

# Botulinum Toxin in Pain Management

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Botulinum toxin is a highly potent neurotoxin elaborated by the spore-forming anaerobe *Clostridium botulinum*. The toxin has at least seven distinct subtypes. Of these, two have been formulated for therapeutic use, these being type A (BT-A) and type B (BT-B). All subtypes of the toxin act at the myoneuronal junction to cause presynaptic inhibition of acetylcholine (ACh) release, though the precise intracellular target varies between the subtypes. BT-A denatures the SNAP proteins which are critical to adherence of the vesicle of ACh to the inner membrane of the nerve terminal. Failure of ACh release thus causes flaccid paralysis of the muscle fibre involved. A salient fact, which was not known when BT-A was first produced for therapeutic use, is that other neurotransmitters apart from ACh are also presynaptically inhibited. It is now known that Substance P, Calcitonin Gene-related Peptide (CGRP) and other transmitters involved in nociception are similarly inhibited. This observation provides the rationale for use of BT-A in prophylaxis of chronic migraine and other painful disorders.<sup>1,2</sup>

## Historical Background

The clinical use of BT-A is a recent phenomenon. However, the initial concept of its use in medical practice was articulated in 1822 by the German physician and poet Justinus Kerner. Kerner described a series of 155 cases of paralysis caused by a fatty acid substance present in unhygienically manufactured sausages. Rather prosaically for a poet, he named the substance “wurstgift” (sausage poison). He concluded his treatise by suggesting that in minute quantities the “wurstgift” could be useful for diseases characterised by painful or inappropriate muscle contractions.<sup>3</sup>

The contamination of food was again the stimulus for the next leap in the development of BT-A. In 1895, an outbreak of mass poisoning from contaminated ham provided the opportunity for the Belgian microbiologist Pierre van Ermingem to apply the newly formulated Koch’s postulates and identify *Bacillus botulinus* as the causative agent. It took a further 33 years to isolate a stable precipitate of toxin from a culture of the organism.

The Second World War focused attention on the toxin as a potential biological weapon. In 1946, a US Army scientist named Edward Schantz became an expert at

purifying the toxin. He produced large quantities of a low-quality toxin preparation for use in bio-warfare and espionage research. The Biological and Toxins Weapons Convention Treaty, ratified in 1972, ended offensive biological weapons programs in the US military. During the 1960s, Schantz collaborated with Dr Alan Scott of the Smith-Kettlewell Eye Research Foundation. As well as demonstrating the efficacy of BT-A in treating strabismus in primates, Scott learned the techniques of producing very high quality toxin preparations. Scott formed a company called Oculinum to develop and test the new therapeutic agent in humans. In 1978, armed with a batch of 150 mg of toxin, he received FDA approval to begin human trials. That initial batch of toxin produced over 250 000 therapeutic doses. Until the Allergan company produced another, even more potent, batch in 1997, it was the sole source of FDA-approved BT-A.

Allergan bought the Oculinum company in 1991 and renamed the product Botox™. In 2002, global sales of Botox™ exceeded US\$400 million, and to date the agent has been reported useful in over 50 conditions.<sup>4</sup> During the 1990s, the Dysport™ brand of BT-A was launched in Europe by Ipsen, and Myobloc™, a preparation of BT-B, was developed for commercial release by Elan Pharmaceuticals. The emerging economy of China now boasts no fewer than 3 brands of BT-A, though all are only used in China. The various preparations available in the West are not bioequivalent, due to differences in the vehicle proteins and the method of derivation of their potency units. Ongoing research will be required, as each product must qualify for regulatory approval independently for each indication sought.

### **Botulinum Toxin and Pain**

Patients receiving high doses of BT-A for cervical dystonia reported significantly reduced muscle pain at non-injected sites. As well, a group of chronic migraine sufferers who underwent cosmetic treatments with BT-A reported dramatic reductions in headache frequency and intensity. Such clinical observations suggested that BT-A could decrease nociceptive signalling. The experimental work which supported this hypothesis is comprehensively summarised by Aoki.<sup>5</sup> BT-A also appears to reduce neuropathic pain in experiments using the classical surgical rat model of sciatica.<sup>6</sup>

### **Headache**

#### *Migraine*

Extrapolating from the clinical observation that injection of the toxin into facial muscles for cosmetic purposes improved migraine symptoms, the initial studies of BT-A in headache used injection protocols based on cosmetic practice. Termed the “fixed site” approach, this involves injection of the procerus, corrugator, frontalis and temporalis muscles in predetermined sites and doses. Typically, multiple sites within each muscle are injected with low doses of toxin.

The mechanism of relief of migraine symptoms by the BT-A is unknown, but is not related to the degree of chemical denervation achieved.<sup>7</sup> Most likely, the release of vasoactive mediators from the trigeminal nucleus in the brainstem, triggered by peripheral activation of the trigeminal nerve, is a contributory event in migraine pathogenesis.<sup>8</sup> This would be inhibited by BT-A. Such a mechanism would provide an explanation for the treatment effect reported. It is interesting that the precise mechanism of the triptan and ergot derivative classes of medications which form the mainstay of current migraine treatment is also unknown.<sup>9</sup>

The first randomised controlled trial (RCT) of BT-A in migraine was that of Silberstein and colleagues.<sup>10</sup> Placebo injections of toxin vehicle protein in identical packaging were compared to commercial Botox™. Treatment groups received a total dose of either 25 or 75 units using a fixed-site approach. At 3-month follow up there was a modest, but statistically significant, improvement in headache frequency and migraine-associated vomiting in the treated groups. The higher dose did not improve overall efficacy and was associated with more adverse effects, though these were not seriously incapacitating. Evers<sup>11</sup> summarized the current published evidence for BT-A in migraine prophylaxis and sounded a note of caution amidst the widespread enthusiasm. He made the point that two out of three RCTs to this point have not shown significant improvements in headache frequency.

Future trials of BT-A in migraine should include a measure of disability such as the Migraine Disability Assessment Score (MIDAS) as in the open-label study of Mathew and colleagues.<sup>12</sup> This showed a dramatic improvement in MIDAS scores obtained, accompanied by a quite modest improvement in purely clinical endpoints, such as acute medication use and headache frequency. This result, if replicated in a RCT, would help explain why the off-label use of BT-A for migraine sufferers has expanded so far ahead of the published efficacy data. For the present, the results of larger double-blinded RCTs are needed to further delineate the potential role of BT-A in migraine.

### *Chronic Daily Headache*

A second approach to site and dose selection has evolved in parallel to the “fixed-site” approach. Sites for injection are chosen by degree of tenderness to palpation and may include the trapezius, splenius capitis, sternomastoid, occipitalis and masseter muscles, in addition to the sites described above. It is termed the “follow the pain” approach by advocates. This has been used in studies examining the role of BT-A in chronic daily headache. In these studies, variability of diagnosis, injection site and dose has resulted in conflicting findings. While a majority of studies have shown a useful treatment effect, the lack of clear efficacy in the best-designed trials<sup>13, 14</sup> suggests that, for tension headache at least, BT-A does not appear to be a specific treatment. The Botox CDH group has recently reported another large RCT, which again failed to show an impressive treatment effect in this diagnostic group.<sup>15</sup>

A significant flaw in methodology has been that no study of migraine or other headache types has rigorously documented intramuscular placement of toxin by use of electromyography or muscle stimulators. Botox™ and Dysport™ both diffuse a short distance through muscle from the injection point, but will not cross tissue planes.<sup>16</sup> Hence, if the toxin is deposited subdermally, intradermally or subperiosteally, it will have no effect. This observation alone could potentially account for the variability in results across studies and makes the need for more rigorous RCT compelling.

### **Myofascial Pain Syndrome (MPS)**

This condition refers specifically to pain which arises from muscle and soft tissue “trigger points”. A myofascial trigger point is defined as a well-localized, highly irritable taut band within skeletal muscle fibres that responds to palpation with a local twitch response and remote referred pain arising from central convergence and facilitation.<sup>17</sup> It is typically a chronic regional problem and is easily differentiated from

the construct of fibromyalgia, which refers to a generalized pain disorder. Royal<sup>18</sup> summarizes these differences comprehensively.

The cornerstone of treatment of MPS is deactivation of the trigger points to enable stretching and strengthening of the tissues involved. This can be achieved with a conservative approach using external pressure, combined with stretching under the guidance of an experienced physiotherapist. Interventions such as trigger point injections and dry needling provide a quicker means to the same end, by mechanically destroying the trigger point area and reducing the tendency to reflex spasm which may limit the patient's ability to participate effectively with the conservative program.

BT-A is a logical choice of agent to trial in this condition, given its ability to reduce both pain and spasm in skeletal muscle. A number of preliminary trials have indicated a consistent treatment effect.<sup>19, 20, 21</sup> Two studies have found that BT-A provides significantly longer duration of relief than does dry needling or local anaesthetic with corticosteroid.<sup>22, 23</sup> Given the inconsistent study methodologies employed to date, additional high-quality research is warranted, but it seems that BT-A may find a role in patients who have had previous useful responses to conventional trigger point treatments, as a way of lessening reliance on medical services.

### **Low Back Pain (LBP)**

Abnormal or hyperactive paraspinal muscle activity, particularly of the lumbar multifidus has been implicated for many years in the pathogenesis of non-specific chronic lumbar pain.<sup>24</sup>

Four possible mechanisms have been suggested by which BT-A may reduce pain in patients with this condition:<sup>25</sup>

1. Reduction of painful paraspinal muscle spasm may result from the chemical denervation effect of the toxin.
2. Reduction of intrafusal muscle spindle discharges which convey non-nociceptive sensations to the spinal cord may reduce input to sensitised wide dynamic range neurons. These have been implicated in the perception of non-nociceptive stimuli as painful (allodynia).
3. Pain signals at the spinal interneuron level may be modified by increasing activity of 1a inhibitory neurons, and possibly by direct inhibition of neurotransmitter release due to retrograde transport of toxin or toxin breakdown product to the dorsal root ganglion.
4. BT-A and its metabolites may have a direct anti-nociceptive effect in the peripheral tissue.

Foster and colleagues<sup>25</sup> published the only double-blinded RCT of Botox™ in LBP. Thirty-one patients were randomised to receive either active toxin or vehicle injections into five sites in the lumbar paravertebral muscles. BT-A was significantly superior to placebo on both physician-rated and patient-rated measures of pain and disability. In particular, at 8-week follow up, 66% of the BT-A group reported significant reduction in disability as measured by the Oswestry LBP questionnaire compared with 18% of patients in the placebo group.

In a focused review, Difazio and Jabbari<sup>26</sup> note that Foster's study remains the sole RCT published. In attempting to answer a series of questions relevant to BT-A treatment of LBP, they add further clinical observations from their own experience. Their major points can be summarised as follows:

1. No particular subset of LBP patients appears to benefit more than any other. Reported responders have included patients with chronic radiculopathy, “failed back surgery” syndrome, non-specific mechanical back pain and intermittent radicular pain. This may reflect the multiple mechanisms of action of BT-A as much as it does the lack of standard treatment protocols. A strong placebo effect cannot be excluded.
2. Treatment response is likely to be maintained in responders over multiple treatments. This is concordant with experience of BT-A treatment of other painful muscular conditions including cervical dystonias and adult spasticity. As the amount of allergenic protein in the “current” batch preparation of Botox™ is less than 20% that of the “original” batch, repeated dosing is unlikely to lead to the development of blocking antibodies.
3. Paravertebral muscle injections appear to be safe, with the chemical denervation not resulting in clinically significant lower limb weakness, gait deviations or balance problems. Other authors have reported that, in general, BT-A treated patients have improved mobility rather than the reverse.<sup>27</sup>
4. Given the low efficacy of current conventional treatment for LBP and the devastating economic and social costs of LBP,<sup>28</sup> a cost-efficiency case can be mounted for intensively investigating BT-A treatment. Although this has relatively high upfront costs, they may be recouped through increasing “return to work” rates and reducing health resource consumption by LBP sufferers.

While BT-A is generally reported to be very safe, a timely reminder of the potential hazards of deep intramuscular injections was the appearance of a case report by Puehler, whose patient suffered multiple deep paravertebral abscesses following repeated injections of local anaesthetic, corticosteroid and BT-A on several occasions over a six-month period.<sup>29</sup> To date, no cases of permanent major neurological disability or death have been reported.

At this stage, treatment of LBP with BT-A should be considered experimental. Before its use for this indication becomes accepted, further larger RCTs are required to establish efficacy, and more open-label studies comparing injection protocols are required.

### Conclusion

Given its established record of safety in other conditions and promising early efficacy data, BT-A can reasonably be considered in individual complex cases of painful conditions. There is no painful condition for which it is a first-line or specific treatment, though it may be particularly useful in long-term prophylaxis of migraine. Individual practitioners should be thoroughly familiar with the injection and handling technique of the toxin products. Use of EMG or stimulation to confirm intramuscular placement should be mandatory.

Notwithstanding the explosion of off-label use of BT-A, many questions regarding the ideal dosing regimen, injection sites and identification of suitable candidates for treatment remain unsettled. These can only be resolved by higher quality research than that undertaken to date. As further research is reported, the role of BT-A treatments in painful conditions will become clearer.

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# Complex Regional Pain Syndrome

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## Introduction

Complex Regional Pain Syndrome (CRPS) has been described as a “strange pain in a strange looking limb”. The pain is “strange” because its severity is out of keeping with the often minor and transient nature of the inciting event. The affected part also looks “strange” (swollen, red, white or blue) and responds in a “strange” manner (hot, cold, sweaty, tremulous or weak). Dysfunction of cortical, sensory, motor and autonomic components of the nervous system along with peripheral inflammatory changes (neurogenic inflammation, tissue ischaemia) may be the patho-physiological basis for CRPS. Psychological and social problems such as anxiety, depression, fear avoidance (of painful movements) and loss of employment may develop. Both the affected body part and the patient as a whole may become “dysfunctional” in CRPS.

Management of CRPS is based on the bio-psycho-social model of pain and should involve a multidisciplinary team. keystones include the provision of effective analgesia, allowing the affected region to be mobilised (physical therapy) and returned to normal function as soon as possible, the “use it or lose it principle”. Psychological, social and occupational rehabilitation should also be provided.

## Definitions and diagnostic criteria

The diagnosis of CRPS remains largely clinical and is based on the taxonomy of the International Association for the Study of Pain (IASP). CRPS type I (reflex sympathetic dystrophy) is diagnosed where there is no evidence of a precipitating nerve injury, in contrast to CRPS Type II (causalgia) where a nerve injury is present. In addition, pain may be classified as sympathetically maintained (SMP) or sympathetically independent (SIP), depending on clinical features or response to sympathetic blockade.<sup>1</sup>

The IASP diagnostic criteria for CRPS have been criticised for lacking specificity and failing to include motor signs and symptoms which are present in a majority of cases. Revised criteria have been proposed, based on the presence of signs and symptoms in each of four categories (sensory, vasomotor, sudomotor and motor/trophic) with improved specificity in diagnosis.<sup>2</sup> CRPS is a diagnosis of exclusion; therefore, disorders that mimic the syndrome such as infection, trauma, vascular disease or neuropathy must be considered.

**Table 1**  
IASP diagnostic criteria for CRPS (Merskey and Bogduk 1994)<sup>1</sup>

*CRPS type I*

1. The presence of an initiating noxious event, or a cause of immobilization.
2. Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event.
3. Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

Note: criteria 2-4 must be satisfied.

*CRPS type II*

1. The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve.
2. Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.
3. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

Note: all three criteria must be satisfied.

### Clinical features of CRPS

In CRPS there is usually a history of an inciting event, such as a nerve or tissue injury (sprain, fracture, surgery) or a period of immobilization. In most cases, the severity of the clinical presentation is disproportionate to the severity of the inciting event. The syndrome may also be triggered by stroke, spinal cord injury, visceral disorders such as myocardial infarction and cholecystitis, and “trivial events” such as bruising and venipuncture. Prolonged use of a surgical tourniquet<sup>3</sup> and psychological stress<sup>4</sup> have also been implicated. Interestingly, some patients with neck pain after whiplash injury exhibit features of CRPS,<sup>5,6</sup> including dystonia.<sup>7</sup>

Patients with CRPS typically present with neuropathic-type pain (tearing, burning, shooting, aching), allodynia (mechanical and cold stimuli), hyperalgesia, oedema, vasomotor changes (warm and red or cool and dusky), sudomotor changes (dry or sweaty), motor dysfunction (weakness, tremor, dystonia) and, in severe cases, dystrophy and atrophy (skin, hair, nails, muscle, bone). Symptoms and signs occur in a regional distribution and not in the territory of a peripheral nerve or dermatome. A syndrome with all the features of CRPS, except for pain, has also been described.<sup>8</sup> Some authorities have proposed distinct clinical stages; however, the validity of this approach is questionable given the variable clinical course of the disorder.<sup>9</sup> The features of CRPS may “spread” contiguously (in the same region), in “mirror-image” fashion (e.g. to the opposite hand) or independently (e.g. from hand to foot). In some cases, “spread” is associated with a new inciting event.<sup>10</sup>

Abnormalities in sensory testing (such as decreased sensation to light touch, pin prick and vibration) may be found in the affected region and adjacent areas, including the corresponding quadrant or hemi-body. There is a higher incidence of motor impairment and mechanical allodynia in patients with widespread sensory impairment.<sup>11</sup> Many patients with CRPS develop “neglect-like symptoms” (similar to those seen after a stroke) in the affected limb.<sup>12</sup> Reports include the feeling that their arm or leg “doesn’t seem to belong to them anymore” (cognitive neglect) or having to “think harder to make it move” (motor neglect). Phantom sensations such as strange limb postures or “extra” body parts have also been described.<sup>13,14</sup>

Abnormalities of limb movement and posture in CRPS may reflect the development of fear-avoidant pain behaviours (kinesiophobia) or motor dysfunction. A causalgia-dystonia syndrome is described, particularly in females and is characterised by a clenched fist (or foot) posture, early onset of contractures and spread to other limbs.<sup>15, 16, 17</sup> Many patients with CRPS develop areas of myofascial dysfunction (MD), with trigger points within the proximal musculature of the affected limb, particularly the arm and shoulder. The incidence of MD is higher in patients with motor neglect or long-standing symptoms.<sup>18, 19</sup>

Psychological factors such as depression, anxiety and post traumatic stress disorder are common, with 80% of patients reporting a stressful life event immediately before the onset of their CRPS.<sup>20</sup> Social and occupational problems such as disruption of family life, injury compensation or loss of employment are frequently present.

The prevalence of clinical features in CRPS is presented in Table 2.

### Epidemiology of CRPS

It is difficult to clearly define the epidemiology and natural history of CRPS, due to variability in diagnostic criteria, taxonomy and treatment regimes. It most commonly

**Table 2**  
Prevalence of clinical features in CRPS (6-12 months post onset of symptoms)

<i>Sensory features and pattern of "spread"</i>	
• Pain	81%-97%
• Mechanical allodynia	54%-74%
• Hyperaesthesia	72%
• Neglect	84% <sup>12</sup>
• Sensory impairment	69%-83% (mean duration of CRPS: 4.1 years) <sup>11</sup>
• Hemi-body or quadrant sensory impairment	50% <sup>11</sup>
• Contiguous spread	100% (mean time to onset: 2.6 months) <sup>10</sup>
• Independent spread	70% (mean time to onset: 2.6 years) <sup>10</sup>
• Mirror spread	15% (mean time to onset: 2.5 years) <sup>10</sup>
<i>Vasomotor changes</i>	
• Skin colour change	87%-92%
• Altered skin temperature	79%-89%
<i>Sudomotor/oedema changes</i>	
• Oedema	61%-97%
• Altered sweating	28%-53%
<i>Motor/trophic changes</i>	
• Motor dysfunction	57%-98%
• Weakness	75%-95%
• Limited range of movement	80%-88%
• Incoordination	47%
• Tremor	48%
• Spasm	13%
• Dystonia	14% <sup>17</sup>
• Myoclonus	4% <sup>11</sup> -20%
• Altered skin growth	39%
• Altered nail growth	28%
• Altered bone growth	48%
<i>Severe complications</i>	7% <sup>24</sup> (infections, ulcers, chronic oedema, dystonia, myoclonus)

Based on data from Veldman et al (1993),<sup>21</sup> Harden (2001),<sup>22</sup> Sandroni et al (2003)<sup>23</sup> and other sources.

presents in middle-aged females. Nearly all patients report an inciting event (most commonly a fracture) and many experience a resolution of symptoms within 60 months, both with treatment and spontaneously. Predictors of a more positive clinical outcome were fracture injury (when compared with sprain) and the absence of sensory symptoms or swelling.<sup>23</sup> A persisting cool limb early in the presentation was associated with the development of severe trophic changes, oedema, infection and motor dysfunction, particularly in young females.<sup>24</sup> (See Table 3.)

**Table 3**  
Epidemiological data for CRPS

<i>Incidence</i>	
CRPS type I	c. 1/20 000
CRPS type II	c. 1/100 000
<i>Prevalence</i>	
CRPS type I	c. 1/5 000
CRPS type II	c. 1/25 000
Ratio of CRPS type I: type II	c. 4:1
Mean age at presentation:	42-50 years
Female to male ratio:	c. 4:1
Upper limb to lower limb ratio	c. 2:1
Inciting event	c. 90% (no inciting event: 6-10%) <sup>21</sup> <ul style="list-style-type: none"> <li>• fracture: 16%-46%</li> <li>• sprain: 16%-29%</li> <li>• immobilization: 47%</li> <li>• post surgery: 3%-24%<sup>26</sup></li> </ul>
Incidence of CRPS	<ul style="list-style-type: none"> <li>• after a fracture: 1%-2%</li> <li>• after Colles fracture: 7%-35%<sup>27</sup></li> <li>• after a nerve injury: 2%-5%<sup>21</sup></li> </ul>
Mean duration of symptoms:	11.6 months (range 1-60 months)
Resolution of symptoms:	74%
Recurrence:	10% (incidence of recurrence c. 2% per year) <sup>28</sup>

Based on Sandroni et al (2003),<sup>23</sup> Veldman et al (1993),<sup>21</sup> Allen et al (1999),<sup>19</sup> Berklein et al (2000),<sup>25</sup> Stanton-Hicks et al (2002),<sup>26</sup> Bickerstaff et al (1994)<sup>27</sup> and Veldman and Goris (1996).<sup>28</sup>

### Occupational issues in CRPS

Approximately 50% of patients developed CRPS after a work related injury and a similar proportion received injury compensation. The highest incidence was in service industries, such as policing, security, restaurant work, clerical and sales professions and manual trades.<sup>19</sup> A 5 year follow up study found that most patients continued to work full time, although one-third had to give up work for at least a year or change occupations.<sup>29</sup>

### CRPS in children and adolescents

21% of children attending a paediatric pain management clinic were diagnosed with CRPS, with a ratio of type I to type II of 10:1 (adults 4:1). The mean age was 13.7 years with a range of 9-17 years. The most common presenting group was pre-pubescent

females, with an overall female to male ratio of 3:1, which is similar to adults. The lower limb was most frequently affected (upper to lower limb ratio of 1:3), in contrast to adults, where the situation is reversed (2:1). Inciting events included minor trauma (41%) and lower limb surgery (3.6%), with twice as many children (20%) as adults reporting no identifiable cause.<sup>30</sup>

Issues such as participation in play and sports (with greater risk of injury), growth and puberty and social factors such as school attendance and lack of injury compensation may affect the presentation and course of CRPS in childhood and adolescence.

### **Patho-physiology of CRPS**

Dysfunction of cortical, sensory, motor and autonomic components of the nervous system, along with peripheral inflammatory changes (neurogenic inflammation, tissue ischaemia) may be the patho-physiological basis of CRPS. Janig and Baron proposed that CRPS is “largely a disease of the central nervous system (CNS) involving sympathetic, afferent and motor systems”.<sup>31, 32</sup>

#### *Abnormal cortical function*

Patients with CRPS demonstrate impaired performance on spatial orientation tasks<sup>33, 34</sup> and altered tactile sensitivity, associated with widespread cortical dysfunction.<sup>35, 36</sup> Trans-cranial magnetic cortical stimulation revealed “hyper-excitability” in sensory and motor areas representing the affected limb<sup>37, 38</sup> and motor cortical stimulation attenuated pain perception.<sup>39</sup> Imaging studies showed changes in the somatosensory cortex during the period of treatment and recovery.<sup>40</sup>

A mismatch of motor intent and sensory feedback to and from a limb (as occurs with immobilization or after amputation) produces dysfunction in the dorso-lateral pre-frontal and inferior parietal cortices, areas involved in generating the somato-spatial “body map”. This may lead to the development of cortical pain, phantom sensation, sensory neglect and dystonia.<sup>41, 42, 43</sup> The concept is similar to developing motion sickness due to conflicting visual and vestibular inputs to the brain. Physical therapies may improve CRPS by correcting motor-sensory mismatch,<sup>44</sup> essentially “re-programming” the cortex.

#### *Central sensitization*

Central sensitization is a state of CNS neuronal hyperactivity due to increased nociceptive input, particularly at the level of the dorsal horn of the spinal cord. This process contributes to pain, allodynia and hyperalgesia in CRPS.

#### *Sympathetic nervous system*

Intradermal injection of noradrenaline into areas affected by CRPS<sup>45</sup> evokes pain and sympathetic ganglion blockade with local anaesthesia may produce analgesia.<sup>46</sup> There is increased expression of adrenoreceptors in nociceptive afferents and sympathetic-sensory neuronal coupling (particularly in deep somatic structures such as muscle) in affected regions. The latter process may explain deep aching pain and mechanical allodynia in the muscles and joints of patients with CRPS.<sup>32</sup> Increased levels of circulating catecholamines were found in patients with SMP compared with normal controls and there was a positive correlation between affective distress on psychological testing and higher adrenaline levels.<sup>47</sup>

The acute phase of CRPS is usually characterised by vasodilation and warmth in the affected region, suggesting a decrease in sympathetic drive. This may be due to CNS inhibition of sympathetic vasoconstrictor activity. In the chronic phase of CRPS, pale or blue skin colour, decreased temperature and dystrophic changes suggest a state of sympathetic overactivity. This may be due to “denervation supersensitivity” to catecholamines, associated with increased adrenoreceptor expression in blood vessels and nerves.<sup>48</sup>

Experimental whole-body cooling only produced increased SNS activity (vasoconstriction), pain and allodynia in patients with SMP.<sup>49</sup> This may explain why only a proportion of patients with CRPS are sensitive to the effects of increased sympathetic drive.

### *Regional inflammation in CRPS*

The cardinal features of inflammation; pain, swelling, redness, heat, and loss of function describe the peripheral features of CRPS precisely.

There is evidence of neurogenic inflammation with the peptidergic neurotransmitter system playing an important role. Sciatic nerve lesions in rats produced a CRPS-like syndrome which was reversed by a Substance P (SP)-Neurokinin-1 (NK1) receptor antagonist.<sup>50</sup> Simulated injury or immobilisation of rodent limbs produced peripheral neurogenic oedema, with antidromic spread of vasoactive neuropeptides such as SP and Calcitonin Gene Related Peptide (CGRP) into the affected region from the spinal cord.<sup>51</sup> Intradermal injection of SP into both the affected and non-affected limbs of patients with CRPS demonstrated a significant increase in protein extravasation at both sites.<sup>52</sup>

Tissue ischaemia may also play a role in the inflammatory processes of CRPS. Constriction injuries in rodent limbs (mimicking surgical tourniquet placement) produced changes similar to CRPS which were reversed by oxygen free radical scavengers.<sup>3</sup> In patients with CRPS, skin capillary haemoglobin oxygenation was decreased compared with normal controls.<sup>53</sup> Other studies demonstrated increased venous oxygen saturation, increased lactate and impaired ATP metabolism in affected tissues.

The generation of pro-inflammatory cytokines such as Tumour Necrosis Factor-alpha (TNF- $\alpha$ ) may contribute to inflammation in CRPS, with inhibitors such as thalidomide being investigated as possible treatments.

### *Genetics*

HLA susceptibility loci for CRPS have been found on chromosome 6, including loci associated with trauma susceptibility or the development of dystonic states.<sup>54</sup>

### *Psychiatry*

Some authorities suggest that CRPS is a somatoform or conversion disorder.<sup>55</sup> A case of psychologically induced CRPS has been described, possibly resulting from abnormal modulation of the peri-aqueductal grey (pain pathway) by the anterior cingulate gyrus (emotion centre).<sup>4</sup>

### **Tests for CRPS**

CRPS remains a clinical diagnosis. There is no “gold standard” investigation. Tests may be useful in detecting diseases that mimic the syndrome such as cellulitis. Despite

the presence of peripheral inflammation in CRPS, inflammatory markers such as ESR and CRP are usually not significantly elevated.

Quantitative Sensory Testing (QST) may demonstrate the presence of allodynia, hyperalgesia and altered sensation in the affected region and beyond. Tests of asymmetrical SNS function such as the resting sweat test, Quantitative Sudomotor Axon Reflex Test (QSART) and galvanometry correlated with a clinical diagnosis of CRPS in 80% of cases.<sup>23</sup> QST, QSART, the cold-pressor test combined with thermography and laser-Doppler flowmetry are the best validated laboratory tools for the investigation of CRPS.<sup>56</sup> Skin temperature asymmetry testing during controlled thermoregulation resulted in a sensitivity of 76% and a specificity of 93% in the diagnosis of CRPS.<sup>48</sup>

Three-phase bone scans may demonstrate features suggestive of CRPS, particularly asymmetrical peri-articular tracer uptake in the delayed phase. Although bone scan changes correlated with a clinical diagnosis of CRPS in 53-85% of patients,<sup>23, 28</sup> many authorities question the utility of this test.<sup>57</sup>

Tests may prove useful in refuting a diagnosis of CRPS where there is clinical uncertainty and the results are negative.<sup>58, 59</sup>

### **Prevention of CRPS**

Prevention of CRPS is based on avoidance of trauma and unnecessary surgery, early mobilization and rehabilitation of an injured body-part, and management of psychological factors such as depression, anxiety and fear-avoidance. Programmes to increase awareness of CRPS amongst medical practitioners may facilitate earlier diagnosis and treatment. Administration of vitamin C decreased the incidence of CRPS after radial fracture.<sup>60</sup>

#### *Prevention of recurrent CRPS after surgery*

Strategies to minimise recurrent CRPS should include a pre-operative assessment of the patient by a pain management specialist and the development of a treatment plan. Indications for surgery should be reviewed; there are reports of surgery being performed to treat a painful mechanical condition where the pain was actually due to CRPS.

Surgery should be limited in extent and duration, particularly avoiding nerve injury and prolonged tourniquet use. Randomised controlled trials (RCTs) suggest that intravenous regional blockade (IVRB) with clonidine and lignocaine,<sup>61</sup> or the administration of vitamin C<sup>60</sup> may reduce recurrence. Sympathetic<sup>62</sup> or neural blockade<sup>63</sup> and multimodal analgesia<sup>64</sup> including the use of ketamine and calcitonin<sup>65</sup> may also prove beneficial, based on case-controlled studies or case series. Post-operative immobilization such as splinting should be minimised, and physiotherapy commenced as soon as possible. Psycho-social problems need to be addressed.

### **Treatment of CRPS**

It is generally agreed that treatment should be instigated early in the course of CRPS in order to improve outcome, although this has never been tested in clinical trials. There is limited evidence to guide the treatment of CRPS. Consensus guidelines advocate the delivery of effective analgesia and intensive physical therapy in order to restore normal function in the affected region, as well as the management of psycho-

social problems such as kinesiophobia, anxiety, depression and occupational issues. This should ideally involve a multidisciplinary pain management team.<sup>26</sup>

### *Pharmacotherapy*

The provision of analgesia in CRPS is based on “rational polypharmacy”, combining analgesics, anti-neuropathic agents and anti-inflammatory drugs. Opioids may be of benefit, but their use should be limited to avoid dependency and opioid induced hyperalgesia. There is no specific evidence to validate the use of anti-depressants, anti-convulsants, membrane stabilisers, NSAIDs, clonidine, opioids, tramadol or topically-applied capsaicin, NSAIDs or local anaesthetics in the treatment of CRPS. Potential benefit is based on evidence for the treatment of other neuropathic pain disorders.<sup>66</sup>

A meta-analysis of five RCTs with quality weighting concluded that salmon calcitonin was beneficial in the treatment of CRPS. However, two of the placebo-controlled trials had contradictory outcomes.<sup>67</sup> RCTs also demonstrated benefit with bisphosphonates,<sup>68, 69, 70</sup> gabapentin,<sup>71</sup> corticosteroids,<sup>72</sup> anti-oxidants such as oral N-acetylcysteine (NAC) or topical dimethylsulfoxide (DMSO) cream,<sup>73</sup> IVRB with lignocaine and clonidine,<sup>61</sup> epidural clonidine<sup>74</sup> and hyperbaric oxygen therapy.<sup>75</sup> There was evidence for limited benefit with intravenous lignocaine infusion,<sup>76</sup> although a Cochrane review suggested that further research was required.<sup>77</sup>

Lamotrigine,<sup>78</sup> epidural ketamine,<sup>79</sup> low-dose intravenous ketamine infusion,<sup>80</sup> topical ketamine,<sup>81</sup> subcutaneous lignocaine infusion,<sup>82</sup> intravenous mannitol infusion<sup>83</sup> or IVRB with clonidine<sup>84</sup> may be useful in the treatment of CRPS based on evidence from case reports.

### *Sympathetic Blockade*

#### IVRB

Despite being the mainstay of treatment of CRPS for many years, a meta-analysis and systematic review concluded that IVRB with guanethidine, reserpine, atropine or droperidol is ineffective.<sup>67, 72, 85</sup> However, there may be limited benefit with ketanserin or bretylium.<sup>72, 85</sup>

#### Sympathetic neural blockade

There are no randomised placebo-controlled trials to substantiate the use of sympathetic neural blockade in the treatment of CRPS. Analysis of pooled data (largely from retrospective case series) from 1144 patients found that only 29% reported complete pain relief after a sympathetic nerve block.<sup>86</sup> However, case-controlled studies,<sup>87, 88</sup> experimental data<sup>46</sup> and clinical consensus suggests these techniques may still be useful in the diagnosis and treatment of SMP.

Evidence of benefit for intravenous phentolamine infusion is contradictory<sup>72</sup> and the use of surgical, chemical or radiofrequency sympathectomy in the treatment of CRPS cannot be validated, due to a lack of adequate clinical trials.<sup>89</sup>

#### *Peripheral neural blockade*

Continuous infusion of ropivacaine via a peri-neural catheter was associated with significant improvement in pain and function in children with CRPS.<sup>90</sup>

### *Physical therapies*

The traditional phases of physiotherapy for CRPS include desensitization of the

painful part, oedema control, passive mobilization, active mobilization and restoration of normal function. A brief “rest period” with splinting may be helpful in the treatment of acute CRPS with severe symptoms.

Despite consensus that physiotherapy and occupational therapy are of paramount importance in the treatment of CRPS, few clinical trials have examined their effectiveness. There was a modest improvement in pain and function in patients with CRPS who received physical or occupational therapy compared with social work therapy controls,<sup>91, 92</sup> Physiotherapy combined with cognitive behavioural therapy<sup>93</sup> or an intensive exercise programme<sup>94</sup> reduced pain and improved function in children with CRPS.

A randomised controlled trial demonstrated that motor imagery training (hand orientation recognition task, imagined movements and “mirror box” training) improved pain (NNT=3), oedema and function in patients with long-standing CRPS of the upper limb.<sup>44</sup> A small pilot study revealed that mirror visual feedback (mirror box) training was effective in the treatment of acute CRPS.<sup>95</sup>

### *Invasive therapies*

Invasive therapies may be employed to treat patients with intractable or severe CRPS. In patients with chronic CRPS, spinal cord stimulation (SCS) produced a modest improvement in pain but no change in function or quality of life when compared with a physical therapy control group after six months.<sup>96</sup> At a two year follow-up, pain relief and “global perceived improvement” were maintained, but there was still no improvement in function.<sup>97</sup> A systematic review of SCS in the treatment of CRPS calculated a NNT of 3 for significant improvement in pain at six months.<sup>98</sup> Although there is evidence of limited benefit with SCS, further RCTs are required before the technique can be fully validated.<sup>99</sup>

Intrathecal baclofen infusion improved dystonia in patients with CRPS of the arm but only had a variable effect on pain and functional outcomes.<sup>100</sup> Neurolysis and amputation failed to produce long term benefit in the management of intractable symptoms.

A summary of the evidence for treatments is presented in the Appendix.

### **Summary**

CRPS is indeed a “complex” disorder in terms of pathophysiology, diagnosis and treatment. It is a multi-system disease typified by widespread nervous system dysfunction and regional tissue inflammation. Treatment is based on a multi-disciplinary pain management approach as outlined below.

#### **A treatment plan for CRPS**

1. Referral to a multidisciplinary pain management service, where possible.
2. Confirmation of diagnosis of CRPS using IASP criteria and exclusion of “mimicking” disorders (trauma, infection, vascular or neurological disease).
3. Bio-psycho-social assessment, including a comprehensive neurological and functional assessment of the affected region and adjacent zones.
4. Resting and splinting of the affected part (for a short period only) if symptoms are severe.
5. Provision of adequate analgesia (“rational polypharmacy” and/or neural blockade):

- a) Tri-cyclic antidepressants, tramadol, paracetamol, NSAIDs, COX-2 selective inhibitors, opioids, clonazepam, gabapentin. If these are inadequate, consider:
- b) Calcitonin injections, low-dose parenteral ketamine infusion. If these are inadequate, consider:
- c) neural blockade with local anaesthesia:
  - continuous peripheral nerve catheter or epidural infusion to provide prolonged analgesia and sympathetic blockade (avoid motor block).
  - targeted sympathetic blockade.
- d) Consider bisphosphonates, vitamin C, clonidine, topical agents, corticosteroids.
6. Physiotherapy programme including cortical “reprogramming” tasks such as motor imagery training.
7. Management of psycho-social disorders (kinesiophobia, anxiety, post-traumatic stress disorder and depression).
8. Functional and occupational rehabilitation.
9. Educate the patient, family and staff about CRPS as they may not be familiar with the condition.
10. Follow up care.

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### Appendix: Evidence for treatments in CRPS

Kingery WS (1997) [72] is a comprehensive review of controlled trials.\*

NHMRC is the National Health and Medical Research Council of Australia. [101]

#### POSSIBLY BENEFICIAL TREATMENTS

Treatment	Comments	NHMRC Evidence Level [101]
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#### Pharmacotherapy

1. salmon calcitonin	meta-analysis of 5x RCTs; n=280: results of two placebo-controlled trials were contradictory	I
2. bisphosphonates		II
3. gabapentin	1 x RCT; n=58	II
4. corticosteroids	2 x RCTs; n=27: oral prednisolone or iv methyl-prednisolone versus placebo for 4 -12 weeks: "strong evidence" (Kingery 1997)*	II
5. anti-oxidants: NAC or DMSO	1x RCT; n= 146: DMSO/placebo versus NAC/placebo	II
6. vitamin C	prevention; 1 x RCT	II
7. IVRB: lignocaine and clonidine	prevention; 1 x RCT	II
8. IVRB: bretylium or ketanserin	"weak evidence" (Kingery, 1997)*	II
9. epidural clonidine	"weak evidence" (Kingery, 1997)*	II
10.intravenous lignocaine infusion	only improved allodynia and hyperalgesia	II
11.hyperbaric oxygen therapy	1x RCT	II
12. a) sympathetic neural blockade	review of "pooled data"; n=1144: 1/3 "complete" pain relief	IV
b) sympathetic neural blockade	case-controlled study; n=43	III-2

#### Physical therapies

13. motor imagery training	1 x RCT; n=13: NNT(pain relief) =3; "long-standing" CRPS	II
14. physical and occupational therapy	modest improvement in pain and function	II

#### Invasive therapies

17. spinal cord stimulation	1 x RCT; n=36: improved pain at 6 M (NNT=3) and 2 years; no improvement in function or QOL at 6 M or 2 years.	II
18. intrathecal baclofen infusion	1 x RCT; n=7: improved dystonia in upper limb CRPS only.	II

#### NON-BENEFICIAL TREATMENTS

1. IVRB: guanethidine, reserpine, atropine or droperidol		I
2. ablative sympathectomy	"lack of adequate trials" (Cochrane)	I
3. intravenous phentolamine	2 x RCTs: "conflicting evidence" (Kingery 1997)*	I