duration and dosage. *B Christensen 1982*

Other considerations

Some studies of limited quality indicate that corticosteroids have a beneficial effect. In light of the side effects, the project group recommends restraint with respect to treating CRPS-I patients with corticosteroids.

Recommendation

One should exercise restraint in treating CRPS-I patients with corticosteroids.

Immunoglobulins

The primary mechanism by which immunoglobulins produce an anti-inflammatory effect is the modulation of the production of cytokines and cytokine antagonists.

Conclusion

Level 3	There is evidence that immunoglobulins reduce pain in patients with CRPS-I. *B Goebel 2010*

Recommendation

The use of immunoglobulins can be considered in the context of a trial.

Other immunomodulators

The use of other immunomodulators, such as TNF-α inhibitors and thalidomide, is only described in case reports or open-label trials (Dirckx et al. 2012), in which they are predominantly found to have a positive effect on the CRPS-I symptoms. However, this will first have to be confirmed in RCTs before any statement can be made about their use.

Other considerations regarding the use of immunomodulators

It is difficult to determine the appropriate period of use for immunomodulators. In fact, it should be determined on a patient-by-patient basis whether there is still inflammation. The only method currently available for this is by determining the cytokine level in blister fluid.

Recommendation

The use of other immunomodulators in the treatment of CRPS-I must only be considered in the context of a trial.

Treatment of CRPS-I osteoclast inhibitors

Bisphosphonates

Bisphosphonates inhibit osteoclasts in bone marrow and are used to treat bone conditions, like Paget's disease, and osteoporosis. However, bisphosphonates also have an 'immunomodulating' effect, by, among other things, influencing the production of pro-inflammatory and anti-inflammatory cytokines.

Conclusion

Level 1	The use of bisphosphonates reduces pain in CRPS-I patients. *A2 Adami 1997, Varenna 2000, Robinson 2004, Manicourt 2004*

Other considerations

While most studies have been conducted with intravenous bisphosphonates, oral bisphosphonates also seem to have an effect, despite the reduced resorption from the stomach. Given the easier use, oral administration should be considered.

Recommendation

The use of bisphosphonates should ideally only take place in the context of a trial, as it is unclear what the specific medication, appropriate dosage, frequency and duration of administration should be.

Calcitonin (subcutaneous and intranasal administration)

Calcitonin, a hormone produced by the C cells in the thyroid gland, inhibits osteoclasts in the bone, thereby reducing bone resorption. It also has an analgesic effect through the release of β-endorphins, and it increases calcium secretion via the kidneys.

Conclusion

Level 1	The evidence for the efficacy of calcitonin (both intranasal and subcutaneous) in treating CRPS-I is conflicting. *A2 Van den Berg 2002, Forouzanfar 2002, Kingery 1999, Perez 2001*

Recommendation

The use of calcitonin in the treatment of CRPS-I patients is not recommended.

Vasodilators

Calcium-channel blockers

The reasoning behind the use of calcium-channel blockers to treat CRPS-I lies in the theory that these drugs should improve peripheral blood circulation in cold CRPS-I (Van der Laan et al. 1997).

Conclusion

Level 3	There is evidence that calcium-channel blockers have some effect in the acute phase of CRPS-I. While they improve blood circulation, they also cause side effects, such as a drop in blood pressure and headache. *C Muizelaar 1997, Prough 1985*

Recommendation

A calcium-channel blocker can be prescribed for patients with a non-inflammatory form of CRPS-I. The effect must be evaluated a week after administration.

Nitric oxide donors (NO donors)

Isosorbide dinitrate (ISDN) splits nitrates. When split from the nitric oxide molecule, nitrates have a relaxing effect on smooth muscle tissue.

Conclusion

Level 3	There is no evidence that the use of isosorbide dinitrate improves symptoms in CRPS-I patients. *B Groeneweg 2009*

Recommendation

The use of isosorbide dinitrate in the treatment of CRPS-I should only be considered in the context of a trial.

Phosphodiesterase type 5 inhibitors (PDE5 inhibitors)

Tadalafil is a selective, reversible inhibitor of the enzyme cGMP-specific phosphodiesterase type 5. This enzyme is responsible for the breakdown of cyclic guanosine monophosphate (cGMP). In this way, tadalafil increases the cGMP concentration, which leads to relaxation of smooth muscle cells.

Conclusion

Level 3	There is evidence that tadalafil has no effect on the circulation, but does reduce pain in patients with cold CRPS-I. *B Groeneweg 2008*

Recommendation

The use of tadalafil can only be considered in the context of a trial for patients with cold CRPS-I.

Invasive and surgical treatment

Sympathetic blockade

Introduction

It is not yet clear to what extent the (ortho)sympathetic system (hereinafter referred to as the sympathetic system) is involved in the pathophysiology of CRPS-I. Hyperactivity of the sympathetic system is suspected in some cases. This hyperactivity ought to be associated with an elevated concentration of adrenaline or noradrenaline in the venous outflow of the

affected limb, but this phenomenon has never been observed in practice (Drummond et al. 1991). Lower levels of adrenaline and noradrenaline have been measured in the limbs, suggesting that the sympathetic receptors in the affected limbs might be hypersensitive (Kurvers et al. 1994).

The role of the sympathetic nervous system in CRPS-I seems unclear at the moment. Various studies have been carried out into the effects of intravenous sympathetic blockade and percutaneous anaesthesiological sympathetic blockade of the upper and lower limbs; these procedures were found to have no effect, or an unclear effect at most.

Intravenous regional sympathetic blockade

Conclusion

Level 1	Intravenous regional sympathetic blockade produces no added value (pain reduction) compared to placebo in CRPS-I patients. *A2 Kingery 1999, Forouzanfar 2002, Perez 2001*

Recommendation

Intravenous sympathetic blockade has no place in the treatment of patients with CRPS-I.

Other intravenous regional treatments

Conclusion

Level 2	There is evidence that regional ketanserin administered by intravenous injection reduces pain in CRPS-I patients. Reserpine, droperidol and atropine do not reduce pain in CRPS-I patients. *A2 Kingery 1999* *B Hanna & Peat 1989, Hord 1992*

Other considerations

Due to the mediocre quality and small size of the studies, the positive findings in relation to the effects of ketanserin and bretylium cannot be confirmed. Bretylium is not authorised in the Netherlands. The intravenous regional blockade technique involves inducing a period of ischaemia in the affected limb by means of a tourniquet. Animal studies have shown that ischaemia has the theoretical disadvantage of exacerbating the inflammatory cascade of an active CRPS-I (De Mos et al. 2009).

Recommendation

The regional administration of medication by intravenous injection is not recommended as a treatment for CRPS-I. The use of ketanserin could possibly be considered, but only in the context of a trial.

Percutaneous sympathetic blockade

Scientific support

Sympathetic nerve blockade is a traditional treatment for CRPS-I patients. For the upper limbs, this could be a blockade of the stellate ganglion or the thoracic sympathetic nerves, and for the lower limbs it could be a blockade of the lumbar sympathetic nerves, usually carried out at L2 and L3. The literature contains few studies into the effect of these blockades.

Conclusion

Level 2	Routine administration of percutaneous sympathetic blockade in patients with CRPS-I is not useful. *A2* *Cepeda 2002* *B* *Bonelli 1983, Dellemijn 1994, Price 1989* *C* *Van Eijs 2012, Forouzanfar 2000, Glynn & Casale 1993, Rocco 1995, Wang 1985*

Recommendation

The use of percutaneous sympathetic blockade is not recommended in patients with CRPS-I. This applies in particular to the blockade of the stellate ganglion.

Spinal cord stimulation in patients with CRPS-I

Spinal cord stimulation is a treatment in which an electrode is placed in the epidural space behind the spinal cord at the level of the nerve roots which innervate the painful area. The electrode produces an electrical current that causes tingling, a sensation that suppresses the pain. The precise mechanism of action is not known. The treatment is uncomfortable and very expensive, and is thus reserved for candidates who meet strict inclusion criteria, in whom psychopathology has been ruled out, in whom trial stimulation has produced clear pain relief and where it has been established that the entire painful region can be covered by tingling (Simpson 1994).

Conclusion

Level 3	There is evidence that spinal cord stimulation administered to CRPS-I patients who are carefully selected and undergo successful trial stimulation causes long-term pain reduction and improves quality of life, but does not improve function. *B* *Kemler 2000* *C* *Bennett 1999, Calvillo 1999, Kemler 1999, 2004, 2008, 2010*

Other considerations

All the studies relate to carefully selected, patients with chronic CRPS-I (6 months or longer after the initial moment) who have been treated with all possible therapies without success; there is no scientific evidence for spinal cord stimulation being effective in acute CRPS-I (Van Eijs et al. 2012). A cost-effectiveness analysis has found that treatment of chronic CRPS-I with spinal cord stimulation is cheaper than standard therapy (Kemler & Furnee 2002). If the pulse generator for the spinal cord stimulation is expected to have a short life span due to intensive use by the patient, a rechargeable pulse generator should be considered (Kemler et al. 2010). Though life-threatening complications associated with spinal cord stimulation are rare, complications requiring further surgery do occur in 25-50% of patients (Turner et al. 1995).

Recommendation

Pain control with spinal cord stimulation can be considered for carefully selected patients with chronic CRPS-I who have not responded to other treatments. Spinal cord stimulation is probably not useful if allodynia is present in the affected limb. If there are no other options, a stimulator is only to be implanted following a successful trial stimulation of at least 2 weeks. If there is doubt about the beneficial effect of the trial stimulation, the treatment should not be continued.

Surgical sympathectomy in patients with CRPS-I

Conclusion

Level 3	There is evidence that surgical sympathectomy can reduce pain in patients with CRPS-I. *B Manjunath 2008* *C AbuRahma 1994, Bandyk 2002, Bosco 2003, Mailis 2003, Schwartzman 1997, Singh 2003*

Other considerations

Surgical sympathectomy is carried out on the basis of poor quality evidence, studies without control groups and personal experience. Though it would appear logical (and has been suggested) that surgical sympathectomy is indicated primarily for patients with confirmed 'sympathetic-dependent pain' (Wang et al. 1985), other authors take the view that the treatment results are not correlated to this (Singh et al. 2003). Eighteen percent of patients undergoing sympathectomy for neuropathic pain experience compensatory hyperhidrosis and 25% experience neuropathic complications (Furlan et al. 2000).

Recommendation

Great restraint is called for when considering surgical sympathectomy for pain control in CRPS-I. The procedure should only be conducted in the context of a trial in order to ascertain the efficacy and potential risks.

Amputation in patients with CRPS-I

Amputation aims to bring about functional recovery and improve the quality of life. It can save lives (severe, untreatable inflammation with the threat of sepsis or in the case of oncological processes). CRPS-I patients who are in despair sometimes request amputation as a last resort.

Conclusion

Level 3	There is insufficient evidence that amputation makes a positive contribution to the treatment of CRPS-I. *C Dielissen 1995, Stam & Van der Rijst 1994, Bodde 2011, Krans 2012*

Other considerations

Amputation of the affected limb cannot always be prevented in cases of potentially life-threatening, untreatable or recurrent infections. It can therefore be considered in specific cases.

Recommendation

Amputation for CRPS-I patients can be considered in order to improve quality of life in the case of severe, recurrent infections and severe functional disorders. It would have to be performed at a specialist centre.

PARAMEDICAL (PHYSIOTHERAPY AND OCCUPATIONAL THERAPY) AND PSYCHOLOGICAL TREATMENT FOR CRPS-I PATIENTS

Introduction

Patients with CRPS-I experience a reduction in the amount of strain the affected limb can bear and also suffer various disorders, including pain. The limb often reacts excessively to the slightest effort. The patient often experiences an extreme increase in pain following the slightest activity.

Patients generally react to this increase in pain in one of two ways:

1. They may decide to immobilise the affected limb, for instance by resting the leg on a cushion or placing the arm in a sling, and keeping it as still as possible. If the limb nonetheless has to be moved, the pain is so intense that the desire to immobilise it is reinforced.

2. The other reaction is for the patient to exercise the limb (much) more than usual, to 'get it fit'. Here again, an excessive pain reaction occurs, but the patient interprets this as a sign that the limb is not fit enough and continues intensive exercise.

Properly adjusted movement and learning to reintegrate the affected limb into everyday activity lead to recovery in CRPS-I patients (Watson & Carlson 1987; Oerlemans et al. 1999; Oerlemans et al. 2000; Ek et al. 2009; van de Meent et al. 2011). A more pain-contingent treatment seems to be indicated for patients who have recently developed CRPS-I, while a time-contingent approach seems more important for longer-established cases of CRPS-I (≥ 6 months after the initial moment), i.e. the chronic pain stage.

The project group is of the opinion that properly adjusted movement is the key to recovery in CRPS-I. Absolute immobilisation is therefore not indicated.

Patients should be referred for multidisciplinary treatment, including psychological treatment, if they are suffering from:

- long-standing CRPS-I with signs of chronic pain behaviour;
- stagnating functional recovery despite adequate somatic treatment;
- indications of psychosocial problems;
- inability to adequately cope with the condition.

If multidisciplinary treatment is given, a case manager is needed to coordinate matters between the various practitioners and the patient.

Conclusions

Level 2	It is likely that pain-contingent treatment (physiotherapy and graded motor imagery) is effective in reducing symptoms caused by upper-limb CRPS-I. *B Oerlemans 1999, 2000, Mosely 2004, 2005,* *C McGabe 2003*

Level 3	There is evidence that occupational treatment has a positive effect on functional disorders, and it is likely that occupational therapy has a positive effect on the activity level of patients with upper-limb CRPS-I. *B Oerlemans 1999, 2000* *D Cup 1999*

Level 3	There is evidence that mirror therapy is effective in reducing symptoms caused by upper-limb CRPS-I. *C McGabe 2003*

Level 3	There is evidence that a time-contingent treatment produces a reduction of symptoms, in both upper-limb and lower-limb CRPS-I. *C Van de Meent 2011, Ek 2009, De Jong 2005, Watson & Carlson 1987*

Level 3	There is evidence that paramedical treatment (exercise therapy, pain exposure physical therapy, graded exposure, stress loading, pain-contingent treatment) is also worthwhile for chronic CRPS-I. *C Ek 2009,* Moseley 2004, 2005, McCabe 2003, *De Jong 2005*

Level 3	There is no evidence that manual lymphatic drainage is effective in the treatment of CRPS-I. *C Uher 2000, Duman 2009*

Level 3	There is evidence that TENS can have a pain-reducing effect in the treatment of CRPS-I. *C Robaina 1989*

Level 3	There is evidence that electromagnetic treatment reduces pain in patients with CRPS-I.

	C Durmus 2004

Level 3	There is evidence that autogenic training is helpful in lowering hand temperature. *C Fialka 1996*

Level 3	There is evidence that a multidisciplinary rehabilitation programme has a positive effect on hand function. *C Singh 2004*

Other considerations

As the severity of symptoms can vary, treatment must be adjusted to the individual. Exercise and advice can be sufficient for mild symptoms. Multidisciplinary treatment is desirable for severe symptoms and should be started as early as possible (Oerlemans et al. 1999; Oerlemans et al. 2000; Vacariu 2002).

Recommendation

It is recommended that patients with CRPS-I receive paramedical treatment (physiotherapy, occupational therapy, hand therapy) as early as possible, beginning with pain-contingent treatment and transitioning to time-contingent treatment. Patients with chronic CRPS-I who have not received adequate paramedical treatment in the past should also be given such treatment.

Further research is necessary to analyse which methods of treatment (pain-contingent or time-contingent) have the most effect during each phase of CRPS-I.

The project group recommends that patients with upper-limb CRPS-I be referred to a physiotherapist and/or occupational therapist.

Influence of psychological factors on the onset and course of CRPS-I

Introduction

As no clear objective somatic cause has so far been found, it has been suggested that CRPS-I might be caused or worsened and maintained by non-somatic factors (Geertzen et al. 1994; Van Houdenhoven et al. 1992). In clinical practice, the feeling that something is “not quite right” with these patients is quite prevalent. A certain premorbid psychological process is thought to be involved. However, it is not clear whether the cause and/or course of the symptoms is determined by mental factors, or whether the mental factors should be seen as the consequence of CRPS-I, and in particular the pain symptoms. There are no known scientific publications about psychological treatments in adults.

Psychological dysfunction in general

Conclusion

Level 2	There is no specific profile within the SCL-90 (Symptom Check List-90) that differentiates patients with CRPS-I from healthy control subjects or other patients with pain. *B Beerthuizen 2011, Van der Laan 1999, Field & Gardner 1997, Ciccone 1997, Bruehl 1996, DeGood 1993*

Other considerations

The SCL-90 is a psychological questionnaire that is not sensitive enough for CRPS-I patients, but it does give an impression of the general level of psychological and physical function.

Life events and coping

Conclusion

Level 2	The role of life events in the development of CRPS-I is not clear. There seems to be no difference in coping strategies between patients with CRPS-I and a group that recovered from CRPS-I. *B Monti 1998, Geertzen 1994, Rose 1992*

Depression

Conclusion

Level 2	There is insufficient evidence that depression plays a role in the onset and/or maintenance of CRPS-I. *B Beerthuizen 2011, Puchalski 2005, Bruehl 2003, Daviet 2002, Ciccone 1997, DeGood 1993, Geertzen 1994, Monti 1998, Feldman 1999*

Other considerations

If treatment is indicated for patients with CRPS-I and depression, preference should be given to amitriptyline (no selective serotonin reuptake inhibitors) in combination with psychological treatment. As severe pain causes emotional suffering, it would be unusual if a CRPS-I patient were to achieve low scores on scales measuring depression and anxiety.

Anxiety

Conclusion

Level 2	No link has been found between anxiety and maintenance of CRPS-I symptoms. *B Van der Laan 1999, Feldman 1999, Ciccone 1997, Geertzen 1994, DeGood 1993*

Other considerations

More attention has been paid to the role of movement anxiety in recent years. The patient is excessively worried that certain activities might lead to tissue damage. We now know that patients with other chronic pain syndromes experience an increase in impairment and pain if they suffer from this form of anxiety (De Jong et al. 2005). The project group is of the opinion that practitioners must be alert to the presence of movement anxiety. This can be done by asking what activities the patient avoids even though he or she should be able to carry them out reasonably well, or by using the TAMPA kinesiophobia scale (TSK) (De Jong et al. 2005; Peters et al. 2004). Effective treatment of movement anxiety leads to a reduction in anxiety, pain and restrictions for patients with CRPS-I and other conditions (De Jong et al. 2005).

Personality

Conclusion

Level 2	There is no indication that CRPS-I patients have a specific personality profile. *B Monti 1998, Geertzen 1994, Zucchini 1989, Subbarao & Stillwell 1981*

Other considerations

Although the questionnaires used do not describe a specific profile for patients with CRPS-I, it would be quite reasonable to carry out further investigation before starting psychological treatment. The SCL-90 is a useful instrument for giving an impression of the general level of mental and physical function. This questionnaire can also serve as an adequate evaluation instrument. It would also appear sensible to make some statement as to the degree of movement anxiety, using the TSK for example (Peters et al. 2004). In view of the (psychometric) match between patients with CRPS-I and patients with a different chronic pain syndrome, cognitive behavioural therapy could be an appropriate form of treatment focusing on the consequences of the condition.

In short, a number of questions can be put to the psychologist:

1. Are there any psychological and/or psychosocial factors that are maintaining and/or aggravating the syndrome, and if so what are they?
2. Is psychological treatment indicated? If so, by whom should it be provided? Is the patient motivated, do you think that the psychological factors that have been determined are susceptible to change?
3. Is there any psychological contraindication against medical and/or psychological treatment? Psychological treatment is contraindicated for patients who are not thought to be capable of self-reflection or behavioural change, or who are not motivated. Another factor that may lead to treatment being withheld is if the patient is involved in legal proceedings.

The psychologist is not concerned with whether the symptoms are caused by psychological factors, but looks at the consequences of the syndrome.

Recommendation

The project group recommends that CRPS-I patients consult a healthcare psychologist or clinical psychologist if the practitioner observes a discrepancy between symptoms that can be clinically described and the patient's (pain-related) behaviour, if stagnation in (somatic) treatment occurs, if the burden of suffering in response to the symptoms is great, or if the patient requests this.

OTHER TREATMENT METHODS

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive technique in which electromagnetic induction is used to stimulate superficial regions of the brain in order to change cortical excitation and inhibition.

Conclusion

Level 3	There is evidence that repetitive transcranial magnetic stimulation reduces pain in CRPS-I patients. *B Picarelli 2010*

Other considerations
One patient experienced a generalised insult, probably induced by rTMS. The effect is also limited to the duration of the treatment and varies greatly from patient to patient. This treatment is still in an experimental stage.

Recommendation

The use of repetitive transcranial magnetic stimulation in the treatment of CRPS-I patients can be considered in the context of a trial.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy involves having the patient inhale 100% oxygen in a high-pressure chamber so as to increase body oxygenation and thereby improve tissue oxygenation.

Conclusion

Level 3	There is evidence that hyperbaric oxygen therapy reduces pain and oedema and increases wrist flexibility in CRPS-I patients. *B Kiralp 2004*

Other considerations
The study was conducted on patients who had had the condition for a very short period of time (“approximately” 1.5 months) and provides little information about the nature of the patients or study design. Hyperbaric oxygen therapy poses demands on the organisation of care.

Recommendation

The use of hyperbaric oxygen therapy to treat CRPS-I patients can be considered in the context of a trial.

Shockwave therapy

Scientific support

Shockwave therapy involves administering audible sonic pulses using an electromagnetic generator.

Conclusion

Level 3	There is evidence that shockwave therapy reduces pain and leads to functional recovery in CRPS-I patients. *C Notarnicola 2010*

Other considerations

The mechanism of action (audible sonic pulses that cause a shockwave) is unclear. Further research into the efficacy is needed to demonstrate the value of this therapy for CRPS-I.

Recommendation

The use of shockwave therapy to treat CRPS-I patients is not recommended.

Occlusional splints

Occlusional splints are mouthguards that are used to reduce symptoms associated with jaw-clenching and temporomandibular disorders. A rationale for the use of these aids to treat pain symptoms other than temporomandibular disorders lies in the nociceptive response of chewing movements through the activation of descending opioidergic modulation.

Conclusion

Level 3	There is no evidence that the use of occlusional splits reduces pain or improves quality of life in CRPS-I patients. *C Fischer 2008*

Other considerations

The mechanism of action for this intervention is unclear.

Recommendation

The use of occlusional splints to treat CRPS-I patients is not recommended.

TREATMENT OF CHILDREN WITH CRPS-I

Medicinal and invasive treatment of children

Scientific support.
There is little literature available on specific medicinal or invasive interventions in children with CRPS-I. Most of the information is limited to descriptions from a multidisciplinary context (Maillard et al. 2004, Murray et al. 2000), with the use of analgesics only mentioned in passing.

Conclusion

Level 3	There is insufficient data to allow any conclusion to be drawn about the effects of continuous peripheral nerve blockade by means of ropivacaine or continuous intravenous infusion with a carbacyclin derivative in children with CRPS-I. *C Dadure 2005, Petje 2005, Olsson 2008*

Level 3	There is evidence that lumbar sympathetic block with lidocaine reduces pain in children with CRPS-I. *B Meier 2009*

Other considerations.
The limited effect of lumbar percutaneous sympathetic blocks in only some of the patients in the study by Meier et al. (2009) calls for prudence. Just as with adults, this intervention should not be routinely used on children.
To sum up, we can say that too little data is available to allow a balanced conclusion to be drawn about the effects of the (aforementioned) medicinal and invasive interventions in children with CRPS-I. This also applies to other interventions described in these guidelines, as they have not been investigated for this target group. Further research is necessary to assess the effects of interventions aimed at CRPS-I on children.
The above comments should be borne in mind by practitioners applying medicinal and invasive treatments described in these guidelines to children. In doing so, the specific aspects of paediatric treatment should not be forgotten; particular attention must be paid to dosage and to supporting the child through the disease process. Close cooperation with a paediatrician appears justified in this context.
Buflomedil solutions for injection are not authorised in the Netherlands.

Recommendation

The project group is of the opinion that further research is needed to assess the effects of medicinal and invasive interventions in children with CRPS-I.

Caution is advised with respect to applying the treatments for adults described in these guidelines to children. Particular attention must be paid to setting the dose and providing (medical) support to the child.

Physiotherapy for children

Scientific support

Physiotherapists are often involved in the treatment of CRPS-I in children. It is generally accepted that the objectives of treating children with CRPS-I are the same as those of treating adults with the condition: reducing pain and increasing the function of the affected limb. The tools available are almost exactly the same as those used with adults: active and passive exercise, massage and physical applications.

Conclusions

Level 3	There is evidence that physiotherapy is helpful for children with CRPS-I. It is not clear what elements of physiotherapy are effective, as different forms of treatment are combined. *B Bialocerkowski 2012* *C Tan 2008, Ayling Campos 2011*

Level 3	There is evidence of a 10-48% chance of relapse in children with CRPS-I after receiving physiotherapy. *B Bialocerkowski 2012* *C Tan 2009*

Other considerations

Various different interventions are usually applied at the same time or in sequence, including exercise therapy, massage, contrast baths and nerve stimulation (Transcutaneous Electrical Nerve Stimulation, or TENS) (Wilder et al. 1992; Murray et al. 2000; Maillard et al. 2004; Lee et al. 2002; Sherry et al. 1999; Kesler et al. 1988; Wesdonk et al. 1991; Stanton et al. 1993). In the Netherlands, children with CRPS-I have the option of receiving treatment from physiotherapists who specialise in children. Psychologists are very often involved (in diagnosis and therapy) in the treatment of children with CRPS-I (Wilder et al. 1992; Murray et al. 2000; Maillard et al. 2004; Lee et al. 2002; Sherry et al. 1999).

Recommendation

The project group recommends that children with CRPS-I should be treated by a (paediatric) physiotherapist.

Occupational therapy for children

Introduction

Occupational therapists are often also involved in the treatment of children with CRPS-I. However, little has been published on the occupational treatment of children with CRPS-I. Hardly any scientific research has been conducted into the effect of occupational therapy in children with CRPS-I and very few publications on this topic can be found.

Conclusion

Level 3	There is evidence that occupational therapy can be beneficial as part of a multidisciplinary approach to treating children with CRPS-I. *C Maillard 2004, Sherry 1999*

Recommendation

The project group advises that occupational therapy should also be a component of multidisciplinary treatment for children with CRPS-I.

Psychological aspects of CRPS-I in children

Treatment

Advice on treatment is based on findings in studies of CRPS-I in adults. Hardly any scientific research has been carried out into the psychological treatment of children with CRPS-I.

Conclusion

Level 2	No conclusions can be drawn as to the effect of cognitive behavioural therapy on children with CRPS-I. *B Lee 2002, Wilder 1992, Logan 2012* *C Sherry 1988*

Other considerations

No psychological questionnaires devised specifically for children with CRPS-I have been investigated. In general, there are hardly any questionnaires validated for children. Practitioners considering treatment could use clinical interviews, drawings of the body and visual analogue scales (VAS). Sometimes, consideration could be given to using the Netherlands Personality Questionnaire for children (NPV-J) and/or the Child Behaviour Check List (CBCL). Treatment for children with CRPS-I focuses mainly on the consequences of the symptoms, as does treatment for adults. Research carried out in the United States indicates that cognitive behavioural therapy, which can include relaxation methods, is effective. It is important to realise that the term ‘cognitive behavioural therapy’ has become somewhat muddled: in the US it often pertains to relaxation therapy and biofeedback, while

in the Netherlands it involves learning to cope with the disease by, among other things, learning to restructure one's thoughts.

When treating children, it is advisable to include the parents or the entire family in the therapy. Contraindications in children are age-dependent. If direct contact with the child is necessary to carry out a procedure, it is important that the child has the necessary intellectual maturity to reflect on how his or her body functions and to control his or her own behaviour. Some children are able to do this prior to the age of ten. Play or mediation therapy could be appropriate for young children. In the case of mediation therapy, the parents would be the 'behaviour-influencing agents'.

Recommendation

Psychological diagnosis and treatment of children with CRPS-I should ideally be carried out by a healthcare psychologist or clinical psychologist specialising in children or adolescents.

WORK AND CRPS-I

Impairment and loss of ability to work due to CRPS-I

A significant number of CRPS-I patients recover completely, or only still suffer mild impairment, within a few months. For the remaining patients, CRPS-I usually means learning to live with severe impairment or invalidity and chronic pain that is often difficult to treat (Goris & Van Weel 2003). CRPS-I can have a major impact on the patient's relationship, job and other activities. Many CRPS-I patients are at risk of becoming socially isolated due to a lack of understanding, pain, impairment and handicap.

Conclusion

Level 3	CRPS-I is a condition that is often associated with significant impairment that can impact the patient's ability to work. *C De Mos 2009, Bricanat 2004, De Jong 2011, Galer 2000, Geertzen 1998, Veldman 1993*

Social consequences of CRPS-I

Data from the Dutch Employee Insurance Agency (UWV) indicate that in 2002 disability benefits (under the Invalidity Insurance Act (WAO), Invalidity Insurance (Self-Employed Persons) Act (WAZ) or Invalidity Insurance (Young Disabled Persons) Act (Wajong)) were paid to 2,443 individuals suffering from CRPS-I (*Ziektediagnosen bij uitkeringen voor arbeidsongeschiktheid 2002*). This accounted for 2.5‰ of disability benefits under the WAO, WAZ and Wajong. Young adults and women are over-represented in the CRPS-I patient population. Seventy-seven percent of people with CRPS-I are women, and women account for 45% of all people who receive disability benefits. Eighty-one percent of those who receive disability benefits for CRPS-I were on the full rate of benefit (as opposed to 73% of the total population of disability benefit recipients). In 2002, 396 new claims for disability benefits due to CRPS-I were accepted, while 150 benefits were discontinued.

Work factors that cause problems

The project group is of the opinion that a number of general principles apply to people who (want be able to) continue working while suffering from CRPS-I. A supportive attitude on the part of colleagues and especially direct superiors is important; the organisation should also ensure that the employee's working conditions are suitable and that the tasks he or she is asked to undertake are adjusted to take account of the condition (Detalle et al. 2003). Adequate climate control (not hot or cold) (Goris & Van Weel 2003; Geertzen et al, 1998), a reduced workload for employees required to adopt postures and undertake movements that impose physical strain (Veldman et al. 1993; Geertzen et al. 1998) and greater flexibility with regard to working hours and travel to work, among other things, are important factors to

workers with CRPS-I. Implementing these measures is often quite straightforward. At the request of the company doctor, an occupational therapist can be consulted to conduct a workplace analysis.

Conclusion

Level 4	Patients with CRPS-I who are in employment often recover more quickly and are more successfully reintegrated into the workplace if their direct superior is supportive, they receive help from care providers focusing on their job, and if their working conditions and role are adjusted to take account of their condition. *D Detaille 2003, Geertzen 1998, Goris & Van Weel 2003, Veldman 1993, CRPS project group members*

Optimising diagnosis, treatment and support

In the Netherlands, patients with CRPS-I are seen by practitioners from different fields. Though 80% ultimately consult one or more medical specialist, 61% first visit their GP (De Mos et al. 2009). Recognition of the clinical syndrome of CRPS-I by first-line practitioners (GPs, (workplace) physiotherapists and company doctors) improves the prognosis, as intervention can start at an earlier stage. The project group is strongly in favour of promoting awareness of CRPS-I so that it can be detected at an early stage.

Conclusion

Level 4	Active sociomedical support aimed at increasing the patient's level of activity, and a time-focused rather than symptom-focused approach, are advisable with a view to promoting functional recovery and resumption of work by CRPS-I patients. *D Opinion of project group members*

CRPS-I should ideally be treated by a multidisciplinary team focusing on functional recovery (Doro et al. 2006). It is essential that the various (para)medical disciplines cooperate. This avoids duplication of tests, time-wasting and confusion, for example if conflicting advice is given. Consultation offers the chance to draw on the expertise of other practitioners and to streamline treatment and support. However, this cooperative approach can make the patient/worker vulnerable, as health is an important factor for his or her position on the labour market. Careless exchange of information about a patient's health can undermine this position. Great care is essential in order to protect the patient's privacy and maintain medical confidentiality. The patient's consent (ideally in writing) must be obtained before any information is exchanged between a doctor treating the patient and his or her company doctor (*Code voor samenwerking arbeidsverzuim 2003*).

Recommendations

- Company doctors and insurance company medical advisers should assess whether workplace adjustments or organisational measures are needed to enable a patient with CRPS-I to work without damaging his or her health and, if such adjustments or measures are needed, what form they should take. This process involves weighing up the workload involved in a job and the patient's ability to bear such a workload.

- If it appears that a time-focused approach is not feasible for CRPS-I patients, or if insufficient information is available for an assessment of the amount of workload that the patient can bear, then the company doctor or insurance company medical adviser should consult the treating physician.

PREVENTION OF CRPS-I

Introduction

Prevention of CRPS-I can be subdivided into primary and secondary prevention. Primary prevention is understood as the prevention of CRPS-I in patients who have never had CRPS-I before and who need to have surgery on a limb, or who have recently suffered trauma to a limb. Secondary prevention (prevention of relapse) is the prevention of CRPS-I in patients who have had CRPS-I in the past.

Primary prevention

Vitamin C

Conclusion

Level 1	It has been demonstrated that the oral administration of 500 mg of vitamin C per day for 50 days from the date of the injury reduces the incidence of CRPS-I in patients with wrist fractures. *A2* *Zollinger 1999,* 2007 *B* *Cazeneuve 2002*

Recommendation

In order to reduce the risk of CRPS-I in adults who have had a wrist fracture, the oral administration 500 mg of vitamin C per day should be prescribed for 50 days.

Conclusion

Level 3	There is evidence that the preoperative administration of 500 mg of vitamin C once a day for 50 days reduces the chance of CRPS-I occurring in patients who undergo prosthesis implantation due to trapeziometacarpal arthrosis. *C* *Zollinger 2010*

Conclusion

Level 3	There is evidence that the postoperative administration of 1 g of vitamin C once a day for 45 days reduces the chance of CRPS-I occurring in patients who undergo foot and ankle surgery. *B* *Besse 2009*

Other considerations

Further research into elective, hand, foot and ankle surgery is needed.

Recommendation

There is currently insufficient evidence to recommend vitamin C in the case of elective hand, foot and ankle surgery. It can be considered in the context of a trial to start with the preoperative oral administration of 500 mg of vitamin C per day for 50 days in patients undergoing elective hand, foot and ankle surgery.

Guanethidine

Conclusion

Level 2	There is no evidence that perioperative intravenous guanethidine in patients undergoing fasciectomy for Dupuytren's disease has any effect on the incidence of CRPS-I. *A2 Gschwind 1995*

Other considerations
Guanethidine is no longer available in the Netherlands.

Recommendation

Perioperative administration of intravenous guanethidine is not advised for primary prevention of CRPS-I.

Calcitonin

Conclusion

Level 3	There is no evidence that subcutaneous administration of calcitonin for four weeks from the onset of the trauma or from the date of surgery can prevent patients from developing CRPS-I (primary prevention). *B Riou 1991*

Recommendation

Perioperative administration of subcutaneous calcitonin is not advised for the primary prevention of CRPS-I.

Secondary prevention

Various interventions or combinations of interventions aimed at preventing relapse of CRPS-I have been described, but very little adequate research has been carried out.

Conclusion

Level 3-4	Despite the lack of evidence, the project group is of the opinion that: - it is best to wait until the signs and symptoms of CRPS-I have abated before conducting surgery on patients with CRPS-I; - patients should ideally be given regional anaesthetic, such as brachial plexus block and epidural anaesthesia. There is limited evidence that daily administration of 100 IU of salmon calcitonin s.c. (perioperatively for four weeks) can prevent a relapse of CRPS-I. There has been no research to show that Mannitol offers any protection against relapse of CRPS-I. *B Kissling 1991* *C Veldman & Goris 1995, Marx 2001*

Other considerations

In general, it seems sensible to wait until the signs and symptoms of CRPS-I have minimised or abated before performing surgery on an individual with CRPS-I (Veldman & Goris 1995; Kissling et al. 1991; Marx et al. 2001). However, it may be that one factor is maintaining the CRPS-I (trigger point) and the surgery is intended to deal with this factor. Under these circumstances surgery should not be postponed (Veldman & Goris 1995). Surgery on cold, oedematous limbs is possibly contraindicated (Veldman & Goris 1995). There is no experience with the use of calcitonin in the Netherlands.

Recommendations

It is recommended that surgery of the (previously) affected limb be postponed until the signs and symptoms of CRPS-I have diminished. This does not apply to operations intended to treat an underlying factor that may be responsible for the CRPS-I.
It is recommended that the duration of the operation and the use of tourniquets be minimised.
The use of regional anaesthesia with a sympathicolytic effect (epidural/spinal analgesia, plexus brachialis blockade), either alone or in combination with general anaesthesia, can be considered in the case of surgery on patients who previously suffered from CRPS-I.
The perioperative use of mannitol to prevent CRPS-I is not advisable.

COMMUNICATION AND INFORMATION

Introduction

Patient information entails not only providing patients with information, but also influencing their emotions and attitudes and changing their behaviour. Patient information should relate to the problems experienced by the patient and the strategies he or she uses to deal with them. Patient information, psychosocial support and help with altering behaviour are all closely interconnected.

Information for patients and their relatives

Conclusion

	No known research has been conducted into the effects of providing information to patients with CRPS-I.

Other considerations

Information is not a one way street. A style of communication in which the doctor gives information not just about physical symptoms but also about emotional aspects and consequences for quality of life is connected to greater patient satisfaction and even to improved health (Steward et al. 1995).

Practitioners must be aware of their own attitude and role when communicating with patients. The practitioner's views on the syndrome and the behaviour that results from it do have an impact on the patient. Prognostic statements must of course be accurate. Trivialising the condition by using phrases such as 'not that serious' or 'to be expected' should be avoided, as should excessively gloomy statements such as 'very serious' or 'highly disabling', because these can cause patients to adopt a defeatist and unnecessarily anxious attitude.

Active listening is just as important in the diagnosis as looking, feeling and measuring. Information is an integral part of treatment, and must be just as obvious a part of medical care as medicinal and invasive treatment. The Medical Treatment Contracts Act (WGBO) states that care providers are expected to have an active attitude.

They are advised to involve relatives in the information provision, as it is often the case that the patient does not (fully) hear or remember the information. In addition, chronic disabling conditions such as CRPS-I have a significant impact on relatives, (Geertzen et al. 1994; Geertzen et al. 1998; Blake 2000; Kemler & Furnee 2002) and so involving them in the information process often leads to greater understanding and better support.

Written information is a vital complement to verbal information.

eHealth as a form of communication and treatment

eHealth has ushered in a new age of communication, information and treatment over the Internet. The use of computer technology in healthcare allows the patient to be actively involved in prevention, research, treatment and after-care. Increasingly more patients want practitioners to give them access to eHealth so that they can have better control over their care, help determine its course and update their own files. Various forms of eHealth allow patients to set up their own appointments, use various apps, submit digital pictures, ask questions and 'attend' online consultations.
It is important that practitioners act as a coach to their patients. This applies all the more with respect to online interventions.

The Netherlands Association of Posttraumatic Dystrophy Patients

The Netherlands Association of Posttraumatic Dystrophy Patients works together closely with practitioners in order to keep patients abreast of new developments in the care for patients with CRPS-I. The association also gives patients the opportunity to share their personal experiences and ask questions.
The association was also involved in drafting the evidence-based guidelines for CRPS type I, and a patient version is being worked on that will enable patients to read and understand the guidelines and enable them to make choices about their care. The Netherlands Association of Posttraumatic Dystrophy Patients sees to it that a summary or flowchart is made available to practitioners.
To find out more about the association, practitioners and patients can visit the association website at www.crps-vereniging.nl.
The association also supports scientific research into the treatment of CRPS-I.

Level 4	There is no scientific support for the use of eHealth communication in treating CRPS-I. There are various promising scientific studies pertaining to Internet intervention for treatment and self-help.

Recommendations

- The project group is of the opinion that doctors and other practitioners must provide information to patients with CRPS-I, taking into account their physical symptoms, behaviour and social factors so that the information is geared to their personal situation.
- This information allows patients to make well-considered decisions, take control of their care and help determine the course of their treatment. eHealth support contributes to this.
- It is recommended that practitioners initiate eHealth in their own work setting in order to provide better quality care and better quality of life.
- The use of Internet-based technology for behaviour interventions in cases of chronic pain is promising. However, it is important that further evidence-based research is

conducted into these intervention methods.

- Practitioners are asked to inform patients about the website of the Netherlands Association of Posttraumatic Dystrophy Patients, where they find specific information about CRPS-I, get in touch with other patients and download brochures, such as a patient version of these guidelines.

Table 4. Proposed clinical diagnostic criteria (the "Budapest criteria") (Harden et al. 2010)

1. Continuing pain which is disproportionate to any inciting event
2. Must report at least one symptom in three of the four following categories:
   - *Sensory* : reports of hyperaesthesia and/or allodynia
   - *Sudomotor/Oedema* : reports of oedema and/or sweating changes and/or sweating asymmetry
   - *Vasomotor* : Reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
   - *Motor/Trophic* : Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign at time of evaluation in two or more of the following categories:
   - *Sensory* : Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
   - *Sudomotor/Oedema* : Evidence of oedema and/or sweating changes and/or sweating asymmetry
   - *Vasomotor*: Evidence of temperature asymmetry and/or skin colour changes and/or asymmetry
   - *Motor/Trophic* : Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms.

*Note: for scientific purposes, research diagnostic criteria can be used which require at least one symptom to be reported in **all four** symptom categories and at least one sign (observed at evaluation) to be displayed in two or more of the symptom categories.*

APPENDIX 2: WHO PAIN LADDER

Modified WHO pain ladder

Step 1:	Paracetamol + NSAIDs ± adjuvant medication
Step 2:	Step 1 + weak opioid