**Potent Efficacy**

Potent, effective relief of pain and inflammation

**Comparable Safety**

Comparable tolerability and safety profile with balanced COX-1/COX-2 inhibition

**Multiple Solutions**

Range of formulations for flexible dosing to suit patient needs

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**References:**

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2. XEFO 8 IV/IM Injection South Africa Package Insert, October 1998.
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Editorial

Editor:
Dr Pauline du Plessis
Anaesthetist
Olivendale Clinic
Randburg, Johannesburg

It is with great excitement that I am writing this editorial. This is the first edition of our pain newsletter. The aim of this newsletter is to discuss practical issues on pain and pain management. Each pain topic is discussed from an academic point, but the authors also brought in practical points that will help us in the management of our pain patients. Therefore you will see that each article comes with a take home message.

There is no other symptom that binds all the medical fraternities as much as pain. Pain is a symptom across all specialities. It is probably the one symptom that binds us all. Many pain conditions cannot be treated in isolation, but involves a general practitioner and a specialist. It crosses all fields of medicine and needs a true interdisciplinary approach, involving doctors, physiotherapists, occupational therapists, psychologists and more.

Therefore I am focusing in this editorial on the multidisciplinary face of pain. Many doctors treat patients segmentally and only focus on their anatomic ‘speciality.’ Pain encourages us to talk to each other as health care professionals. Otherwise our patients will not get better.

This is clear if you look at the wonderful compilation of authors we have for our first issue. Dr Fourie sheds some light on the abstract concept of neuropathic pain. She gives us a few practical tips on how to diagnose it accurately and discusses the neuropathic pain treatment guidelines.

Neuropathic pain can also be experienced by cancer patients and is often mixed with nociceptive pain. Dr Naicker gives an excellent review of this complex topic.

Muscular pain is probably one of the most common syndromes we see in practice. It rarely stands alone, but can be part of a musculoskeletal or myofascial pain syndrome. Muscular pain contributes to most painful conditions and we give a few guidelines on how to diagnose and treat it in this issue.

We also discuss the difficult issue of complex regional pain syndrome (CRPS), where Dr Madden gives a comprehensive summary of which treatments might work for CRPS. Again in this condition, we cannot underestimate the power of the different doctors and the physiotherapist working together.

I want to thank Takeda and the authors and the publishers who made our first issue possible. I also want to thank you, the reader to take time out of your busy practice to read on this ever present, all encompassing topic of pain.

Pauline
How important can a muscle be?

Dr Pauline du Plessis
Anaesthetist
Olivedale Clinic
Randburg
Johannesburg

Pain is such a severe and debilitating symptom that we always believe it should come from a very important structure. These structures are mostly bones, joints and ligaments. We forget that a tender muscle or a muscle spasm can cause a range of painful syndromes that could easily be treated.

Because of this, interventions in theatre for pain relief can frequently be unsuccessful. Many interventional procedures addresses painful joints and bones, but painful muscle groups are not addressed. Therefore a patient might return to your office after an interventional pain procedure (like facet joint, sacro-iliac joint or other injections), with severe spasms in a specific muscular group. Simple trigger point injections of these muscles or guided stretching and exercises by a skilled physiotherapist will then give the patient the full relief of the specific pain procedure.

This review will focus on painful muscle conditions, but since this is a very large topic, I will focus on the classification of muscular pain and myofascial pain syndrome

Classification of soft tissue pain disorders
Soft tissue pain disorders can be divided into localised, regional and generalised categories.

Localised soft tissue pain conditions (STP)
Most of the localised conditions are believed to result from repetitive mechanical injury to inadequately conditioned tissues.

They tend to be named anatomically and are disclosed by a typical history plus the exquisite tenderness elicited by digital palpation of the affected structure.

Structures affected in localised soft tissue pain disorders:
- Bursitis (subacromial, olecranon, trochanteric, prepatellar)
- Tendinitis (biceps, supraspinatus, achilles)

Regional STP conditions are limited in anatomic scope to a region or body quadrant. This category includes the following:
- Myofascial pain syndrome (MPS). This has the potential to involve any muscle of the body. Common syndromes involves the trapezius, piriformis and iliopsoas muscles
- Myofascial pain dysfunction syndrome (MPDS). This involves myofascial pain of the muscles of mastication
- Complex regional pain syndrome
- Nerve entrapment syndromes (carpal tunnel, tarsal tunnel, sciatica from piriformis muscle syndrome)
- Pain referral syndromes. This includes pain referred from visceral structures or joints to soft tissue regions e.g. referral from angina, abdominal pain referral patterns

Generalised STP conditions
- Fibromyalgia syndrome
- Hypermobility syndrome
- Polymyalgia rheumatica (painful shoulder and pelvic girdle)
- Statin induced myalgia

How to approach this type of patient
1. Firstly, it is very important to make a diagnosis. Anatomical location is of extreme importance. Some of the diagnoses are diagnoses of exclusion. Red flags should be excluded. It is very important to know that even a skeletal problem, usually affects the muscles as well. Therefore the muscular component is of much greater importance than we usually anticipate.
2. Pain localisation is poor in deep tissue, and it is difficult to differentiate pain arising from muscles, tendons, ligaments and bones as well as from joints and their capsules
3. History and examination is of prime importance. Search for trigger points if you suspect a muscular problem
- Trigger points are hyperirritable localised taut bands of skeletal muscle that produce characteristic referral patterns. A trigger point may occur in isolation or concomitantly with myofascial pain syndrome or pain generating syndromes. Affected muscles are painful on resistance to movement as during manual muscle strength testing. Trigger points and severe muscle spasms usually cause a referred pain in a “reference pain zone”. A muscle with a trigger point can twitch with pressure or when a needle is inserted into the muscle
- Trigger points are not to be confused with tender points commonly present in patients with fibromyalgia in which pressure in the tender points cause pain but no distant reference zone
- Special investigations can be done, but remember that only an ultrasound and magnetic resonance imaging can show soft tissue lesions. Other investigations like nerve conduction studies for nerve entrapments and nuclear medicine scans to find areas of inflammation can also be helpful
The rest of the review will focus on myofascial pain syndrome specifically.

**What is myofascial pain syndrome (MPS)?**

MPS refers to pain and presumed inflammation in the body’s soft tissues or muscles. MPS is a chronic, painful condition that affects the fascia and muscles. It may involve either a single muscle or a muscle group.

**Proposed pathogenesis of MPS**

Authors have suggested predisposing factors and initiating events, such as body asymmetry, poor posture, mechanical stressors, nutritional inadequacies, endocrine dysfunctions and psychological factors as causes for MPS.

Exploration of the trigger point using needle electromyography in a rabbit model of MPS and in symptomatic humans has led to the finding of spontaneous electrical activity (SEA).

The trigger point is a spinal reflex that could involve the muscle spindle and neuromuscular junction within the muscle, spinal cord and radicular nerves that connect the muscle to the cord.

The most dramatic demonstration of objective abnormalities in MPS has come from microanalysis of interstitial fluid samples obtained from human skeletal muscle trigger points. The concentrations of proteins, bradykinin, calcitonin gene-related peptide, substance P, tumor necrosis factor α, interleukin-1β, serotonin and norepinephrine were found to be significantly higher in this fluid. Local ischemia is suggested by a lower than normal pH in the region of the trigger point. It is this ischemia that is responsible for the lack of removal of waste products and the build-up of inflammatory mediators.

**What are the symptoms of myofascial pain syndrome?**

MPS symptoms usually involve muscle pain with specific trigger points. The pain can be made worse with activity or stress. MPS can often refer to specific areas. In addition to the local or regional pain associated with MPS, people with the disorder can also suffer from depression, fatigue and behavioral disturbances.

**How is myofascial pain diagnosed?**

Kellgren injected muscles in 1939 with hypertonic saline and mapped the locations of the resulting zones of pain reference. Since then the diagnosis of MPS has been a contentious issue.

The implications of the active trigger point are that the examiner should expect to find spot tenderness with deep palpation over the trigger point, leading to the patient’s recognition of the induced discomfort as a familiar pain, and concomitant referral of pain to a zone of reference that is fairly predictable for irritation within the affected muscle.

A latent trigger point is defined as one for which there is no current experience of spontaneous pain, but pain is still inducible by manipulation of the trigger point. Clinicians who are skilled in diagnosing MPS must have a phenomenal knowledge of neuromuscular anatomy and function. A challenge in diagnosing these painful muscular groups accurately is the issue of excessive adipose tissue.

**Validity of examination findings for documenting the myofascial pain syndrome**

- Tender spot (trigger point) in an affected muscle
- Referral of pain to a zone of reference
- Reproducing the patient’s usual pain

**Management approach to MPS**

The use of a systematic, comprehensive, multidisciplinary approach is necessary. Predisposing and perpetuating factors should be identified. Both physical modalities and medications are used to treat these conditions.

A simple physical intervention involves repeatedly applying a cold spray over the trigger point in line with the involved muscle fibers, followed by a gentle massage of the trigger point, with stretching of the affected muscle. This also presents a teachable moment for patient education, because the patient can learn to abort progression of future attacks at an early stage by applying his own local stretch and massage. However, this approach is more readily applied to a superficial muscle, such as the trapezius fibers around the neck, than for a more deeply positioned muscle, such as the piriformis or iliopsoas muscles.

The skills of an experienced physiotherapist can be used to teach better posture, body mechanics and relaxation techniques and to provide trigger point massage.

Tobacco use and caffeinated beverages should be discontinued. Caffeine and nicotine are stimulants and have been found to irritate the muscles.

Centrally acting skeletal muscle relaxants (SMRs) are frequently prescribed. Studies have suggested that these drugs are effective, have tolerable side effects and can be an adjunct in the treatment of painful musculoskeletal conditions with
Two additional drugs with muscle relaxant effects may be useful in the treatment of the pain patient, specifically the benzodiazepine, diazepam and the antispasmodic agent, baclofen. Baclofen is a chemical analog of GABA, which is an inhibitory neurotransmitter.\(^5\)

A more invasive approach to therapy is local injection or dry needling of the trigger point. After the symptomatic trigger point has been identified, small amounts of local anaesthetic can be injected into the muscle using short jabs of the needle into the location of the trigger point.\(^1\)

With dry needling, the effectiveness of the needling procedure is explained by local structural damage to the trigger point, caused by repeated passes of the needle. Typically, several local needlings over a period of weeks or months are required to achieve a cure.

Some have found additional usefulness in the injection of botulinum toxin, but others have failed to demonstrate a significant effect in controlled clinical trials.\(^1\)

**Medication that can be injected into trigger points**\(^3\)
- Lignocaine, mepacaine, ropivacaine
- +/- corticosteroid (dexamethasone, triamcinolone, methylprednisolone)
- The purpose of adding corticosteroids is to treat the local inflammation in the trigger point
- Botulinum toxin A

**Technique of trigger point injections**\(^3\)
- Identify and mark with sterile marker the trigger point locations as well as the most painful area within the trigger point
- Spray the taut band with ethyl chloride
- Feel the needle advancing through skin, subcutaneous tissue, normal muscle, and contacting the trigger point
- After negative aspiration of blood, fluid or air inject a total of 3 ml of solution per trigger point
- A gentle massage can now be done in the area
- The success of the procedure is dependent on the diagnosis and localisation of the trigger point\(^1\)
- Patients with chronic widespread pain or psychological disorders may be less likely to respond to trigger points

**Post-injection instructions**\(^3\)
- No heavy activity or exercise except for gentle stretching on the day of the procedure and apply heat to the injection site for 15 minutes for 2-3 times per day
- Give the patient a post injection stretching and stabilisation

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\(^5\) The most common centrally acting muscle relaxants used in South Africa is cyclobenzaprine hydrochloride, methocarbamol and orphenadrine citrate. When SMRs are used in combination with an analgesic, pain relief is superior to that of either drug alone. Thus it is worthwhile to use a centrally acting muscle relaxant such as cyclobenzaprine hydrochloride with a non-steroidal anti-inflammatory drug or a selective COX2 inhibitor. By giving the patient a muscle relaxant and an anti-inflammatory drug together it addresses the spasm itself and the inflammatory component of the spasms. This treatment can only be done for a limited period, but if it is successful, it can be repeated in a patient with frequent severe muscle spasms.\(^5\)

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**Anatomy of a trigger point injection**
(https://www.fairview.org/HealthLibrary/Article/83753)

**Common dorsal trigger points**
(https://www.fairview.org/HealthLibrary/Article/83753)
programme and education on proper posture, spine mechanics and ergonomics. It is here where the support of a good physiotherapist is very valuable.

Potential complications
- Infection, bleeding, reaction to the medications used, vasovagal reaction, injection site pain (temporary flare up), intravascular injection or more serious complications such as pneumothorax
- If using steroids be aware of potential skin depigmentation changes and possible skin atrophy particularly on thin patients and with superficial muscles
- Vertebral and carotid artery injections with even low volume of local anaesthetics can cause seizures and death
- As with all interventional procedures, it is important to use caution and carefully weigh the risks and benefits of the proposed procedures

Contraindications
- Infection, systemic or local
- Coagulopathy
- Distorted anatomy
- Patient refusal

Lastly I want to mention the exciting and ever-expanding diagnosis of peripheral nerve entrapments.

Peripheral nerve entrapments: general principles
- An entrapment neuropathy is defined as a pressure-induced injury to a peripheral nerve in a segment of its course due to anatomic structures or pathologic processes.
- Peripheral nerve entrapment occurs at anatomic sites where the nerve changes direction to enter a fibrous or osseofibrous tunnel, or where the nerve passes over a fibrous or muscular band, and that entrapment occurs at these sites because mechanically induced irritation is most likely to occur at these locations
- Many of the trigger point pathologies entrap nerves, such as the greater occipital nerve by the trapezius muscle, the axillary nerve within the quadrangular space and the sciatic nerve by the piriformis muscle. In these syndromes, treatment of the myofascial spasm will result in release of the entrapment

Conclusion
Recognition of the potential myofascial contribution to pain conditions could decrease misdiagnosis and therefore ineffective treatments. We should remember to examine our patients every time we see them. Even if a patient has a known skeletal condition, the muscular component could be a major contributor to the patient’s pain.

References
Going beyond the pain threshold
Continuing Medical Education

We are all, on a daily basis, confronted by patients presenting with pain. Treating the patient with acute pain is mostly easy, as the reason for the pain is easily visible or easily diagnosed. It is the patient with chronic pain that can make life difficult, as these patients come back again and again, leaving us as physicians with our hands in our hair. According to statistics, chronic pain is among the most common reasons patients seek medical attention\(^1,2\) and it is thought that approximately 20% of the adult population has suffered from chronic pain, with over 5% experiencing severe, disabling pain.\(^3,4\) According to the International Association for the Study of Pain chronic pain is defined as any pain persisting longer than expected. The history in the patient with chronic pain is often difficult, with complex etiology, and these patients do not respond to conventional pain management. Most often their quality of life is severely affected, making them depressed and miserable.

Chronic pain falls in one of two categories. Nociceptive pain is caused by damage to body tissue, usually described as sharp, aching, or throbbing. On the other hand, neuropathic pain occurs when there is actual nerve injury or malfunction, affecting the nerves connecting the brain with the skin, muscles and internal organs. Both the central and the peripheral nervous system is involved in this type of pain.\(^5\) This article will focus on the diagnosis and management of chronic, neuropathic pain.

### Neurobiology of pain\(^6\)

Injury to the nervous system results in maladaptive plasticity, which severely alters the function of the somatosensory system at multiple levels, from the peripheral nervous system all the way to the cortex. How we experience pain is a combination of nociception and higher brain activities, through combination of central and peripheral sensitization.

<table>
<thead>
<tr>
<th>Central neuropathic pain</th>
<th>Peripheral neuropathic pain</th>
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<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>Diabetic peripheral neuropathy</td>
</tr>
<tr>
<td>Stroke</td>
<td>Post herpetic neuralgia</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>Complex regional pain syndrome</td>
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</tbody>
</table>

- The noxious stimuli in the periphery is conveyed in the sensory pathway through the dorsal horn, via the thalamus, to the somatosensory cortex. This discriminatory pathway carries the information regarding the intensity and the site of the painful stimuli.
- A second pathway projects via the brainstem to the thalamus and the limbic structures. This emotional pathway leads to the unique experience of pain.
- The information of these two pathways are combined in the periaqueductal gray, and the sensation of “pain” is now experienced.
- The amygdala integrates sensory and cognitive input, also playing a role in mood, anxiety and fear, strengthening the idea that pain disorders are related to anxiety and mood disorders.
- Neurons, at first, fire in a frequency proportional to the intensity of the stimulus. There are numerous neurotransmitters that can be released at the level of the dorsal horn. These neurotransmitters can modulate the perception of pain.
- Repetitive or strong action potentials can lead to excessive release of neurotransmitters, excessive stimulation of the postsynaptic neuron, and therefore the experience of excessive pain.
- There are also descending pathways, noradrenergic and serotonergic in nature, that inhibits the neurotransmitter release. A deficiency in this pathway may lead to chronic pain.
- Central sensitisation lead to a lower stimulus threshold to evoke pain.
- On the other hand, peripheral sensitisation can lead to the sensation of pain in the absence of a painful stimuli with hypersensitivity to stimuli (chemical, thermal, mechanical). This can also be a reason for ongoing pain in the chronic pain patient.
- When the neurons in the dorsal horn increase their response to repetitive noxious stimuli, there is an increased perception of pain due to wind-up of these nociceptive neurons.
- Wind-up can also occur when one’s own neurons exaggerate their response where the sensory input is occurring.
- Longstanding chronic pain can cause changes in the brain, with gray matter decrease, and this can correlate with a decreased endogenous inhibition of pain. It can also be linked to symptoms such as forgetfulness, sensory overload, a decreased ability to process information and difficulty following a conversation.
What does this mean in practice?
It seems as if a mixture of genetics and environmental factors play a role in chronic pain.7 Chronic pain symptoms can therefore increase with increasing number of life experiences of stressful or painful stimuli. A big problem with neuropathic pain disorders are that they are generally progressive. If this cycle is not stopped, the changes discussed above can lead to new symptoms and even treatment resistance. Early and accurate diagnosis is therefore of utmost importance to prevent or halt this maladaptive process, and to increase the chance of a positive outcome.

Clinical features of neuropathic pain8
The painful symptoms include both evoked pain and spontaneous pain (continuous or paroxysmal). Common terminology to describe this pain or unpleasant sensations (dysaesthesias) including burning, shooting, stabbing and an electric shock-like pain. Tingling and pins and needles describe a sensation that is not unpleasant (paraesthesias), and stimulus-evoked pain is described as alldynia and hyperalgesia.

How do you make the diagnosis of neuropathic pain?9,10
When a patient presents with chronic pain, a proper history is important, followed by a clinical examination. Special investigations might be indicated in some patients. You must be able to answer two questions after the consultation:

1. Where is the lesion? (peripheral or central, plexus, nerve root, cerebral hemisphere)
2. What is the lesion? (diagnosing causative disease or event)

The use of screening tools assists in the identification and classification of neuropathic pain. The DN4 Questionnaire11 was developed to differentiate between nociceptive and neuropathic pain, and is easy to use in a busy practice.

Motor examination includes power, tone and evaluation of the tendon reflexes. Proper sensory testing at the bedside can be done with basic tools, ie. cotton wool, wooden cocktail stick, cold and warm object, and a tuning fork. Grade the response to each stimulus as normal, increased or decreased. Compare site affected with contralateral side, or a more proximal site. Remember to test the cranial nerves and look at the autonomic system (temperature and colour of the skin and sudomotor function).

You cannot treat the patient with neuropathic pain without gaining more information on their psychosocial status. Ask specifically about sleep, comorbidities, impairment in work, family and social life, mood disorders and anxiety associated with the pain condition.

Treatment of neuropathic pain
The management of patients with chronic neuropathic pain remains a challenge.12 Optimal patient outcomes and improvement of the pain often only results by combining multiple approaches, including pharmacologic, physical medicine, behavioural medicine, neuromodulation, interventional and surgical approaches.13,14

The South African guidelines on the management of neuropathic pain gives a clear, stepwise approach to the management of these patients.15

![Figure 1](image1.png)

**Figure 1**

![Figure 2](image2.png)

**Figure 2**
The choice of treatment should address the possible pain mechanisms as well as the comorbid conditions associated with pain (sleep disorders, anxiety and depression). It should also take into consideration the efficacy and side-effect profile of each drug.

Proper patient education is a crucial aspect in the management of the patient with neuropathic pain. They should clearly understand the mechanisms of this pain, and have realistic goals of treatment. In most analgesic effect takes time, and a complete relief of pain is unrealistic. Non-pharmacological management should be included in the management plan, and education on the importance of stress reduction and a good sleep hygiene cannot be overemphasized.

**References**

11. Bouhassira D, Attal, Alchaae H et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005;114:29-36. This questionnaire has been reproduced with permission of the IASP.

**Take-home message**

- Neuropathic pain is a condition than can result in severe suffering, disability and reduced quality of life.
- This condition has an enormous impact in the patient’s ability to work, their social life and the lives of the family.
- Early diagnosis is of utmost importance.
- Differentiate between nociceptive and neuropathic pain.
- Reduce this burden in your patient by providing early appropriate and effective therapy.
Going beyond the pain threshold
Continuing Medical Education

Like pain affecting non-cancer patients, there is much heterogeneity in how pain manifests, and how it is experienced in patients with cancer. It is a complex symptom that affects daily activity, physical functioning, emotional and psychological wellbeing, and social life. As many as one third of patients receiving anti-cancer therapy, and two thirds of patients with advanced cancer, will require treatment for pain. Like all syndromes in medicine, an exact diagnosis is essential for successfully managing pain in cancer patients.

In this article I will briefly look at the different pain syndromes in cancer, touch on a simplistic approach to pain management, and review neuropathic pain.

Cancer pain can be divided into acute and chronic pain syndromes, and the main backbone for managing these is drug therapy. Within a short space of time most pain can be controlled. One dilemma in cancer patients though is the exacerbations in pain or new pain which may be interpreted as progression of disease. Therefore, anxiety often coexists and may even aggravate the perception of pain. Thus treating the cognitive and somatic aspects of pain is vital.

Acute pain syndromes
Acute pain syndromes are usually iatrogenic, related to a diagnostic test or to a therapeutic intervention, for example, intercostal drain insertion for a recalcitrant pleural effusion, lumbar puncture, and a bone marrow biopsy. However, some may be directly related to cancer itself. Examples here include haemorrhage into a tumour, pathological fractures, hollow organ perforation, herpes zoster and post herpetic neuralgia, and pain related to blood clots.

Acute pain may also be related to anti-cancer therapies (chemotherapy, immunotherapy, endocrine therapy, and radiation). Oral mucositis is the most common in this category and may extend throughout the entire gastrointestinal tract. Acute neuropathies may complicate therapies with platinum-based drugs or vinca-alkaloids, and plexopathies and enteritis may complicate radiation therapy. Most radiation complications are self-limiting; with newer methods of radiation therapy substantially reducing the incidence of these.

Chronic pain syndromes
These include nociceptive (somatic and visceral), or neuropathic pain that may be due to direct effects of the malignancy or secondary to treatment. Examples include the pain of bone metastases, and direct extension of tumour into nerves or soft tissue. Other causes of chronic pain in cancer patients are antineoplastic treatments and disorders unrelated to the disease or its treatment.

Management of cancer pain
The WHO guidelines for cancer pain are widely accepted as it provides an easy-to-use stepwise approach to pain control. Essentially, pain management should be simple to administer (oral/transdermal), and should be given timeously depending on the drug’s half-life (“by the clock”) rather than “on demand”. It was based upon pain intensity and opioid strength, and combining opioids and non-opioids. One of the biggest drawbacks of these guidelines is that it fails to take into account the underlying mechanisms of the aetiology of pain. This is easily transgressed by a combination of the simplicity of the WHO ladder and approaching the respective pain mechanism.

Assessment of pain should be ongoing, titrating drug doses, or using adjuvant therapies to achieve resolution of symptoms. This can be achieved by employing the Visual Analogue Scale, the Verbal Rating Scale, or a Numerical Rating Scale. Patients should always be informed of the possible onset of pain during their treatment and during the course of their disease. Communication between the patient and physician/nurse is essential in achieving adequate pain management, and involving the patient in pain management may have a beneficial effect on the patient’s pain experience.

Figure 1. Pain ladder

Dr Poobalan Jason Naicker MBBCh FCP(SA)
Oncologist
Parktown
Johannesburg
WHO step I
Non opioids are prescribed for mild pain. The majority of patients describe a ‘stabbing’ quality to their pain and are able to easily localise the site. The non-steroidal anti-inflammatory drugs (NSAIDS) such as ibuprofen, etoricoxib, and lornoxicam, and paracetamol are effective when nociceptive pain is predominant (usually musculoskeletal). Pain from bone metastases may also benefit from NSAIDS. As with all NSAIDS, the risk of renal dysfunction and gastrointestinal tract (GIT) bleeding must be taken into account and needs to be weighed against the benefits individually. These should be prescribed with a PPI if there is a moderate risk of GIT bleeding. In general, the different NSAIDS should not be combined though in some settings NSAIDS may be used with paracetamol.

WHO step II
The Step I drugs are chosen for mild pain. However, the majority of cancer patients need additional analgesics, in particular when the disease progresses. In cases of moderate pain, weak opioids should be used (codeine, tramadol). Traditionally, patients with mild–moderate pain have been treated with a combination product containing paracetamol, an NSAID plus a weak immediate-release opioid such as codeine, dihydrocodeine, tramadol³.

The use of drugs of the second step of the WHO ladder has several controversial aspects. The first criticism concerns the absence of a definitive proof of efficacy of weak opioids: in a meta-analysis of data reported from clinical randomised controlled trials⁵, no significant difference was found in the effectiveness between nonopioid analgesics alone, and the combination of these with weak opioids. The available studies do not demonstrate a clear difference in the effectiveness of the drugs between the first and the second step⁴. Uncontrolled studies also show that the effectiveness of the second step of the WHO ladder has a time limit of 30–40 days for most patients and that the shift to the third step is mainly due to insufficient analgesia achieved, rather than to adverse effects⁶. A further limitation in the use of weak opioids is represented by the ‘ceiling effect’, for which more than a certain threshold of dose cannot increase the effectiveness of the drug, but only influence the appearance of side effects. As a result, many authors, and the European Association for Palliative Care have suggested that strong opioids in lower doses (morphine ≤ 30 mg, oxycodone ≤20mg) be combined in Step II with the non-opioids.

WHO step III
Opioids are essential in treating cancer pain, and for many years, morphine has been the gold standard. Evidence on and the use of other opioids has evolved over the past decade, and now morphine and oxycodone given orally can be used as first choice for moderate to severe cancer pain. New opioid analgesics are available, e.g. oxycodone/naloxone combination, which have been shown to be effective and potentially have fewer side effects in some clinical settings.

Alternatives to oral opioids are transdermal fentanyl and buprenorphine. Both drugs may be the preferred step III opioid for some patients, in particular if patients are unable to swallow. These drugs are also preferred in the setting of patients with chronic kidney disease.

Most commonly, patients treated with opioids complain of nausea, vomiting, and constipation. They may also cause sedation, dry mouth, confusion, hallucinations, urinary retention, and itching. Co-medication as prophylaxis or treatment of these side effects is often necessary on a temporary or continuous basis.

Fear of addiction when using opioids is often a reason for caution and reluctance by patients and doctors alike when this class of drugs is prescribed, even in advanced disease. Addiction is rare in patients with pain resulting from tumour progression, and it is actually pre-existing addiction to drugs and alcohol that are unfavourable prognostic factors in pain management.

Sometimes patients as well as professionals are concerned about problems like respiratory depression or that starting an opioid may be “the beginning of the end”. Good communication is paramount as there is no reason for such concerns when good principles in pain management are adhered to.

Neuropathic pain
Cancer-related neuropathic pain is considered to be frequent in this group of patients, and is often difficult to manage. Its origin may be found in the disease itself (cancer-related neuropathic pain), as a side effect of treatment (chemotherapy-induced neuropathic pain), or in pre-existing co-morbidities such as diabetes.

Drugs used for managing neuropathic pain

Opioids
The role of opioids is still debated. Not much evidence exists to support its use in this setting, however, it still considered good clinical practice to apply the principles of the WHO analgesic ladder in cancer pain patients, including patients experiencing neuropathic pain.

Antidepressants
The effectiveness of antidepressants in neuropathic pain has been known for many years. Published data shows superiority over placebo for amitriptyline, duloxetine, and venlafaxine. A Cochrane review on the effect of amitriptyline in neuropathic pain did not find enough evidence to support it use⁶. But, despite this, amitriptyline is still considered to be helpful, and clinical experience should not be neglected when one
evaluates its role. Duloxetine and venlafaxine have been proven to be effective, especially in chemotherapy-induced neuropathic pain; with the latter even being efficient in preventing this condition.\(^7\)

**Anticonvulsants**

Lamotrigine, gabapentin and pregabalin are widely used alternatives to or in combination with other drugs in the treatment of neuropathic pain. However, not much evidence exists for the efficacy of pregabalin and lamotrigine.\(^8\) Recent literature suggests gabapentin as the ideal anticonvulsant in the treatment of neuropathic cancer pain.

**Basic treatment algorithm for neuropathic pain**

See Figure 2

**Conclusion**

The distinction between nociceptive and neuropathic pain mechanisms is of clinical relevance in the management of cancer pain. Fear of side effects, addiction, and ‘giving up’ needs to be waylaid from the onset for a patient to experience to most benefit of pain control. An adequate pain assessment and healthcare professionals who are empowered to properly treat pain will dramatically aid in making the tumultuous course of having cancer a little more pleasant to cope with.

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**Figure 2. Basic treatment algorithm for neuropathic pain**

**References**

6. Moore RA, Derry S, Aldington D. Amitriptyline for chronic pain, each differing in their causes and treatment
7. Pain management involves ongoing assessments to ensure a good quality of life
8. The WHO pain ladder stills forms the basis of treatment of somatic pain
9. Adjuvant therapies such as radiation are a good addition in ongoing pain management
10. The use of opioids should not be a hindrance to adequate pain control, good communication is paramount to allay any fear from the patient and/or family
11. Neuropathic pain poses more of a challenge to manage with anticonvulsants, opioids and antidepressants being used alone or in combination

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**Semantic descriptor of neuropathic pain**

- Alldynia: pain caused by a stimulus which normally does not provoke pain
- Central pain: pain associated with a lesion of the central nervous system
- Central sensitisation: increased sensitivity to specific stimuli
- Dysesthesia: unpleasant sensation of tingling, stabbing or burning whether spontaneous or provoked
- Hyperalgesia: increased response to a stimulus which is normally painful
- Hyperesthesia: increased sensitivity to specific stimuli
- Hypoalgesia: decreased sensitivity to specific stimuli
- Hypoesthesia: decreased sensitivity to specific stimuli
- Neuropathic pain: pain caused by a lesion or latent of the peripheral nervous system
- Peripheral sensitisation: increased sensitivity to specific stimuli
- Paresthesia: abnormal sensation, either spontaneous or evoked.

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**Assessment tools for neuropathic pain**

- Neuropathic Pain Symptom Inventory
- Scale of pain (LANS)
- Neuropathic Pain Questionnaire
- Neuropathic Pain Symptom Inventory

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**Clinical assessment of neuropathic pain**

- Compression, distalation, stretching of (sensitive nervous structures)
- Neoplastic infiltration (nerve, central centres)
- Latrogenic cause: (neuropathy caused by antitumor and/or treatments: drugs, RT, surgery)

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**Take-home message**

- Cancer pain is heterogeneous. A thorough assessment by a healthcare provider will enable ‘tailor-made’ pain management
- The two main types of cancer pain are acute and chronic pain, each differing in their causes and treatment
- Pain management involves ongoing assessments to ensure a good quality of life
- The WHO pain ladder stills forms the basis of treatment of somatic pain
- Adjuvant therapies such as radiation are a good addition in ongoing pain management
- The use of opioids should not be a hindrance to adequate pain control, good communication is paramount to allay any fear from the patient and/or family
- Neuropathic pain poses more of a challenge to manage with anticonvulsants, opioids and antidepressants being used alone or in combination

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**Figure 2. Basic treatment algorithm for neuropathic pain**

- Non opioid +/- Strong opioids +/- Amitriptyline 25-75 mg/day or Gabapentin 300-3600mg/day
- RT for neuropathic pain due to bone metastases

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**References**

Complex Regional Pain Syndrome type 1

Dr Tory Madden
Postdoctoral Research Fellow
Department of Anaesthesia and Perioperative Medicine
Department of Psychiatry and Mental Health
University of Cape Town, Cape Town

What is Complex Regional Pain Syndrome?

Box 1: Clinical Vignette

Tracy fractured her left wrist 2 years ago. She describes it as a very painful injury. She had an open reduction and internal fixation and achieved bony union by 6/52, but she had unrelenting pain. After many cycles of trying to wait it out and then trying to force herself to move the wrist, she comes to see you. She reports a burning 3/10 pain at rest and 10/10 pain on attempted wrist or hand movement. On examination, the left hand is cooler and paler than the right. The skin looks smooth and shiny. The nail cuticles are dry and cracked. She doesn’t like you touching the wrist or hand, even gently – she says your touch feels sharp and painful. Tracy says her hand feels big and swollen, but circumferential measurements of the left are similar to the right. She can bend her fingers a little but her movement is jerky and she says she is horribly sore and she is scared of moving. She doesn’t use the hand at all anymore; she wraps it up in a scarf to try to keep it warm, and protects it. But it always feels cold. She cannot pick up her 5-year old son, and she is scared of hugging him, because he is jerky and she says she is horribly sore and she is scared of moving. She doesn’t use the hand at all anymore; she wraps it up in a scarf to try to keep it warm, and protects it. But it always feels cold. She cannot pick up her 5-year old son, and she is scared of hugging him, because he sometimes knocks her left hand accidentally.

Tracy’s presentation is consistent with Complex Regional Pain Syndrome type 1 (CRPS-1), which has previously been called Causalgia or Reflex Sympathetic Dystrophy. The latter term has largely fallen out of use in response to evidence that not every case of CRPS-1 is sympathetically driven. CRPS-1 is characterised by pain that is disproportional to the inciting injury or event, or to the stage of tissue healing. It usually affects one extremity with a distal spread from the original site, although it can spread proximally or to another extremity. Pain is not restricted to the distribution of a single peripheral nerve. The most common inciting injury is a wrist fracture – these patients report pain that has either increased or remained undiminished despite evidence of healing. However, the inciting event can be as minor as a thorn prick.

Pain is not the only problem in CRPS-1. Some patients will present with a limb that is hot, swollen and shiny. Others (like Tracy) may have a ‘cold-type’ CRPS, in which the limb is pale, sometimes clammy, and cool to touch. There may be altered nail and hair growth, abnormal sweating, swelling or oedema, and sometimes osteopaenia. Some patients will have dystonia, weakness or tremor. Some patients also report a sense of disownership or hostility towards the limb. Interestingly, this disownership resembles that seen in unilateral neglect after stroke, but it is not a lack of awareness – rather, patients report not wanting or not caring about the limb. There is often a perception that the limb is altered in shape or size that does not match the actual shape or size of the limb. These perceptual distortions are thought to point towards disruption of the brain-held maps of that body part. CRPS-1 is critically distinguished from CRPS type 2 on the basis of no obvious nerve damage that is sufficient to explain the signs and symptoms seen (see Box 2).

The evidence base for CRPS treatments is reasonably thin, barring a few tools that have been the subject of rigorous research. A Cochrane review by O’Connell et al provides a useful guide to the evidence. Table 1 draws from that paper to list the treatments that have been tested at systematic review level, noting the quality of evidence and conclusions drawn. The art of applying this evidence to treat a patient with CRPS-1 requires careful clinical reasoning – in fact, as a syndrome that clearly manifests in several different bodily systems, CRPS-1 presents a fascinating challenge to clinical reasoning. Patients will present with different combinations of signs and symptoms, and a well-informed clinician can tailor the treatment strategy to the individual patient’s profile.

Prevention and early detection

The optimal approach to CRPS-1 is to prevent it altogether. Good early treatment of pain is important. There is little clarity about why some people develop CRPS while others don’t, but the following risk factors have been studied. Anxiety and depression are not predictive. Demonstrated risk factors include immobilisation after injury, the use of ACE inhibitors at the time of trauma, and a history of migraine or asthma. Females who develop CRPS-1 are more likely to have a more severe variant, and a cold-type CRPS-1 has a worse prognosis. (As a female, Tracy was at risk for a more severe type of CRPS, which is what she seems to have – a cold type, which usually has a worse prognosis.) Pain greater than 5/10 on day 2 after conservatively managed wrist fracture has been put forward as a possible red flag for CRPS-1. It stands to reason that excessive pain after any trauma could place a patient at risk. Clinicians ought to detect and assess pain immediately and pain treatment should
be prioritised. Such pain treatment should include optimal non-pharmacological treatment such as education about pain neurophysiology (see Box 3), reassurance about tissue healing, and early movement, as well as suitable analgesic medication.

Assessment, diagnosis and treatment
The clinical diagnosis of CRPS-1 is made according to the clinical version of the International Association for the Study of Pain’s current ‘Budapest Criteria’ (see Box 2). However, the diagnostic criteria do not fully elucidate all the clinical features that should be assessed and, because treatment of CRPS-1 is partly guided by the unique set of signs and symptoms with which each patient presents, it is essential that the clinician establishes a clear picture of each patient’s presentation.

Box 2: The ‘Budapest Criteria’ for clinical diagnosis of CRPS-1

CRPS is usually classified as either Type 1 or 2, according to the presence or absence of an identifiable neural lesion:

- **Type 1** involves no neural lesion, or a small lesion that is insufficient to account for the signs and symptoms.
- **Type 2** includes a neural lesion that accounts for the signs and symptoms seen.

To make the clinical diagnosis, the following criteria must be met:

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
   - **Vasomotor:** Reports of temperature asymmetry and/or skin colour changes and/or skin colour symmetry
   - **Sudomotor/Oedema:** Reports of oedema and/or sweating changes and/or sweating 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 temperature sensation and/or deep somatic pressure and/or joint movement)
   - **Vasomotor:** Evidence of temperature asymmetry (>1°C) and/or skin colour changes and/or asymmetry
   - **Sudomotor/Oedema:** Evidence of oedema and/or sweating changes and/or sweating 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**

The clinician who listens carefully to the patient and uses skilled open questioning can elicit important information that might not be revealed with a more restrictive style of history-taking. Patients with CRPS-1 are frequently distressed, they have often seen multiple practitioners and they may have been told they are imagining the pain. Furthermore, the disruptions to cortical mapping of the affected body part may be associated with perceptual disturbances that patients may not think to report or may be reluctant to report for fear of being labelled as ‘crazy’. A conventional history-taking can miss these features, but they can be explored with careful questions that tap into particular experiences that may seem absurd to a patient, yet are typical for the syndrome. For example, Tracy reported feeling as though her hand was big and swollen, even though it wasn’t objectively swollen. One can ask explicitly about the patient’s sense of their body’s boundaries, or about their sense of the relative sizes of their body parts (for guidance, see references 3, 7). Disruptions to one’s sense of the affected body part (e.g. feeling as though it is distorted in shape or size) may indicate underlying changes in the brain-held maps that represent the affected body part.

As for all complex pain conditions, careful and individually tailored education about the neurophysiology of pain is important.8 The emphasis, here, is on facilitating conceptual change such that the patient reaches a practically useful understanding of central topics (see Box 3). This type of neurophysiological education has been shown to be capable of eliciting rapid change in disability and pain in other chronic pain conditions9 and, importantly, patients tend to understand the concepts better than most health care professionals anticipate.10 The patient can be referred to a clinician with special training in pain for this educational treatment, but it is optimal that the primary care clinician also obtains training in pain, so that the whole healthcare team can ‘sing from the same song sheet’ and ensure consistency of the explanations being given to the patient.

Box 3: Suggested topics in pain neurophysiology education for patients with CRPS-1

- The disconnect between pain and tissue damage – pain is an unreliable indicator of damage to bodily tissue.
- Pain as a response to implicit threat – pain is critically influenced by the brain’s conclusion that bodily tissue is in danger.
- Context potently influences pain.
- Multiple bodily systems are involved in protecting us from danger, and they influence each other.
- Our systems adapt to become more efficient at transmitting danger signals, which increases pain.
- Our systems can adapt to reduce danger signalling.
- Adaptation often takes some time.
- The mechanisms by which each treatment tool is expected to act.
# Table 1: Summary of the findings of a Cochrane review of treatment of CRPS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Evidence quality</th>
<th>Conclusion drawn</th>
<th>Caveats/details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacotherapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Low</td>
<td>Decreased pain</td>
<td>Patients with clinical evidence of osteopaenia</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Low</td>
<td>Decreased pain</td>
<td>Patients with clinical evidence of osteopaenia; some conflicting evidence</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Very low</td>
<td>Not effective</td>
<td></td>
</tr>
<tr>
<td>Intravenous ketamine, daily</td>
<td>Low</td>
<td>Decreased pain</td>
<td>Effective for up to 11 weeks; associated with risks</td>
</tr>
<tr>
<td>Free radical scavengers</td>
<td>Very low</td>
<td>Not effective</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Very low</td>
<td>Not effective</td>
<td></td>
</tr>
<tr>
<td>Sarpogrelate hydrochloride</td>
<td>Very low</td>
<td>Not effective</td>
<td></td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Very low</td>
<td>Not effective</td>
<td></td>
</tr>
<tr>
<td>Systemic local anaesthetic agents</td>
<td>Very low</td>
<td>Decreased pain</td>
<td>Very brief effect</td>
</tr>
<tr>
<td><strong>Interventional procedures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidural clonidine</td>
<td>Very low</td>
<td>Decreased pain</td>
<td>Brief effect (6 hours)</td>
</tr>
<tr>
<td>IVRB guanethidine</td>
<td>Moderate</td>
<td>Not effective</td>
<td></td>
</tr>
<tr>
<td>IVRB other agents</td>
<td>Very low</td>
<td>Not effective</td>
<td></td>
</tr>
<tr>
<td>LASB (lidocaine or bupivacaine)</td>
<td>Very low</td>
<td>Not effective</td>
<td></td>
</tr>
<tr>
<td>LASB Botulinum toxin</td>
<td>Very low</td>
<td>Decreases pain more than conventional LASB</td>
<td>Note that conventional LASB is no more effective than placebo</td>
</tr>
<tr>
<td>Surgical sympathectomy</td>
<td>No evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal cord stimulation</td>
<td>Very low</td>
<td>Decreases pain; does not improve function</td>
<td>High risk of complications</td>
</tr>
<tr>
<td>Repetitive TMS (motor cortex)</td>
<td>Very low</td>
<td>Not effective</td>
<td></td>
</tr>
<tr>
<td><strong>Physical/rehabilitation therapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiotherapy*</td>
<td>Low</td>
<td>Decreased pain; improved function</td>
<td>Participants followed up to 6 months</td>
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<tr>
<td>Occupational therapy*</td>
<td>Low</td>
<td>More helpful than passive control</td>
<td>Not as helpful as physiotherapy</td>
</tr>
<tr>
<td>Pulsed electromagnetic field therapy</td>
<td>Very low</td>
<td>Not effective</td>
<td></td>
</tr>
<tr>
<td>Mirror therapy*</td>
<td>Low</td>
<td>Decreased pain</td>
<td>In post-stroke CRPS of the upper limb</td>
</tr>
<tr>
<td>Graded motor imagery*</td>
<td>Low</td>
<td>Decreased pain; improved function</td>
<td>37% reduction in pain intensity at 2-3 months.</td>
</tr>
<tr>
<td><strong>Alternative therapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acupuncture</td>
<td>Very low</td>
<td>Not effective</td>
<td></td>
</tr>
<tr>
<td>Relaxation training*</td>
<td>Very low</td>
<td>Not effective</td>
<td></td>
</tr>
<tr>
<td>Qigong therapy</td>
<td>Very low</td>
<td>May decrease pain</td>
<td>Effect size not reported</td>
</tr>
</tbody>
</table>

The review considered evidence provided by systematic reviews of randomised controlled trials. * Treatments associated with a favourable risk profile are marked with *. IVRB: intravenous regional anaesthetic block; LASB: local anaesthetic sympathetic blockade; TMS = transcranial magnetic stimulation.
Here, we summarise the application of the findings of the most recent Cochrane review on treatment options\textsuperscript{1} to provide guidance on their application to patients in the acute and chronic stages of CRPS-1. Table 1 summarises the findings of that review, including treatments found to be ineffective.

In the acute stage, patients who show signs of osteopaenia or osteoporosis may experience pain relief when treated with calcitonin or bisphosphonates. The evidence suggests that daily intravenous ketamine may provide some pain relief and that epidural clonidine could be used for very short-lived pain relief (in the region of 6 hours), but the practicalities of using treatments that provide such brief analgesia must also be considered, as must the risks associated with them. Conventional physiotherapy has been found to decrease pain and improve function in the first year, and the Graded Motor Imagery programme (GMI, see Box 4)\textsuperscript{7,12,13} has shown even better results than conventional physiotherapy. The (somewhat controversial) option of spinal cord stimulation may decrease pain and improve quality of life, but has failed to improve function and carries noteworthy risks.

Once a patient has had CRPS-1 for more than 3 months, the treatment options seem more limited. Daily intravenous ketamine and spinal cord stimulation may improve pain in this phase, but both still carry risks. The GMI programme also appears to decrease pain and improve function, and has also shown efficacy in patients with truly chronic CRPS-1 (33-88 weeks’ duration). It does not appear to be associated with noteworthy risks. As such, it is arguably the most sensible first line of treatment for these patients, but must be coupled with clear education on pain neurophysiology.

The interdisciplinary approach is likely to be beneficial for a patient with CRPS-1. The members of the team can be selected to match the patient’s presentation. A list of possibilities (which is certainly not exhaustive) includes the patient (decision-making; primary protagonist), general practitioner or nurse (education on pain neurophysiology; co-ordination of team), physiotherapist (education on pain neurophysiology; restoration of movement and function), psychologist (support; emotional processing), and anaesthesiologist (prescribed medication), as well as others who may be brought in to manage specific concerns.

Conclusion
The clinician who suspects CRPS-1 in a patient with otherwise unexplained limb pain should:

- perform a thorough assessment, considering all alternative diagnostic possibilities,
- explain pain neurophysiology to the patient,
- gather a multidisciplinary team with expertise in complex pain conditions and
- negotiate treatment options with the patient (and family, where necessary), with a view to agreeing on an individually tailored treatment plan.

**Box 4: The Graded Motor Imagery Programme**

This rehabilitation programme\textsuperscript{7} was developed in response to evidence that CRPS-1 is characterised by alterations to the brain-held maps of the body – the ‘cortical body matrix’ (e.g. 14, 15-19). These alterations seem to involve a loss of appropriate inhibition of the sensory and motor cortices. The GMI programme aims to re-establish this inhibition in three sequential stages:

1. implicit motor imagery tasks in which the patient must identify pictures of body parts as belonging to the left or right side of the body
2. explicit motor imagery tasks in which the patient imagines moving the affected body part without producing actual movement
3. actual movement performed by both sides of the body, with the affected body part hidden behind a mirror. The patient watches the mirror image of the unaffected body part during the exercises.

The GMI programme must be preceded by thorough education on pain neurophysiology and the exercises are performed frequently in order to reinstate inhibition. An early RCT of this treatment for a heterogenous group of patients (with CRPS, phantom limb pain and brachial plexus axonal injury) showed impressive ‘numbers needed to treat’ of 2 and 3 for pain (50% reduction) and function (4/10 improvement) respectively.\textsuperscript{13}

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1. XEFO 4 and 8 mg Tablets South Africa Package Insert, October 1998.
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