Can complex regional pain syndrome type 1 be circumvented? A case report

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Complex Regional Pain Syndrome (CRPS) Type 1 has fascinated and intrigued clinicians and health professionals since it was first identified in Silas Weir Mitchell's observations of patients with chronic pain after gunshot wounds during the American Civil War in 1864.[1] This is due to its unusual presentation and the disproportionate spread of often severe sensory, motor and autonomic symptoms.

The types of trauma that would precipitate this condition may include contusions, fractures, sprain, skin lesions, surgery, stroke, remote trauma to the visceral domain[2]; repetitive strain injuries, immobilisation and disease. Even emotional factors, such as anger or fear may presdispose or precipitate the condition,[3] and according to Geertzen et al. stressful life events may have some significance in patients with CRPS 1.[4]

It is intended to bring attention to the early recognition of this condition, thus resulting in a positive outcome. Diagnosis is often delayed due to the resemblance to normal post-traumatic signs in the early stage of CRPS 1. If undiagnosed or unrecognised, it can lead to lifelong suffering and functional debility resulting in financial loss for patients and society.[5] Mention has been made of over-diagnosis of this condition or presentation of some but not all of the previously mentioned symptoms (pain, autonomic, motor and trophic).[6] However it is suggested that it would be best to treat any symptom/s of CRPS 1 as soon as they present themselves rather than wait for the condition to fulminate; this immediate response may thus circumvent the development of a possibly irreversible situation.

The most significant features of this condition are that the findings exceed the expected magnitude of the response to known physical damage. CRPS 1 is a painful disorder that develops usually as a disproportionate consequence of trauma. It is most commonly found in the limbs, and is characterised by:

- regional pain and sensory changes (spontaneous pain, hyperaesthesia, hyperalgesia, allodynia)
- active and passive movement disorders (including an increased physiological tremor)
- abnormal regulation of blood flow such as temperature changes and sweating (hyperhydrosis in the early stages or hypohydrosis in the latter stages)
- oedema of the skin and subcutaneous tissues
- trophic changes of skin (including changes in skin colour and thickness), organs of the skin and subcutaneous tissues.[7]

The pain and sensory changes that occur may reflect impairment in 70% of cases, and usually shows a stocking or glove-like pattern.[8] It has a tendency to spread distally and proximally, as it may involve the entire limb, and occasionally the ipsilateral quadrant of the body.[8,9,10] Recently a complex regional painless syndrome was described.[11] It has also been observed that a complaint of stiffness (although this could be ascribed to the constellation of motor dysfunctions) rather than pain, may be the prevailing symptom in a patient who manifests the other characteristics of CRPS 1.[12]

In the affected limb, the symptoms do not conform to known segmental or peripheral nerve distribution. The site of the lesion does not dictate the location of the symptoms and all symptoms may be present irrespective of the type of preceding lesion.[2] Central effects are evidenced by changes in somatic sensations (including pain), the motor system and peripheral autonomically regulated effector systems (vasculature, sweat glands, inflammatory cells etc), and it is suggested that CRPS I is a systemic disease of these neuronal systems.[13] Increased excitability in the spinal cord with repetitive transmission results in sensitisation (resulting in allodynia) of wide dynamic range neurons causing increased responsiveness to all subsequent afferent input.[14] This leads to reduction in stimulation threshold with alteration in temporal patterns and increased responsiveness, leading to expansion of receptive fields with pain and sensory impairment extending to other parts of the body.[8] Impairment of motor function in the affected extremity is thought to be a neglect-like syndrome with some evidence

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of medullary dysfunction in patients with CRPS 1.[10]

The classification of CRPS is based on a consensus between clinicians and basic scientists and is practice-based not mechanism-based. The pathophysiological mechanisms, especially the role of the sympathetic nervous system is still unclear. It is submitted that the initiating event, often a minor trauma, sensitises C-nociceptive fibres.[15] Stimulation of C-fibres can evoke an axon-reflex, an anti-dromic excitation of C-fibres which leads to the release of vasoactive agents such as substance P and calcitonin gene related peptides, which may initiate the acute stage of CRPS when increased blood flow and oedema are the predominant features.[16] The early symptoms of CRPS may be interpreted as a prolonged regional inflammation.[17] There is also some evidence of autonomic denervation in early states of the disease, as a diminished vasoconstrictive response was induced by lowering of the affected extremity which would correspond to the observed aggravation in swelling and pain.[18] It is assumed that disturbed C-fibres and connected blood vessels develop a supersensitivity to circulating catecholamines, leading to pronounced vasoconstriction. This in turn may even contribute to altered pain sensation which presents with sweaty, cyanotic or pale and predominantly cool skin, evidenced by a decreased blood flow and increased venous alpha-adrenoceptor responsiveness.[19] There is no evidence of a sympathetic hypersensitivity due to the hypothesis that in a sympathetic denervation, the concentration of plasma noradrenaline was found to be lower on the painful side.[20]

The diagnosis of CRPS 1 was initially made through identification of the symptoms described, and excludes those conditions that would otherwise account for the degree of pain and dysfunction. The symptoms that appeared were initially divided into three stages. However, according to Baron et al. 2002 individual patients do not pass through the three stages, and therefore staging was no longer a useful concept for a diagnosis of the syndrome.[21]

There are three grades – severe (with pain, vasomotor and sudomotor disturbances), moderate and mild. The latter presents the border zone between a normal response of an extremity to trauma.[8]

There is no specific diagnostic test that identifies CRPS 1, but many tests have provided information that may expose the degree of autonomic, sensory and motor disturbance that exists in these patients.

More than 90% of patients showed temperature changes with infrared thermography with the affected extremity being colder.[22] Quantitative sensory testing (QST) enables the function of the small fibres to be tested as electromyographic-nerve conduction samples only large fibre function. QST may show a typical pattern of hypothermoaesthesia to warm stimulus with reduced heat pain thresholds.[23] Veldman et al. described hypothermoaesthesia in 69% and hyperalgesia in 75% of cases.[23, 17] Quantitative sudomotor axon reflex test, resting sweat output and sympathetic skin response, tests the sudomotor involvement with sweating abnormalities being an inconstant symptom of CRPS I, occurring in 50% of cases.[17] In bone scintigraphy increased tracer accumulation typically affects the whole limb only in the early stages when increased blood flow is present.[24, 25] Typical roentgenograms may reflect spotty osteoporosis in some cases in the late stages, and magnetic resonance imaging may be helpful to differentiate

CRPS from bone marrow oedema or bone tumours.[26] There is still no direct evidence for the existence of psychological influences on the development of CRPS 1, although stressful life events were found significantly pronounced in these patients.[27]

Therapy for CRPS 1 involves a multi-modal and a multi-disciplinary approach with the main goal of all therapeutic interventions being functional restoration with specific exercise therapy. The previous terminology for this condition – reflex sympathetic dystrophy has been abandoned, following inconsistent results with sympathetic blockade, due to its unreliability in providing relief, even though initially the primary target of therapy was the sympathetic nervous system and pain relief was used as a diagnostic tool.[9] It has also been observed that some patients have sympathetically maintained pain (SMP) when responsive to sympathetic blocks, and yet others do not. Changes may occur in the same patient when the patient who was previously sympathetically maintained becomes sympathetically independent.

Many interventions as elucidated by Vacariu[8] from regional anaesthesia and neuromodulation to pharmacological treatment are used to facilitate the main aim of treatment - functional restoration typically performed by both the physiotherapist and occupational therapist such as exercise therapy, occupational therapy, manual lymph drainage, cryotherapy and transcutaneous electrical nerve stimulation (TENS).[28]

The analgesic treatment regimens include:
- pharmacological therapy: non-steroidal anti-inflammatory drugs, glucocorticoids, calcitonin, opioids, tricyclic anti-depressants and membrane stabilisers; carbamazepin, gabapentin, lidocaine, mexiletine; NMDA-receptor antagonists (ketamine); GABA-agonists (baclofen), adrenoceptor antagonists such as clonidine and phentolamine;
- topical therapy: clonidine, lidocaine, DMSA (dimethylsulfoxyde) and capsaicin
- regional anaesthetic techniques: sympathetic ganglion block with local anaesthetics and continuous conduction block of brachial or lumbar plexus
- neuromodulation: spinal cord stimulation (SCS) and percutaneous nerve stimulation (PNS).[8]

The role of some of the above pharmacological and interventional therapies may prove controversial due to insufficient numbers of evidence-based studies in some instances, adverse side effects, ineffectiveness in some patients, and inconsistent results.

Significant improvements in CRPS 1 are also obtained by psychological interventions becoming a useful part of the comprehensive multidisciplinary treatment package. The psychological pain management routine should include relaxation and imagery training assisted with biofeedback as well as cognitive and behavioural components.[29]

A case history will be evaluated and a discussion will ensue on the recent advances available and suggestions recommended for future management of the condition.

A case report of the presentation of Complex regional pain syndrome (CRPS 1) in the upper limb

A female, aged 52 years, was referred for physiotherapy by her orthopaedic surgeon after a tennis elbow release. The di-

agnosis was mild RSD and the treatment requested was for regaining range of movement and reduction of pain.

The patient had a right tennis elbow release 6 weeks previously, and presented with constant dull pain anteriorly in the shoulder with limited internal rotation and abduction, also severe pain in the elbow, burning pain in the posterior aspect of the tennis elbow injury region, mild hyperaesthesia and a sensation of 'pulling tightly' in the olecranon area with flexion of the elbow. The elbow was limited in both flexion and extension by 30 degrees, reduced supination of 10 degrees, and the patient was unable to make contact with her mouth, throat or the right side of her head. On palpation of the arm there appeared to be a fibrous tissue thickening (dystrophic changes?) of the deltoid, biceps and brachioradialis muscles. The middle finger appeared swollen and disturbed the patient at night with sharp pain and difficulty in flexing the interphalangeal joint. A feeling of the whole arm tightening and with the opposite arm also feeling 'slightly uncomfortable' was also present. The patient was anxious, miserable and desperate to improve as she was leaving for New Zealand within two weeks of her first physiotherapy appointment. She also had to travel with an invalided mother who required her physical assistance both at home and on this journey. Her pain score on the visual analogue scale score (VAS) was 9/10

The history prior to surgery was a tennis elbow that had developed immediately after playing a game of tennis over one year previously. The patient confided that she disliked playing tennis and her daughter, whom she had not seen for some time had arrived from London and had persuaded her to "play the game". The patient had received analgesic and anti-inflammatory medication and two cortisone injections into the elbow, which provided temporary relief only. When there was no change in the condition after a year, the orthopaedic surgeon decided to surgically release the tennis elbow. Prior to surgery there were no symptoms in the shoulder or hand. Other history of previous problems involved pain in the left hip and right knee that resolved spontaneously. Her normal activities included walking twice weekly for general exercise and she worked three times a week as a personal assistant.

Psychologically the patient was deeply angry that she had been persuaded to play tennis with her daughter, irritated that the injury had taken so long to respond to treatment and distressed (tearful) that her pain was worse and more extensive after the surgery.

Management
It was difficult to administer physiotherapy as she was nervous and suspicious of the treatment, thus limiting the treatment modalities available to her, especially acupuncture. She was, however, a very active person and would perform any mobilising activity necessary to help improve her condition.

She received six treatments before leaving for New Zealand.

The first treatment included
- Laser acupuncture to the ear on the areas of the ear representing autonomic, pain relief, elbow and shoulder regions
- Laser to the areas on the elbow of hyperaesthesia and the injury site
- TENS on the spinal somatic and autonomic nerve supply of the arm from cervical 2 to thoracic 6 (C 2 – T 6)
- A capsaicin derivative cream for home application and

TENS for home use. This was recommended over three days for eight hours per day from the shoulder to below the elbow region (pain site).

Subsequent treatments
The mobility had improved by 50% and the pain had reduced to 6/10. The patient was able to brush her hair and touch her neck, mouth and face. The pain in the finger had improved and swelling had reduced. There was still tenderness in the shoulder and elbow but reduced hyperaesthesia in the elbow. The tense musculature remained in the anterior shoulder and upper arm especially throughout the biceps muscle to its insertion in the forearm.

The patient was also instructed in breathing exercises, visualisation and relaxation to reduce the impact of sympathetic nervous system activity and to minimise pain and distress. She was educated as to her condition in that her nervous system had become dysfunctional and oversensitive, and that it may produce unwarranted pain and limitation. She was instructed on the use of TENS to break the pain cycle, and on capsaicin to reduce the harmful effects of substance P that may occur with stress and pain.

Normal physiotherapy continued, with four treatments, which included mobilisation of the elbow, ultrasound, massage, laser to the ear and elbow region, modified direct current therapy (APS) and active exercises.

Result
The elbow resumed almost full mobility and minimal discomfort and all the previous symptoms disappeared except that the shoulder continued to be painful and limited. The patient was given exercises to mobilise and strengthen her shoulder.

She was then referred once again by her orthopaedic surgeon after a cortisone injection into her shoulder. She presented with a painful shoulder with minimal discomfort in the elbow (-5 degrees off full extension) and the hand feeling 'tight' at times. She was referred for gentle physiotherapy for a frozen shoulder and hydrotherapy.

The patient complained of burning pain around the shoulder and limitation of shoulder flexion and abduction beyond 70 degrees and internal rotation of less than 10 degrees. She received two hydrotherapy sessions, and three physiotherapy sessions which included acupuncture to improve pain and mobility, TENS for home use, ultrasound, APS, Laser, massage and active assisted exercise.

After a poor response she was referred back to the orthopaedic surgeon at her own request for re-evaluation.

Outcome
This patient did not have a successful outcome in her shoulder, although the elbow responded positively. She probably requires months of treatment to relieve her pain and restore her shoulder to normal mobility (she may have developed a secondary tendonitis with the frozen shoulder). She was understandably impatient and irritated and believed that no amount of treatment would ease her shoulder.

The major predisposing factors for developing CRPS 1 included:
1. A long standing problem with limited shoulder/elbow mobility (disuse occurring) by maintaining a flexed elbow prior

to and post surgery, even if only temporarily. Dystrophic changes in the arm prior to the surgery may have gone unnoticed and the orthopaedic surgeon was only consulted sporadically, and therefore careful monitoring of the arm may not have been possible, or may even have gone unnoticed by the patient as being unimportant compared to the original injury.

2. The surgery itself may have contributed to the problem although there was no evidence of iatrogenic interference with the shoulder during the procedure.

3. The symptoms of distal pain referral from the elbow into the middle finger, burning pain and hyperaesthesia of the elbow, fibrous tension in the upper arm musculature, severe limitation of movement of the elbow and the shoulder (pain/dysfunction moving proximally), tightening sensation in the whole arm and some discomfort in the opposite arm. (According to Bruehl and Chung, objective signs of CRPS 1 such as skin temperature and colour changes are often phasic rather than tonic, resulting in patient-reported symptoms that may not be observed at the time of the physical examination.[29])

4. The patient's nature and attitude. She was initially distressed that the elbow problem had become prolonged, and that it was not responding to the usual regimen of treatment. She was also disappointed that the operation did not 'fix' the problem. As previously mentioned the patient had emotional issues with her family compounded by having to travel a great distance with a painful arm. The patient was anxious and impatient in nature, with an attitude that may interfere with the execution of recommended treatment protocols due to fear, disbelief in the veracity of treatment, anger at the inability to heal and a desire to restrict treatment when results were not obtainable in a specific period. According to Fernandez, anger may precipitate or predispose an individual to pain, exacerbate pain, become a consequence of pain or even perpetuate pain.[30]

According to Bruehl and Carlson, certain uncontrolled studies have often reported psychological factors to be an apparent contributor to the onset of CRPS 1.[31] Despite the absence of definitive studies, theoretical mechanisms exist through which psychological factors might affect the development and maintenance of CRPS 1. Charney DS et al. and Light KC et al. found that life stress and dysphoric emotional states (anxiety, anger and depression) are associated with altered catecholaminergic activity and through this mechanism could interact with pathophysiological processes.[32,33]

Discussion

It is now well accepted that early recognition will prevent CRPS 1 from developing and will also facilitate a positive response to treatment. It therefore becomes incumbent upon all the health professionals observing or treating patients who may have sustained a peripheral injury or trauma, or even having a prolonged pain in any area of the body, to be aware of the symptoms of CRPS1 and its consequences.

Treatment must focus on pain control and functional restoration.

Initially pain control should commence with anti-inflammatory and analgesic medication and a trial of TENS to break into the pain cycle.

- The anti-inflammatory aspect of treatment is necessary due to the supposition that neurogenic inflammation is a relevant pathogenic factor.[34,15] Injury of C-nociceptive fibres releases vasoactive substances such as substance P and calcitonin-gene related peptides in the acute stage of CRPS when increased blood flow and oedema are the prominent features.[18,16]

- TENS (Transcutaneous Electrical Nerve Stimulation): there is empirical evidence that TENS-therapy may be helpful for CRPS.[35] Recent research indicates that the most likely mechanism for pain control with TENS is the activation of segmental inhibitory circuits in the spinal cord.[36] These are supplemented by descending inhibitory pathways sending descending inhibition to the spinal cord and periphery.

There are patients that may be referred to as "complete TENS responders". Judging from clinical experience and a study , it seems that at least 10% of patients, especially those with a condition that is pain-driven (possibly neuropathic) may achieve a 100% improvement in their pain and condition.[37] With the correct positioning, frequency and duration of treatment with TENS, this figure may even reach 30%. It may appear that 10% to 30% of patients are a small number of patients, but if only two or three treatments of TENS are necessary to attain complete pain relief, this result is indeed excellent.

Patients who do not respond completely to the TENS may be the "partial TENS responders". These patients may achieve 60% to 80% relief from their pain. Because pain is decreased and quality of life is improved, TENS may be considered another useful coping mechanism and it may also result in the reduced use of medication. It is probable that 20% of patients may have no pain-relieving response to TENS. This is a relatively small number so it is considered worthwhile to give every patient a trial of TENS.

Children also respond particularly well to TENS. A study by Stilz indicated successful treatment with TENS of unrelenting pain as a result of reflex sympathetic dystrophy in children.[38]

Most of the previous research recommended that TENS be used at "high" frequencies of between 50 and 80 Hz, or between 70 and 150 Hz, for a period of 20 minutes. Recently, however, many researchers have examined the value of using higher frequencies (above 150 Hz) and for longer periods (at least 40 minutes), for greater effectiveness.[39]

Research also indicates that, in certain circumstances, patients may lose their responsiveness to TENS, due to tolerance of the endogenous opioids that are released with this therapy.[40] This may take place after three days, is less noticeable with high frequency TENS than low frequency and may be reduced by concomitant administration of other analgesics. It is also noted that the tolerance may be reduced if TENS is discontinued after three days and reinstated after another three days. Intermittent periods of TENS may then become more effective.

Patients who have been on consistent administration of morphine may not respond to TENS without modification of their drug regimen to accommodate TENS.

Other substances, such as cholecystokinin octapeptide (CCK-8), are widely distributed throughout the nervous sys-

tem and may impact upon endogenous endorphin-modulated analgesia by blocking the effects of morphine or TENS. New studies will investigate the administration of CCK-8 antagonists in combination with TENS and/or acupuncture to improve the efficacy of these treatments.

TENS may however aggravate symptoms when central pain mechanisms are involved, especially when dynamic mechanical allodynia is present.[41,42]

Other treatments

- Electrical current like other physical modalities e.g. ultrasound, can lead to depletion of substance P and other vasoactive substances, but it must be used with caution to prevent irritation and increased sensitisation.[43]
- Heat and cold may also prove valuable in the treatment of CRPS 1 but as hypersensitivity to heat (increased blood flow and oedema) is one of the most consistent symptoms in patients with acute CRPS 1, heat should be avoided initially.
- Cryotherapy may provide substantial pain reduction but tissue temperature should not be lowered more than 16 degrees centigrade to avoid the hunting reaction of a vasodilatation in response to cold.[44]
- Acupuncture: many studies have indicated that acupuncture may be valuable for relieving pain by the following mechanisms:[45] activation of the serotonergic system in the brain and spinal cord; stimulation of the synthesis and release of norepinephrine (NE) in different areas of the central nervous system, with a depletion of this substance occurring simultaneously in other tissues. Acupuncture is capable of releasing beta-endorphin in the brain, as well as dynorphin and enkephalin in the spinal cord. The frequency of acupuncture stimulation has been found to stimulate different substances. Therefore, different frequencies will produce different substances in different areas of the nervous system. According to Lundberg, acupuncture excites receptors or nerve fibres in the stimulated tissue which are also physiologically activated by strong muscle contractions and the effects are similar to those obtained by protracted exercise.[46]
- Exercise therapy is difficult to execute due to alterations of central processing in CPRS 1 patients. Thus regimens must be found that do not increase pain and sensitisation. Aggressive or passive range of motion exercises should be avoided.[8] Initially the patient and therapist must form an alliance that engenders trust and confidence that pain will not be increased and that activity is the only way that improvement will occur. Due to pain and tactile hyperaesthesia it may be necessary to commence therapeutic exercise on the opposite side of the body and a mirror may be helpful to stimulate visual-motor acuity. Active assisted exercises and hydrotherapy are encouraged to restore the whole range of motion and provide the patient with confidence. Research has verified that pain perception is altered after exercise probably via non-opioid mechanisms.[39,12] Pain relief is dependent on exercise duration, regularity and water temperature. Thus exercising in warm water relieves pain and has anti-depressive actions.[12] Active assisted exercise can also be combined with proprioceptive neuromuscular facilitation techniques[47], postural normalisation, stabilisation and balanced use of the limb. Biofeedback techniques may also prove helpful.[48] Oedema thought to be caused by high hydrostatic pressure due to venoconstriction, and capillary membrane leakage can be influenced by elevation of the affected limb and manual lymph drainage may restore normal sensation to tactile stimuli and has some benefit in reducing pain.[49] According to Mucha, CO_2 baths with a cool temperature have also been of benefit in the early treatment of CRPS 1, and could reduce swelling and pain, as compared with a control group.[50]

- Occupational therapy: Normalisation of function in the affected limb is the primary goal of the occupational therapist. Initially, desensitisation training should be commenced using coarse textures for massage and proprioceptive challenges that include scrubbing and weight bearing.[8] Splinting overnight may be useful in the beginning, but casting or splinting that results in immobility is counterproductive. When improvement occurs, dynamic splinting may sometimes be necessary to regain a complete range of motion.[46] As improvement continues, special training for vocational rehabilitation is commenced including progressive stress loading and work hardening .[28]

- Psychological intervention: Psychological factors may, both in theory and from experimental evidence, be more directly involved in the onset and maintenance of CRPS 1, due to the neurochemical sequelae of psychological and emotional stress interacting with the pathophysiological mechanisms involved in this condition. Bruehl S, et al. showed a significant correlation between emotional distress and pain intensity in CRPS patients.[51] There is also evidence shown by Arena JG, et al. and Affleck G, et al. that dysphoric mood states directly exacerbate pain intensity in various other chronic pain syndromes.[52,53] In a study, Moseley found that when 'training the brain' in CRPS 1 patients, it is important to activate the premotor followed by the primary motor networks, to reduce pain.[54] Significant symptom reduction was observed in a small group of 12 male patients through regular performance of 'virtual', followed by imagined, and then mirror movements. Virtual movements involve recognition of the laterality of pictured hands. Both virtual movements and imagined movements are thought to activate cortical motor networks, but do not involve movement of the affected limb. Imagined movements alone, in this study, were not found to have these effects. The conclusion from this astounding therapeutic approach is that the sensory, motor and autonomic changes in these chronic CRPS patients are maintained by the central sensorimotor mismatch, and that these changes can be reversed by training the brain.[55] Another aspect of psychological intervention is to expose the patient to feared activities by graded activities and in vivo exposure, if fear avoidance is a high concern for the individual patient.[56] Fear avoidance suggests a direct effect of learning processes resulting from increased physiological activation, which may be especially marked at the site of an injury.[57] Thus exposure to the feared event ,or moving a painful region with graded activity and a controlled supportive environment may reverse these physiological changes. Explanation is another important route to pain relief as patients' who have understood their condition (sensitisation of the nervous system) and the importance of improving control and mobility will be more at ease and relaxed (reduced muscle tension), less stressed

and their endogenous opioid mechanisms may be more accessible and this may facilitate pain relief and improvement in function.[58]

Conclusion

All post-trauma/injury patients, and those with chronic pain conditions, should be viewed critically to evaluate early signs of CRPS 1. Once the diagnosis has been identified as CRPS 1, even in a mild form that is within the border zone between a normal response of an extremity to trauma, the condition should be treated immediately, to relieve pain and restore function. Any treatment that aggravates the condition must be discontinued, due to it being counter-productive and possibly causing exacerbation of the condition.[8]

Finally, close integration of psychological assessment and cognitive-behavioural pain management treatment with medical, physical and occupational therapies, is likely to optimise treatment outcomes. Evidence is accumulating that there is interaction between central and peripheral mechanisms.[59,60,54]

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