



Abstracts from Proceedings Cork CRPS 2017: IASP Special Interest Group in Complex Regional Pain Syndrome (CRPS)

Dominic Hegarty

Recently Cork hosted the specialist interest group of the IASP world conference on CRPS. It was the largest gather ever of specialists in this field with 240 delegates from 20 different countries in attendance. Chaired by Dr Dominic Hegarty (Consultant in Pain Management & Neuromodulation) the theme of the conference was “*Working together to succeed.*”

Dr Hegarty explains that “The conference focused on the role of multidisciplinary team management and the importance of partnership to help identify, treat and understand the nature of this disabling pain condition.” Under the guidance of Dr Lone Knsuden (Scientific Committee Chair) and the late Prof. Roberto Pervez an excellent programme was developed. High-calibre international speakers, excellent networking opportunities and a range of cutting-edge demonstrations ensured that this conference was a huge success.

In particular the conference dealt with several important areas including Prof. Lorimer Moseley (University of South Australia) on the ability of using Brain Training in CRPS. The aspect of Spatial Neglect and Chronic CRPS, was addressed by Prof Andre Mouraux, (Belgium), while Prof Lance McCracken (London) considered the evidence for Acceptance & Commitment Therapy (ACT) and the influence it has on outcomes in CRPS. The potential for Graded Motor Imagery to “rewire” the brain was presented by Prof Tim Beames (UK).

Dr Jenny Lewis (Bath, UK) presented her research on Body Perception Disturbance in CRPS and this was followed by very challenging research on the where the physical limits of pain are in CRPS by Prof Van Dongen (Netherlands).

Prof Candy McCabe (Bath, UK) summarised the lessons of 30 years of experience to advise on designing the “perfect” MDT team and this was illustrated by the combined work of the Walton Centre Liverpool and the experience of the team at the Cork CRPS Forum. Dr A. Goebel (Liverpool, Chair SIG CRPS) led a fascinating and highly engaging debate on the concerns of amputation as a line of treatment for persistent CRPS pain.

Pain medicine in Cork has a strong partnership with Tyndall National Institute, UCC, and this was underlined when Dr Hegarty and Dr Paul Galvin (Tyndall National Institute, UCC) co-chaired

a fascinating session focusing on the role of technology in the diagnosis and therapy strategies for the future. Prof Slavin (Chicago) and Prof. Huyen (Netherlands) emphasized the potential in this area. Discussion on the development of new novel pharmacological based treatment will depend on greater understanding of the bioscience and here too exciting new options are emerging.

Another first for the local organising committee was the inclusion of a poster and oral presentation section. There were 24 exciting new projects presented. This was so successful it has already been proposed for the next CRPS meeting in Italy in 2019.

Dominic Hegarty
Chair CRPS Cork 2017

Disclosure:

The author declares no conflicts of interest.

Abstracts

Development of a relaxation workbook to support self-management of complex regional pain syndrome (CRPS)- an evaluation of patient experience

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Introduction: The importance of relaxation in managing CRPS symptoms is highlighted within the UK CRPS treatment guidelines (Goebel et al. 2012). Daily relaxation sessions are part of The Bath 2-week CRPS multidisciplinary inpatient programme. Some patients reported difficulty practising relaxation post-discharge, not always maintaining this important component of rehabilitation. Appropriate preparation is essential in equipping patients to self-manage CRPS in the long-term (Rodham et al. 2012). To develop a Relaxation Workbook and evaluate patient experience of its effectiveness in supporting self-management.

Methods: We designed a patient-held Relaxation Workbook that includes relaxation and mindfulness techniques, a practise record, creative activities and gratitude diary. It was issued to 33 patients within their first programme week and 28 provided written feedback prior to discharge. Feedback included what patients found most/least useful in supporting them to continue relaxation independently. Thematic analysis was used to evaluate the workbook.

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Results: Feedback from 28 patients showed that the workbook supported independent relaxation practise during the programme, sparking ideas regarding continuing post-discharge. Patient reported themes included “Ownership,” regarding the importance of independent tasks to complete mid-programme, “Outside-the-box,” in terms of using creativity in relaxation, and “Making it happen,” concerning development of a routine.

Conclusion: Findings demonstrated that a Relaxation Workbook allowed patients to further develop their own style and routine of relaxation practise, in order to self-manage post-discharge, highlighting the need to introduce self-management skills in relaxation at an early stage in the programme. Further work to explore whether patients continue practise post-discharge is required.

The authors have no conflicts of interest to declare.

Challenges in selecting objective outcome measures in global clinical trials in complex regional pain syndrome

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Introduction: The COMPACT consortium developed and agreed on a minimum core set of standardized outcome measures for use in CRPS clinical trials, not including objective quantitative measurements of CRPS signs. Well-chosen measurements in adequate and well controlled clinical trials might provide additional support of treatment effectiveness and lead to optimized labels for new medicinal products. Our goal was to select relevant and feasible objective outcome measures applicable in global clinical trials of Complex Regional Pain Syndrome (CRPS).

Methods: Literature research, interviews with CRPS experts.

Results: In global clinical trials involving different countries and a high number of trial sites, objective measurements can only effectively be applied if they can be easily trained and performed by site staff and understood by patients. The measurements and tools must have clear instructions, be proved as valid, reliable, with low inter- and intra-rater variability and able to produce statistically sound data. In addition, they need to reflect frequent and clinically relevant signs of CRPS. Four objective measurements of CRPS signs fulfilling the above requirements were identified: dynamic mechanical allodynia and pressure pain threshold as described in the Quantitative Sensory Testing protocol of the German Research Network on Neuropathic Pain, edema of the hand and foot with the figure-of-eight method and the active range of motion of the wrist and ankle using a hand-held goniometer.

Conclusion: The identified 4 objective quantitative measures are fit for use in global clinical trials and reflective of frequent and clinically meaningful CRPS signs.

The authors have no conflicts of interest to declare.

Complex regional pain syndrome: a new model of care improving patient outcomes

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Introduction: CRPS literature indicates <50% of patients diagnosed with CRPS will not return to the workforce. Clinical

opinion and current literature indicates early recognition of CRPS can improve patient outcomes. Patients presenting with CRPS within Royal Melbourne Hospital (RMH) were frequently not identified, resulting in multiple emergency department presentations and high healthcare utilisation. Care was provided in silos and lacked co-ordination resulting in persistent symptoms and long term healthcare needs.

Methods: (1) Facilitate early access to assessment and intervention; (2) Provide intervention in a co-ordinated, evidence based and well-supported approach, reducing variation in care, reducing healthcare utilisation and improving outcomes; (3) Received Department of Health & Human Services Advanced practice grant; (4) Developed and implemented clinician resources including identification tool and clinical algorithm; (5) Established early and direct referral pathway to assist clinicians in the emergency department and key hospital areas to identify patients.

Results: Sixty-five patients were referred in the first 12 months and 33 patients met Budapest diagnostic criteria (clinical). Statically significant reductions in health care utilization 90% of patients have returned to their pre-injury workplace. Statically significant improvements in function.

Conclusion: Hand therapy in collaboration with pain management services developed and implemented an innovative clinical approach to the management of patients with signs and symptoms of CRPS. This model provides a single point of contact and enables patients to access the right care at the right time. Effectiveness has been demonstrated by reducing health care utilisation, improving patient access to care, whilst also improving patient outcomes.

The authors have no conflicts of interest to declare.

Bioanalytical techniques for potential CRPS biomarker assemblies

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Introduction: Since there is a significant need for studies of CRPS on the molecular level novel bioanalytical tools and strategies are required. Thus, the aim here is to develop multifactorial biomarker analysis schemes considering the multifaceted character of CRPS.

Methods: Trypsin digestion (TD) and immunoprecipitation (IP) sample preparation, and capillary electrophoresis (CE) and nano liquid chromatography (nLC) separation, with or without coupling to electrospray ionisation mass spectrometry (ESI-MS) characterisation of μ L sized samples were performed. Matrix assisted laser desorption/ionisation (MALDI) MS was used for analysis of TD- and IP-samples. Database search was utilised for identification. Substances included were neuropeptides substance P (SP) and bradykinin (BK), and osteoporosis related osteoprotegerin (OPG) and osteopontin (OPN), with albumin and immunoglobulin G (IgG) representing major blood plasma components.

Results: Using CE with different buffer additives showed to be promising separating OPG, OPN, SP, BK, albumin and IgG. Connection to ESI-MS allowed identification. For alternative selectivity nLC-UV was utilised obtaining detection of glycosylated OPN at 8 nM, while MALDI-MS and nLC fractionation to MALDI-MS revealed a Mw of 67.2 kDa. OPG at 8 nM could be detected with IP and MALDI-MS. nLC-ESI-MS using TD gave identification of OPG, as did MALDI-MS-MS analysis.

Conclusion: Bioanalytical techniques are promising tools for studies of substances related to CRPS. Combinations of techniques are needed to obtain selectivity and sensitivity necessary for analysis of analytes at low concentration in complex clinical samples. Further improvements to increase resolution, yield and detectability, and adaptation for other biomolecules of interest could be done.

The authors have no conflicts of interest to declare.

“Emotional skills to manage chronic pain”—an 8 week community mental health based intervention

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Introduction: In response to an observed need in a North Cork Adult Secondary Care Adult Mental Health Service, a pilot group focusing on coping skills to better manage chronic pain was developed and implemented. The group was primarily Cognitive Behavioural Therapy (CBT) based but also encompassed elements of Acceptance Commitment Therapy (ACT) mindfulness for chronic pain and the opportunity for peer support. The group is open to service users of North Cork Adult Mental Health Services with pre-morbid mental health difficulties and/or difficulties secondary to the onset of chronic pain.

Methods: Prior to engagement, candidates were screened for suitability to engage with the skills format, the group context and any accommodations that might be necessary to facilitate their involvement. The group maintained some flexibility in its proposed programme to allow for service user suggestions on topics related to chronic pain but not included in the planned format. The group has been facilitated on 3 occasions in the North Cork Adult Mental Health Service and qualitative reflections on the utility and cost-effectiveness and barriers to the effectiveness of the intervention are explored.

Results: The sense of peer support, mindfulness and CBT skills were noted by participants to be helpful aspects of group attendance.

Conclusion: Clinicians observe that the group may provide a beneficial community based service outlet to enable participants to explore an alternative narrative of their chronic pain experience.

The authors have no conflicts of interest to declare.

Living with CRPS: patients in partnership

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Introduction: The aim is to describe the partnerships and resources accessed by individuals before and after diagnosis with CRPS.

Methods: Individuals around the world who have been formally diagnosed with CRPS were interviewed face to face and on Skype. Interviews and analysis will conclude in July.

Results: While waiting for formal diagnosis and treatment, people with CRPS turn to the internet for information. Websites and support groups are relatively easy to find and the individuals form partnerships with peers through online environments. These sites, however, offer varying levels of correct and appropriate information, posts often catastrophize the condition, question

treatment options, and do not demonstrate that full recovery or remission is possible. Multidisciplinary health care teams offer much to the patient but occasionally the health practitioner does not understand the lived experience of the patient and does not partner with the patient on the health journey. As one participant said: “... the hardest thing is that my life is not my own. You make the decisions as to what my life is going to be and I’ve got to do whatever I can to convince you to help me because I’m stuffed without you.”

Conclusion: Better CRPS treatment can result from better understanding the lived experience of patients. Offering valuable insight into the condition, patients can be a valuable member of the healthcare team treating this condition. Such a partnership may result in better health outcomes and improved quality of life through client empowerment.

The authors have no conflicts of interest to declare.

Pharmacologic blockade of Nav1.7 as a potential analgesic treatment for CRPS

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Introduction: Treatment of CRPS is extremely difficult. Blockade of the Voltage gated sodium channel Nav1.7 has shown promise, as this channel appears to be essential for pain perception. Our group recognized a 2 amino acid distinction at the pore of the primate Nav1.7 channel, changing affinity for naturally occurring pore-blockers such as saxitoxin. Thus, we synthesized, *de novo*, derivatives of saxitoxin with high in vitro levels of selectivity for the primate Nav1.7 channel. This study used a primate model to test the analgesic potential and safety of one of these molecules.

Methods: A macaque model tested the efficacy of this molecule on acute thermonociceptive responses. Physiologic measures (eg, SpO₂, heart rate, respiratory rate) were also assessed. Periodic blood and CSF samples were taken for assessment of pharmacokinetics.

Results: A Nav1.7 targeting saxitoxin derivative produced robust, dose-dependent analgesia for thermonociceptive responses with the highest doses producing complete analgesia for at least 90 minutes. Samples taken at the time demonstrated blood levels necessary to establish these effects. No side-effects attributable to blockade of other Navs were observed, agreeing with the selectivity demonstrated in the in vitro studies.

Conclusion: SiteOne’s selective Nav1.7 blocker produced robust, sustained analgesia in a primate model without off-target side effects. These results indicate that these molecules are likely to be useful as systemic analgesics with the potential to alleviate pain associated with CRPS.

J. Mulcahy, A. Delwig, J. Beckley are employees and D. C. Yeomans and J. DuBois are founders of SiteOne, which funded the study along with the state of Montana.

A single-center randomized controlled trial of local calcitonin injection for complex regional pain syndrome

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Introduction: This study explored the efficacy of local calcitonin injection in relieving pain and improving the quality of life among subjects with complex regional pain syndrome.

Methods: A single-center, randomized controlled trial of local calcitonin injection was performed. Twenty-seven subjects (29–52 years) with complex regional pain syndrome lasting for 30 days were enrolled. Subjects were randomized to receive local calcitonin injection ($N = 14$), oral vitamin C ($N = 13$) for 4 weeks. The worst pain severity, oedema, global impression of change, and interference with activities of daily living and quality of life were assessed.

Results: Time per group interaction, different group difference and effect on overall pain at each follow-up point were statistically significant ($P < 0.05$) between groups. In the injected calcitonin group, the overall pain ($P < 0.001$), allodynia ($P < 0.05$), continuing pain ($P < 0.05$) and oedema ($P < 0.05$) revealed a significant effect at each follow-up point as compared to the vitamin C group. Activities of daily living, quality of life in the injected calcitonin group improved significantly as compared to the vitamin C group ($P < 0.05$). The oral vitamin C did not provide any significantly pain relief ($P > 0.05$).

Conclusion: Local calcitonin injection was not only efficacious in relieving pain, but also appears to be tolerable and safer choice of treatment for complex regional pain syndrome.

The authors have no conflicts of interest to declare.

CRPS-1 in children: psychiatric comorbidity and history of stress

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Introduction: Chronic pain in children is often related to a history of stress and psychiatric comorbidity is often seen. Since 1984 crps in children has been an issue of special interest and approximately 350 cases are seen during these 33 years. The last 15 years the main therapeutic tool has been a modern model of cognitive behavior therapy (Acceptance and Commitment Therapy, ACT). Therapy is focused on function and valued daily activities including exposure for normal physical activity and allodynia. The team working with these patients include pain physician, psychologist and physiotherapist. The Bruhl and Harden criteria are used for establishing diagnosis. Project aim is to demonstrate psychiatric comorbidity and history of stress in children with crps and to correlate this to outcome.

Methods: A retrospective study. Data from history and signs from the primary visit were retrieved. The psychologist asks for the history of psychiatric diagnoses and symptoms and a history of child abuse, bullying, and other stress factors are asked for. It is common that the child has high expectations for their performance in school and/or sports. Data of this will be presented as well as its relation to outcome.

Results: Preliminary results indicate that psychiatric comorbidity not seems to be more common in children with crps compared to children with other types of chronic pain. A history of stress is very common—most commonly is high expectations of performance in school and/or sport.

Conclusion: Children with crps should be carefully examined for a history of stress and this should possibly be thoroughly addressed in the treatment.

The authors have no conflicts of interest to declare.

Histopathology of amputation for CRPS: a review of the literature

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Introduction: Amputation is an uncommon treatment for CRPS. Thus, amputation represents a rare opportunity to study the histopathology of CRPS. This literature review examines the frequency that histopathology is reported following amputation for CRPS.

Methods: The Pubmed, MEDLINE, LILACS, OpenGrey and ClinicalTrials.gov databases were searched with the following strategy ([MeSH term “reflex sympathetic dystrophy”] OR [keywords “reflex sympathetic dystrophy” OR “RSD” OR “complex regional pain syndrome” OR “CRPS” OR “causalgia” OR “Sudeck” OR “algodystrophy”]) AND (“amputation”), limited to humans.

Results: Of 328 retrieved records, 44 were included for analysis. Articles included 35 case series or reports, 6 letters to the editor, 2 literature reviews and 1 commentary. The articles describe 192 unique limb amputations. Articles addressed peri-operative course (8), clinical outcome (16), or clinical opinion regarding amputation (8). Two articles describe synovial sarcoma developing in a limb affected by CRPS. Ten articles (23%) describe histopathology findings in the amputated limb: skin (5), skeletal muscle (5), peripheral nerve (3), blood vessels (3), bone (2), intra-epidermal nerve fibers (1), joint (1) and/or tendon (1).

Conclusion: The standard pathology approach to a benign amputation specimen is to sample the neurovascular, cutaneous and bony margins for viability. In addition, representative sections of the lesion(s) are examined. The salient histopathologic features of CRPS have not been defined. A comprehensive literature review of the histopathology of CRPS is needed for pathologists, clinicians and researchers. Such a summary of our current knowledge would guide a more informative examination of future amputation specimens for CRPS.

The authors have no conflicts of interest to declare.

Patients with CRPS can both over- and under-represent the affected side of space according to straight ahead pointing judgements

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Introduction: CRPS patients can show inattention to the affected side of space. This resembles Hemispatial Neglect (“neglect”), a syndrome that follows stroke and is characterised by under-representation of the contralesional side of space. However, CRPS patients appear to over-represent the affected side when judging when a visual target is straight ahead of their body. A challenge to resolving this contradiction is that little is known about visual straight-ahead judgements of neglect patients. This study therefore examined the representation of space in CRPS patients using straight ahead pointing (SAP), a more common measure.

Methods: Twenty-six CRPS patients (14UL, 12LL) and 28 controls pointed under an occluding panel with both hands. Participants pointed straight ahead of their body midline with their eyes closed (SAP); or with open eyes to targets that were straight ahead (target-pointing; TP). TP allowed measurement of arm proprioception without subjective midline judgement. Trials were

interspersed with left and right target-pointing to prevent carry-over effects. Pointing errors were calculated using marks on the occluding panel.

Results: Patients' TPs and SAPs did not deviate towards or away from the affected side relative to controls'. There were, however, subsets of patients with larger-than-normal biases in both directions. Analysis of absolute errors showed that patients had significantly larger SAP errors for the affected hand. These could not be attributed to proprioceptive impairment, because patients' absolute TP errors were similar to controls'.

Conclusion: Different individuals with CRPS might over- or under-represent the affected side of space in straight ahead pointing.

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Low dose outpatient ketamine infusion improves pain, function and mood in patients with complex regional pain syndrome

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Introduction: The N-methyl-D-aspartate receptor (NMDAR) plays a pivotal role in the pathophysiology of complex regional pain syndrome (CRPS). Subanesthetic doses of the NMDAR antagonist ketamine have been effective in treating CRPS. While ketamine has been shown to reduce pain in CRPS, functional improvement remains controversial. Aim: Review the efficacy of the subanesthetic ketamine infusion protocol used at Dartmouth-Hitchcock Medical Center (DHMC).

Methods: Nine patients with treatment refractory CRPS, presented to the DHMC Pain Clinic. Diagnoses were confirmed using the Budapest Criteria. (1) Ketamine was infused at 50 mg/h over 4 hours for 18 sessions. Psychological and cardiac evaluations were done prior to infusion. Treatment protocol required that patients could not be using opioids or tobacco. Pain levels (11 point VRS) at rest were recorded at infusion visits. Patients were contacted 1 to 13 months post infusion to determine percentage of pain relief and improvements in activity, function and mood.

Results: Average pain level at rest was 7.28 pre-treatment and 2.8 post-treatment. Seven out of 9 patients (78%) had positive improvement in all categories. Twenty-two percent were non-responders. Improvements were reported in pain (78%), activity (75%) and mood (71%). Patients reported improvement in ADLs, exercise, social interaction, hobby engagement, housework performance and work duties.

Conclusion: This review demonstrates that subanesthetic ketamine infusions can lead to improvement in pain, function and mood. Additional study is warranted, to quantify potential activity and mood improvement, in order to support the treatment of CRPS with ketamine infusion.

The authors have no conflicts of interest to declare.

The role of deep somatic tissue during sympathetic modulation in CRPS

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Introduction: To investigate the behavior of deep somatic tissue in CRPS during modulation of the sympathetic nervous system (SNS).

Methods: Nine patients with chronic CRPS (4 males, 5 females, 49 ± 13 years) and 8 healthy controls (5 males, 3 females, 47 ± 14 years) were investigated with near-red infrared spectroscopy (NIRS) on both body sides of extensor carpi radialis brevis muscle and gastrocnemius muscle (medial belly) during whole body cooling (activation of the SNS) and warming (inhibition of the SNS). Regional blood flow, blood volume and tissue saturation (blood supply) were measured during the whole time of examination in order to investigate the dynamic of oxygen consumption and microvascular reactivity.

Results: Mean duration of CRPS was 1577 ± 1277 (range 147–4363) days. Mean pain was rated 6.5 ± 1.2 NRS. Sixty-three percent of patients and 33% of controls were smokers (n.s.). During sympathetic activation (cooling), total (tHb) and oxygenated hemoglobin (OxHb) were lower on the affected compared to the unaffected arm whereas no differences were observed between both (unaffected) legs or in controls. Upon sympathetic inhibition (warming) tHb and OxHb showed an overshooting increase on the affected extremity compared to the contralateral extremity. Since deoxygenated hemoglobin did not differ between affected and unaffected extremity, tissue saturation index was lower on the affected compared to the contralateral extremity in CRPS during cooling.

Conclusion: Sympathetic vasoconstriction (with reduced tissue perfusion) can contribute to ischemia and pain in CRPS where impaired oxygen utilization might be present. Improvement of blood supply might improve symptoms.

The authors have no conflicts of interest to declare.

Sensory modulation dysfunction may predict CRPS

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Introduction: Complex Regional Pain Syndrome (CRPS), a chronic pain condition, develops mainly after limb trauma and severely inhibits function. Central sensitization is a primordial mechanism in the development of CRPS involving sensory as well as motor CNS alterations. While early diagnosis is crucial, factors for CRPS onset are elusive. Therefore, identifying those at risk is essential. Sensory modulation dysfunction (SMD) is a neurodevelopmental health condition characterized by sensory under- or over-responsiveness to daily sensations. Laboratory findings as well as ecological testing found hyperalgesia and prolonged and intense after-sensation, suggestive of endogenous pain processing alterations. The aim of this study was to test SMD as a risk factor for CRPS.

Methods: Forty-four individuals with CRPS (29.9 ± 11 years, 27 men), diagnosed according to the Budapest criteria, 3 months to 12-years post diagnosis, and 204 healthy controls (27.4 ± 3.7 years, men) completed the Sensory Responsiveness Questionnaire-Intensity Scale (SRQ-IS). No group differences were found in sex distribution and mean age ($P = 0.233$; 0.130 , respectively).

Results: Group differences were found in SMD distribution; 34% (N = 15) of individuals with CRPS and 12.8% (N = 26) of healthy controls were identified with SMD ($P < 0.001$). Logistic regression modeling revealed that the risk for developing CRPS is 2.68 and 8.21 times higher for individuals with sensory over- and sensory under-responsiveness compared to non-SMD individuals ($P = 0.03$; 0.01 respectively).

Conclusion: SMD, particularly sensory under-responsiveness, might serve as a risk factor for developing CRPS and therefore screening for SMD after limb trauma is recommended.

The authors have no conflicts of interest to declare.

CT targeted touch—a new therapeutic target for CRPS patients?

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Introduction: Human hairy but not glabrous skin is equipped with a subgroup of C-fibers, the so-called C-tactile (CT) fibers that are low-threshold-mechanical-afferents that do not mediate pain but affective aspects of touch. Previous studies showed that CT-fibers reduce experimental pain if they are intact. In this study, we investigated possible pain modulating capacities of CT-afferents in CRPS-I and -II.

Methods: Ten CRPS patients (median age 33.1; CRPS-II n = 2) and 11 healthy controls (median age 46.0) participated in this study. CT-targeted touch (brush-stroking; velocity: 3 cm/s) was applied on hairy and glabrous skin on the affected and the unaffected limb in CRPS. The patients rated the pleasantness of CT-targeted touch (anchors 1–4). Pain intensity (NRS 0–10) was assessed before, directly after and 30, 60 and 120 minutes after each experimental session. CT-stimulation was performed twice daily for 10 days.

Results: CT-targeted-touch was felt significantly more pleasant on the non-affected than the affected side on hairy ($P = 0.000$) and glabrous skin ($P = 0.002$) in CRPS. The pleasantness rating of the contralateral limb did not show significant differences between CRPS patients and volunteers whereas CT-stimulation on the affected limb was significantly less pleasant ($P = 0.01$). Pain ratings remained unchanged by CT-activation.

Conclusion: CT-stimulation did not reduce pain intensity in CRPS-I and -II patients and was less pleasant on the affected limb. Therefore, we present evidence that CT-afferents lose their pain modulating properties in a chronic pain condition, no matter if they are intact (CRPS-I) or impaired (CRPS-II). It appears possible that CT-afferents might contribute to chronic pain in CRPS.

The authors have no conflicts of interest to declare.

A review of patients referred to the paediatric liaison service with a chronic/complex pain presentation over a 12 month period: findings and recommendations for treatment

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Introduction: The Paediatric Liaison Service (PLS) provides multidisciplinary (MDT) input to young people with mental health

needs attending Temple Street Children's University Hospital (TSCUH) on an on-going basis. There is an absence of international best practice guidelines on MDT treatment of mental health needs in paediatric pain, and the impact on activities of daily life (ADLs). Our study aims to explore the mental health needs, treatments and outcomes for this cohort, in striving to continually improve service delivery. Particular attention is given to the Complex Regional Pain Syndrome (CRPS) sub-group within this cohort.

Method: A retrospective chart review of cases accepted by the PLS between March 2016 and 2017 was conducted to gather this data.

Results: Referrals to the PLS requesting MDT input for young people with chronic/complex pain accounted for 21% (n = 59) of all referrals accepted, compared with 11% (n = 18) in the previous year. Twelve (n = 7) of this year's cohort had a diagnosis of CRPS. Mental health needs for patients with/without CRPS included features of conversion disorder, pain management skills, anxiety and low mood. The main areas of functional impairment related to school attendance, self-care, sleep, leisure and social activities. A number of service-related issues such as types of referrals, waiting times and intervention approaches are also presented.

Conclusion: Our study indicates there is a growing number of young people presenting with chronic/complex pain who have co-morbid mental health needs that impact on their ADLs. Education to referrers, standardised MDT treatment approaches, and use of outcome measures warrant further consideration.

The authors have no conflicts of interest to declare.

Pain reduction by inducing sensory-motor adaptation: CRPS PRISMA trial protocol

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Introduction: People with CRPS can show changes in their perception of and attention to the affected limb and its surrounding space that suggest possible neuropsychological components to the disorder. These include discrepancies between sensory and motor representations of the body and space. Here we present a protocol for a clinical trial evaluating the efficacy of a sensory-motor training technique called prism adaptation (PA) previously shown to alleviate CRPS symptoms in small exploratory studies. It will further examine how neuropsychological changes relate to clinical manifestations of CRPS.

Methods: This double-blind, randomised controlled trial will enroll 42 upper-limb CRPS-I patients to undergo 2 weeks of twice-daily real or sham PA. Primary outcome measures are pain intensity and CRPS severity. Secondary measures include self-report questionnaires, clinical assessments, and psychophysical and computer-based tests of physical and neuropsychological symptoms. Data are collected at 4 and 0 weeks pre-treatment; and at 0, 4, 12 and 24 weeks post-treatment. Ethical approval was granted by the Oxford A REC (12/sc/0667).

Results: We predict greater reduction in pain and CRPS severity, and other clinical and neuropsychological signs, after real PA compared to sham treatment. We further expect more pronounced alterations in the perception of and attention to the

affected limb to be associated with more severe physical symptoms of CRPS at baseline.

Conclusion: This study will provide a robust evaluation of the therapeutic effects of PA, determining its potential for CRPS rehabilitation. Furthermore, these findings will provide insights into the role of neuropsychological changes in CRPS.

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Assessment of DRG surface binding by CRPS-serum-IgG using primary mouse cells

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Introduction: Recent works suggest that in some patients with CRPS there is an autoantibody response against surface markers on primary neurons, but cellular and molecular targets are unknown. Using FACS analysis we investigate surface epitope binding of CRPS-serum-IgG to murine primary dorsal root ganglion cells.

Methods: Dorsal root ganglia (DRGs), harvested from female C57Bl/6J mice, were dissociated. Isolated primary sensory neurons were either directly stained or plated and placed at 37°C under a 5% CO₂ atmosphere for 24 hours; plated cells were scraped and incubated with purified serum-IgG from CRPS patients or healthy volunteers and then stained. To confirm the role of inflammation in activating the patient IgG, isolated DRG neurons were also incubated with inflammatory mediators and cytokines before assessing the IgG binding.

Results: Directly stained neurons had variable histogram patterns and only in rare cases the mean fluorescence values were higher for CRPS patients than for healthy volunteers. On the contrary, plated neurons had more repeatable histogram patterns and CRPS samples always had higher mean fluorescence values than healthy volunteers. When neurons were incubated with inflammatory mediators there was no significant increase of mean fluorescence. Depending on CRPS patient IgGs, cytokines treatment significantly increased either the mean fluorescence or cell percentage involved in IgG binding.

Conclusion: In this assessment of DRG surface binding by CRPS serum IgG, the majority of plated neurons have a stronger and standardised binding with human IgGs than directly stained neurons. This effect appears to be increased only by cytokines and not by inflammatory mediators.

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Core outcome measurement set for complex regional pain syndrome clinical studies (COMPACT): the next steps

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Introduction: Complex Regional Pain Syndrome (CRPS) clinical studies have historically used many different outcome measures to capture the multidimensional nature of the condition. This has been a limiting factor in bringing together our understandings of the mechanisms and management of CRPS. A minimum core set of standardised outcome measures (COMPACT), for use in all future CRPS clinical studies, was developed by an international consortium of patients, clinicians, researchers and industry representatives. The published COMPACT includes the following patient-reported outcome measures: pain intensity (average, worst, least), 6 neuropathic items from the revised Short-form McGill Pain Questionnaire, PROMIS 29 Profile (version 2) and PROMIS suicide ideation question, Pain Catastrophizing Scale, EQ-5D-5L, Pain Self Efficacy Questionnaire, patient's global impression of change and CRPS symptom questions. There is an additional clinician-reported measure: the CRPS severity score.

Methods: In order to inform an optimum future protocol, an international, multi-centre study will be conducted to test the feasibility and acceptability of collecting the COMPACT data (adults with CRPS I or II, meeting the Budapest diagnostic criteria). An electronic data management system will be developed and refined to collect and manage the COMPACT data.

Results: The final COMPACT data collection tools and processes will be informed by the findings from the feasibility study and development of the data management system.

Conclusion: COMPACT will provide access to a large, consistent and expanding data set of outcome measures and demographic data. The COMPACT online community comprises ≥60 members from 16 countries. Email: ruh-tr.compact@nhs.net to join the community and receive COMPACT updates.

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Differential DNA Methylation and protein expression levels in CRPS vs Non-CRPS pain patients

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Introduction: Little is known about epigenetic factors contributing to CRPS risk. This study examined whether CRPS risk might derive in part from differential DNA methylation profiles, and also tested for differential protein expression.

Methods: Subjects were military traumatic amputees reporting ongoing limb pain, classified into those with features consistent with CRPS (n = 10) vs non-CRPS pain (n = 43). Blood samples were analyzed for DNA methylation at >450,000 CpG sites (Infinium HumanMethylation450 BeadChip) and for levels of 276 proteins (mass spectrometry). Findings were replicated using de-identified clinical phenotype data tied to

a DNA biobank (“BioVU”) reflecting >40,000 hospital patients seen at Vanderbilt University Medical Center.

Results: In primary data, nominally significant ($P < 0.05$) differential methylation between groups was observed for over 100 CpG sites, including genes involved in immunomodulation of the NF-kappaB inflammation pathway, endocannabinoid signaling, and inflammatory mediator regulation of TRP channels. Functional analysis revealed 5 functional categories significantly enriched (FDR-corrected $P < 0.05$ level) for differentially methylated sites, including phosphoproteins, insulin secretion, acetylation, oocyte meiosis, and alternative splicing (the latter potentially having broad effects). Multiple nominally significant protein expression differences were also observed between groups (eg, ITIH1, a protein involved in inflammatory diseases). Numerous identified differential methylation sites and proteins independently replicated in the large BioVU dataset (“limb pain” phenotype vs other patients).

Conclusion: These independently replicated findings suggest that risk for CRPS following injury may be linked to epigenetic changes involving sensory systems, immune- and inflammatory-related factors, and neurotransmitter function. Differential expression of proteins, including those involved in inflammation, may also contribute.

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Reliability and validity of the hamilton inventory for complex regional pain syndrome

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Introduction: There is a need for robust condition-specific tools to evaluate and monitor the spectrum of symptoms experienced by persons with CRPS. The Hamilton Inventory for CRPS (HI-CRPS) was developed to comprehensively evaluate using both clinician observations (CB: 14 items) and patient-report (PR: 40 items). This study provides preliminary estimates for the reliability and validity.

Methods: Participants were recruited as part of a pilot study for a novel treatment for CRPS, and included persons with upper limb CRPS, known nerve injury, or hand fracture. Two blinded evaluators completed measures at baseline, with re-administration one week later prior to commencing treatment, and at 3 months post treatment. Comparison measures included the Pain Catastrophizing Scale, McGill Pain Questionnaire, ROM, and grip strength.

Results: Internal consistency ($n = 39$) for the CB-HI-CRPS was $\alpha = 0.80$; the PR-HI-CRPS Symptoms scale was $\alpha = 0.95$, Daily function scale $\alpha = 0.95$, and Coping/Social Supports scale $\alpha = 0.92$. Inter-rater reliability ($n = 30$) for the CB-HI-CRPS was 0.90, and test-retest was 0.87 ($n = 21$). The PR-HI-CRPS test-retest reliability was 0.94 for $n = 27$. Persons with CRPS scored higher on the evaluations than those with other diagnoses (CB-HI-CRPS $P = 0.006$, PR-HI-CRPS $P = 0.009$), supporting discriminative validity. Construct validity was supported by a strong correlation ($r = 0.72$) between the CB and PR Symptoms

scale, and $r = 0.73$ between PR Coping/Social supports & catastrophizing.

Conclusion: This study provides promising estimates for the reliability and validity of the HI-CRPS from a small sample, and supports continued pursuit of larger investigations of the measurement properties of these tools.

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The role of acupuncture in upper limb complex regional pain syndrome: a retrospective patient evaluation

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Introduction: Acupuncture is recognised as a treatment option in several chronic pain conditions. Our centre offers patients diagnosed with Complex Regional Pain Syndrome (CRPS) acupuncture as an adjunct modality to standard physiotherapy. The objective was to retrospectively evaluate the patients’ perception of outcome following acupuncture (AP) for CRPS.

Methods: Following ethical approval all patients diagnosed with CRPS of the upper limb using the Budapest Criteria who received AP were invited to complete a patient satisfaction questionnaire. Current pain intensity scores (VAS pain score [0–10]), current Sheehan Disability Scales (SDS) and questions related to clinical outcome following AP treatment (sleeping, emotional wellbeing etc.) were recorded. Demographic and clinical details were retrieved from hospital medical charts. A single physiotherapist provided all acupuncture treatments.

Results: Overall 10 patients met the inclusion criteria; 9 patients (90%) returned questionnaires for analysis (M:F = 3:6, mean age 53.3 ± 8.3 years). Typically AP was commenced 15.4 ± 10.9 weeks post injury, with 16 ± 9 AP sessions provided. Average follow-up time was 23.8 ± 14.1 months (range 2–44 months). Individuals reported being “very much better” and “quite a bit better” in terms of ability to sleep (89%), emotional wellbeing (89%), social functioning (78%) and improvements in pain intensity (78%) post AP. Current VAS pain ratings were 3.1 ± 2.4 at rest; 4.5 ± 2.4 with activity, with average current SDS ratings 11.5 ± 9.1 .

Conclusion: Despite the limitations of a retrospective design results suggest that there is a role for AP as an adjunct modality in the treatment of CRPS.

The authors have no conflicts of interest to declare.

Bilaterally reduced intraepidermal nerve fiber density on unilateral SRPS-1

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Introduction: Studies of small nerve fiber damage in CRPS-I have not included a matched healthy control group. The aim was to assess intraepidermal nerve fiber density (IENFD) in relation to thermal sensitivity of the same skin areas in CRPS-I patients and a gender- and age-matched healthy control group.

Methods: IENFD was investigated in skin biopsies from the CRPS-affected and contralateral limbs of 8 CRPS-I patients and from an equivalent site in 8 gender- and age-matched healthy controls (HCs). Thermal thresholds (cold/warm detection, cold- and heat-pain detection) were assessed on the affected limb, the contralateral limb and on the equivalent limbs of HCs, and participants rated the intensity of cold/heat and pain to static thermal stimulation (5°C/40°C) on the same limbs. The study was approved by the local ethics committee, and informed consent was obtained from each participant.

Results: IENFD was lower in both the affected and contralateral limb of patients than HCs. IENFD did not differ between the affected and contralateral limb of patients. The heat-pain threshold was lower in the affected limb of patients than in HCs, but all other thermal thresholds were similar in both groups. Patients rated the cold stimulus as colder and more painful in the affected limb, and the warm stimulus as hotter, bilaterally, than the HCs.

Conclusion: CRPS-I may be associated with bilateral small fiber damage, and perhaps small fiber neuropathy, and bilateral disturbances in thermo-sensory perception. These disturbances could stem from a systemic response to injury, or might increase the risk of developing CRPS-I after physical trauma.

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Clinical subphenotypes in complex regional pain syndrome

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Introduction: The phenotypic structure of complex regional pain syndrome (CRPS) is still puzzling. We pursued the hypothesis that CRPS signs observed by standardized neurological examination display a cluster structure allowing for alignment of patients to subphenotypes.

Methods: Clinical examination data was obtained from an evaluation cohort of N = 466 CRPS patients (mean age: 52.6 ± 13.6 years, 143 men) from the Department of Neurology of the University Medical Center Mainz. The structure among the various symptoms was analyzed using hierarchical Ward clustering. The statistically derived cluster structure was validated in an independent external cohort of N = 398 CRPS patients

(validation sample; mean age: 50.7 ± 14.1 years, 105 men) equally examined at the Departments of Neurology of the University hospitals of Erlangen and Fürth and by means of an identical clustering procedure.

Results: Four subclusters symptom structure was identically identifiable in the evaluation and validation cohorts. Subclusters #1 to #4 comprise the following symptoms subgrouping: (#1) hyperreflexia, minor injury and motor disorders; (#2) allodynia and glove/stocking-like sensory deficits; (#3) edema, skin colour changes and skin temperature changes; (#4) sweating and trophic changes. Subclusters correspond to 2 higher-order clusters resembling proposed CRPS subphenotypes: (1) CRPS with dominant central nervous system component (cluster #1 & 2) and (2) CRPS with strong peripheral inflammatory component (cluster #3 & 4).

Conclusion: The statistically uncovered CRPS subphenotypes represent 2 major pathophysiological mechanisms of (a) peripheral inflammation and (b) central maladaptive reorganization and could improve the prediction of clinical courses in this population

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Report on epidural injection of polydeoxyribonucleotide (PDRN) for CRPS

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Introduction: Transforaminal epidural glucocorticoids administration is widely performed for management of Complex Regional Pain Syndrome (CRPS) or Lumbosacral radiculopathy. However, it may worsen the condition of patient. Previous studies have been done to find out alternative agents that can replace glucocorticoids. Polydeoxyribonucleotide (PDRN) is recently noted as substitute for glucocorticoids.

Methods: A 44-year-old male patient was admitted to the our pain clinic with symptoms of low back pain with severe pain and tingling sensation of left posterolateral thigh. He has type 2 DM for which he takes Glimperide and Metformin. However, his blood glucose level was 367 mg/dL. He declined to use glucocorticoid. He was diagnosed left foraminal disc protrusion at L4-5, left subarticular disc protrusion at L5-S1, R/O CRPS. Fluoroscopically guided transforaminal epidural PDRN injections were carried out.

Results: The patient was followed-up for more than 6 months and demonstrated good improvement in lumbosacral radiculopathy without any complications.

Conclusion: This is the first successful report on epidural injection of PDRN.

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