J Neuroimmune Pharmacol (2013) 8:477–488
DOI 10.1007/s11481-012-9376-x

PERSPECTIVE

Improving the Diagnosis and Treatment of CRPS: Insights from a Clinical Immunologist's Personal Experience with an Underrecognized Neuroinflammatory Disorder

Karen E Binkley

Received: 24 February 2012 / Accepted: 7 May 2012 / Published online: 16 May 2012

Abstract Complex regional pain syndrome is a neuroinflammatory condition associated with overactive glial cells that can be challenging to diagnose and treat. Early recognition and treatment are thought to be critical for good outcomes, yet many patients experience a delay in diagnosis and have difficulty accessing expert medical care. While there are no universally effective treatments, there are several promising new therapies, but these are not widely available. Some of the specific barriers to diagnosis and treatment are reviewed, with suggestions as to how they might be eliminated, leading to better care for all patients with CRPS.

Keywords CRPS

Introduction

As an academic physician who developed CRPS after an otherwise trivial fracture, one might have predicted that I would have received prompt access to expert medical care. However, the reality of my experience highlights ongoing barriers to the diagnosis and appropriate treatment of this challenging condition.

My experience with CRPS has similarities to the difficulties of many other CRPS patients, including a delay in diagnosis, difficulty accessing expert medical care, and lack of universally effective treatments. However, the challenges that I have encountered with this chronic neuroinflammatory disorder likely would be much more difficult for a non-physician patient to overcome.

In this article some of the specific barriers I encountered are identified, and suggestions are made as to how they might be eliminated, leading to better care for all patients who suffer from CRPS. In addition, existing resources that assisted in my treatment are reviewed, with the intent that increased awareness will allow others to take better advantage of them.

Delay in diagnosis

CRPS is a neuroinflammatory condition that typically occurs after trauma or occasionally after immobilization, and is characterized clinically by pain out of proportion to the inciting event, sensory changes (hyperesthesia and/or allodynia), vasomotor changes (temperature or skin color asymmetry), sudomotor symptoms (edema or sweating asymmetry), and motor/trophic changes (weakness, tremor, dystonia; trophic changes in skin, nails, hair) (Harden 2006). Despite displaying all these classic signs, like many patients with CRPS, I experienced a delay in diagnosis.

The proximal injury leading to CRPS occurred June 27, 2007 with a fracture to my left fifth proximal phalanx. CRPS symptoms developed three weeks later, but were not initially recognized despite being seen by two family physicians, a senior orthopedic resident, a staff orthopedic surgeon, a podiatrist, and two cast technicians. All but one family physician and one cast technician were associated with major university teaching hospitals, and none of them considered the diagnosis of CRPS despite the presence of most of the classic signs. In fact, no one really offered any possible diagnosis, except for one family physician, who thought I had a metatarsalgia. This delay in diagnosis led to

K. E. Binkley (✉)
Division of Clinical Immunology and Allergy,
University of Toronto,
Toronto, Ontario, Canada
e-mail: binkleyk@smh.ca

treatment (casting of the fracture for almost 3 months after the development of CRPS) that most certainly worsened my outcome (immobilization itself is a risk factor for CRPS).

The most obvious problem was that no one thought of the diagnosis of CRPS. The most efficient way of remedying this might be to target fracture clinics, the point of contact where physicians and technicians would encounter affected patients. Posters targeted to physicians reminding them of the signs and symptoms of CRPS could be displayed in patient care areas; posters targeted to patients could be displayed in waiting areas. The cost of such posters might be covered by organizations that promote awareness of CRPS, insurance carriers, or medical liability insurance carriers. It might also be useful to distribute reminder notices of the signs and symptoms for CRPS diagnosis to relevant targeted groups, such as orthopedic surgeons, fracture clinics, and physiotherapists, including these in their usual mail-outs or e-mail reminders.

Once the diagnosis of CRPS is considered, further investigations can confirm its presence. Currently, the triple-phase bone scan appears to be the most useful imaging modality due to its greater sensitivity and higher negative predictive value (Cappello et al. 2012). However, the recent identification of autoantibodies to the beta adrenergic receptor or the M2R muscarinic acetylcholine receptor, with 90 % of CRPS patients having autoantibodies to at least one receptor, and 55 % having auto antibodies to both receptors, suggests it may be possible to develop an ELISA test to provide a means of early screening for CRPS (Kohr et al. 2011), at a time when all the classic features might not be present. Such an assay might also be useful for long-term monitoring of disease progress.

It is also worth noting that although the pain of CRPS is often severe, that is not always the case, particularly at onset. In my own case, for example, the pain was not severe, just out of proportion to the clinical situation; the pain from the fracture had resolved weeks earlier, but then returned for no obvious reason. If the pain had been greater, the diagnosis of CRPS might have been considered earlier, but it is important to consider the diagnosis whenever pain is out of proportion to the clinical situation, in order to initiate treatment and improve outcomes.

Ironically, it was the old nomenclature that led to the diagnosis in my own case. Pain and swelling due to undiagnosed CRPS had been present for almost 3 months. Cyanosis of my toes on the affected foot began after it was casted, several weeks later, which I initially attributed to pressure from the cast provoking my pre-existing Raynaud's. One night, the cyanosis had progressed proximally, and involved the leg above the area of the cast, I recall thinking how odd that the sympathetic tone to the whole limb had increased, and remembered a term I had not encountered since medical school: reflex sympathetic dystrophy. That night the pain was significant, and I was waiting for an over the counter analgesic I had just taken to start to take effect before trying to sleep, so I decided to look up the term for my own edification, not thinking that it would be relevant to my condition. I pulled out some old textbooks, and as I started reading, I realized that this is exactly what I had. My family physician saw me the next day and confirmed the diagnosis of RSD/CRPS. The cast was removed, and treatment, including aggressive physiotherapy was started immediately.

That increased awareness and better education regarding CRPS in general is needed was most clearly illustrated to me on a personal level when I was seen by a senior orthopedic resident in Fracture Clinic, after the diagnosis of CRPS had already been made. Disturbingly, although I had all the classic signs and symptoms, and both my family physician and I (Assistant and Associate Professors of Family and Internal Medicine at a university teaching hospital, respectively) agreed that CRPS was the appropriate diagnosis, this resident confidently and adamantly rejected the possibility.

Delay in accessing expert medical care

Prompt treatment of CRPS is thought to be important for a good outcome, yet in Canada, at least, there can be unacceptably long waits, often up to a year, for appointments at specialty pain clinics, or with neurologists. In my own case, despite being able to articulate the need for a timely assessment and suggesting that I take any appointment that became available due to a cancellation, I had to wait for many weeks for an initial pain clinic appointment, and several months for appointments with neurologists. During the critical time after initial diagnosis, my family physician and I pooled our efforts to review extensive current treatment guidelines to ensure that I got appropriate treatment. Other CRPS patients might not be as lucky to have a family physician as determined and confident to initiate treatments with which they were not familiar. Ideally, mechanisms should be in place so that all CRPS patients could be assured prompt assessment by specialist physicians.

Initial treatments

Multiple treatments have been suggested for CRPS, though none are universally effective (Harden 2006; Netherlands Society of Rehabilitation Specialists and Netherlands Society of Anaesthesiologists 2006). Different aspects of CRPS are targeted by various treatments. Physiotherapy aims to regain range of motion and maintain muscle. Topical capsacin is thought to deplete substance P and block pain signals (Ribbers and Stam 2001), although its role in CRPS management

is not well accepted (Netherlands Society of Rehabilitation Specialists and Netherlands Society of Anaesthesiologists 2006). Sympatholytics, such as alpha blockers have been used to block increased sympathetic tone, and dilate constricted blood vessels (Harden 2006; Netherlands Society of Rehabilitation Specialists and Netherlands Society of Anaesthesiologists 2006; Inchiosa and Kizelshteyn 2008). Sympathetic blocks have been used with similar rationale (Harden 2006; Netherlands Society of Rehabilitation Specialists and Netherlands Society of Anaesthesiologists 2006). Calcium channel blockers have also been used to dilate constricted blood vessels (Harden 2006; Netherlands Society of Rehabilitation Specialists and Netherlands Society of Anaesthesiologists 2006). Non-steroidal anti-inflammatory drugs have been used to control pain and reduce inflammation (Harden 2006; Netherlands Society of Rehabilitation Specialists and Netherlands Society of Anaesthesiologists 2006). High dose vitamin C has been shown to reduce the risk of CRPS after high risk wrist fractures, presumably by reducing reactive intermediates and inflammation (Zollinger et al. 2007). It is often given to patients with established CRPS to prevent spread, though there are no studies to support this practice. N-acetyl cysteine has been used with similiar rationale, but studies on efficacy are mixed (Netherlands Society of Rehabilitation Specialists and Netherlands Society of Anaesthesiologists 2006; Perez et al. 2003). Intranasal calcitonin has been used to reduce pain associated with fracture, and well as to reduce the bone resorption that can occur in CRPS (Netherlands Society of Rehabilitation Specialists and Netherlands Society of Anaesthesiologists 2006; Maihöfner et al. 2010). Bisphosphonates have also been suggested for treatment of CRPS (Netherlands Society of Rehabilitation Specialists and Netherlands Society of Anaesthesiologists 2006; Maihöfner et al. 2010). Anti-epileptic agents have been used to reduce neuropathic pain (Netherlands Society of Rehabilitation Specialists and Netherlands Society of Anaesthesiologists 2006; Jensen et al. 2011). Oral corticosteroids (Kozin et al. 1981; Bianchi et al. 2006) and anti-TNF agents have been used to reduce inflammation (Bernateck et al. 2010; Huygen et al. 2004). Baclofen is used to control tremours (Netherlands Society of Rehabilitation Specialists and Netherlands Society of Anaesthesiologists 2006). Mirror therapy has been used to address cortical reorganization (McCabe et al. 2008). NMDA receptor antagonists (Sinis et al. 2006, 2007; Schwartzman et al. 2009; Goldberg et al. 2005; Kiefer et al. 2008; Villanueva-Perez et al. 2007) and anti-TLR 4 agents are used to decrease glial activation (Hutchinson et al. 2008), and intravenous immunolglobulin to reduce inflammation (Goebel 2010; Goebel et al. 2010). Numerous other treatments are reviewed elsewhere (Harden 2006; Netherlands Society of Rehabilitation Specialists and Netherlands Society of Anaesthesiologists 2006).

Like most CRPS patients, I have had multiple treatments. Of all of them, oral corticosteroids have been the single most important and effective treatment for my condition, but predictably, have caused significant side effects. Once the diagnosis of CRPS was established, the cast was removed from my foot and I started aggressive physiotherapy and mobilization, though it took many months until I regained full range of motion in my ankle and toes. As more conservative treatments failed, or were only partially effective in reducing pain, edema, vasoconstriction, and weakness (including intranasal calcitonin topical capsacin, non-steroidal anti-inflammatory agents, alpha blockers, and calcium channel blockers), a short course of prednisone, 35 to 40 mg per day, helped achieve remission. Unfortunately, there were subsequent spontaneous flares, and additional short courses were required to settle symptoms. These became more frequent and prolonged, and after a year, I required continuous low dose prednisone, about 2 mg per day. Over time, it was necessary to increase the dose to maintain control of pain and debilitating motor symptoms, despite attempts to find prednisone sparing agents. The efficacy of oral corticosteroids in CRPS is documented (Kozin et al. 1981; Bianchi et al. 2006), but they are likely underused. It was through my family physician's review of treatment guidelines that we became aware of the use of corticosteroids, but neither of my initial pain specialists seemed to be particularly familiar with their use for CRPS. As it becomes more evident that CRPS is a neuroinflammatory disorder, there is certainly a rational basis for the use of corticosteroids, and I suspect that more patients would benefit from them if there was greater awareness of their efficacy, although there is understandable concern over side effects. However, many of the side effects can be managed, and in many cases, the side effects of corticosteroids may be preferable to the symptoms of CRPS.

The most troubling side effect has been insomnia. To some extent, this has been mitigated by the sedating properties of other medications, including, at various times, pregabalin, baclofen and ketamine, but with higher doses of prednisone it has sometimes been necessary to take a small dose of trazadone, prescribed by my family physician, in order to sleep sufficiently to function well at work the next day. Blood pressure elevation caused by the prednisone is controlled with antihypertensive agents, titrated as prednisone doses are adjusted. Oral bisphosphonates, to protect bone density caused severe esophagitis, so an intravenous bisphosphonate is now prescribed, and although there are anecdotal reports of bisphosphonates reducing CRPS symptoms, I have not found them to be helpful in my case. One of the greatest concerns I have about the long term use of oral corticosteroids is the possibility of osteonecrosis of the hips. If that occurred, the pain would exacerbate the CRPS, as would hip replacement surgery. This has been a very strong motivating factor to find treatments that would allow me to

reduce my prednisone dose. Novel corticosteroids that eliminate some of the unwanted side effects of those currently available are in development (De Bosscher 2010), and might be a welcome addition to treatment options for CRPS.

There are anecdotal reports that anti-TNF agents are helpful in treating CRPS (Huygen et al. 2004). After I first became dependent on low dose oral corticosteroids to control symptoms, a short course of an anti-TNF agent allowed me to completely discontinue prednisone. However, symptoms eventually recurred and prednisone was restarted, but a second trial of the same anti-TNF agent had no effect. The reason for this is unclear. Did I develop antibodies to the anti-TNF agent, or did my underlying condition evolve to become dependent on different mediators? Would an alternate anti-TNF agent be efficacious? There is no data to answer this question. Further studies would be useful.

During the early phase of my treatments, I avoided a potential pitfall. When I was initially evaluated at the pain clinic, my pain was relatively severe, and I was offered potent narcotic analgesics. I declined at the time since I felt they would interfere with my ability to function at work, and I did not believe that they would be a long-term solution to my problem. This was a fortuitous decision, as I later learned that narcotics tend to activate glial cells, and so may have worsened my condition. In fact, many CRPS experts insist that patients taper and discontinue narcotic analgesics as part of their treatment regime. It is therefore somewhat concerning that narcotics should have been offered to me as a CRPS patient. While undoubtedly appropriate for other pain states, many experts feel that narcotics are relatively contraindicated in CRPS for the above reasons. It would seem that pain specialists treating CRPS should be aware of this, however, clearly this may not be the case, and better education is needed.

In hindsight, there is a procedure that I probably should have accepted early in my treatment, but which I declined: a sympathetic block. When I was initially seen in pain clinic, there was significant cyanosis of my entire left leg, due in part to sympathetically mediated vasoconstriction. A sympathetic block at the time may have helped restore proper blood flow to the limb, but I declined it, hoping to avoid an invasive procedure, and instead chose to rely on oral medications, including alpha and calcium channel blockers. These were likely less effective. When I eventually agreed to lumbar sympathetic blocks, in conjunction with other treatment modalities, later in the course of my CRPS, the sympathetic blocks were ineffective. I suspect I would have had a different result had I consented to them initially.

One of the treatments that I have some regrets about persisting with was pregabalin, a medication used to treat seizures as well as chronic pain. While this medication had some benefits in that it had calming effects, and help to mitigate some of the side effects of the oral corticosteroids I was taking, it significantly interfered with my cognitive abilities. Although this medication was supposed be taken twice daily, I took it only once daily, immediately after finishing work, so that it would not interfere with my ability to work during the day. It did interfere with my cognitive abilities during the evening hours, and I believe this left me less time to reflect on my own treatment regime. The pregabalin did not alter the course of my CRPS, and I probably should have abandoned it sooner, but because of the effect on my thinking processes in the evening, it took me longer to realize this than it should have. While this drug may benefit other patients, it did not appear to help me. However, had I been under the care of a physician with more expertise in treating CRPS at the time, that physician may have recognized the futility of using pregabalin earlier.

Deciding to seek second or third opinions was more difficult than I would have thought. Despite the fact that as a physician, I am well aware that my colleagues often have different levels of expertise, different approaches and different opinions on how to treat various conditions, I found it difficult to leave to care of my treating physicians even when I strongly felt we were not on the right course. I have enormous respect for my colleagues and their expertise. I understood that they should know more about treating my condition than I did, since CRPS was not a condition normally treated by physicians in my specialty. My treating pain specialists were well-trained, caring and compassionate individuals who were trying to help me. But I had the motivation and expertise to spend a lot of time reviewing medical literature, and I came to realize that perhaps we were not pursuing the most appropriate course of treatment. Confident as I was in this conclusion, I still felt guilty about leaving the care of my initial treating physicians; I did not wish to seem ungrateful for their attempts to help me. I can only imagine how much more difficult it would be for non-physician patient to seek additional opinions. The difficulty would be compounded if they did not have a supportive family physician, as I did. The need to seek second or third opinions might be eliminated if the standard of care for CRPS could be raised to a uniform level through better education.

Another privilege afforded to me by the fact that I was a physician was that I was given some leeway in adjusting the dose is my medications, for example, titrating my oral corticosteroids up or down to control symptoms and limit side effects and my anti-hypertensive agents to control corticosteroid related increased blood pressure, through home monitoring. Other CRPS patients could be taught to adjust their own medications for symptom control, analogous to plans for other chronic conditions like diabetes or asthma.

Non-uniformity of expert medical care

Like many CRPS patients, during the course of my CRPS, I have seen several different specialists. There has been a surprising variability in the knowledge base of these specialists, who would be expected to be familiar with the features and treatment of this condition.

a. Awareness of Complications: Spreading CRPS and Motor Disturbances.

It became apparent that even specialists treating CRPS were not always fully aware of some of the features of the condition, specifically CRPS spreading and CRPS motor symptoms.

CRPS usually involves a single limb, but in some cases can spread both ipsalaterally or contralaterally (so-called "mirror spread") (van Rijn et al. 2011). Indeed, individuals who experience spread of CRPS to multiple limbs appear to be more likely to have motor symptoms and a more severely affected phenotype (van Rijn et al. 2011). With the initial diagnosis established, I was referred on to specialized Pain Clinics for treatment. Although I achieved complete remission initially, symptoms recurred spontaneously months later, and despite treatment, additional complications developed. At the beginning, my left leg had been affected, but insidiously over the next year I began to develop weakness and clumsiness of my left arm and hand. Despite my reporting this to my pain specialist, this was not recognized or treated as spread of my CRPS, which I believe represented a missed opportunity for early treatment and prevention of progression. In fact, over the next year there was continued spread to involve the entire left and right side of my body and the left half of my face.

It became apparent to me that even well-trained academically-based pain specialists, often coming from anaesthesia backgrounds, are not aware of the full range of neurological complications that can occur with CRPS. In fact, only one of three such pain specialists that I have seen was aware of the phenomena of contiguous spread along spinal segments, mirror image spread to contralateral side of the body, or the development of significant motor symptoms, including weakness, tremor, and dystonias, despite these all being well documented in the medical literature. Three academically-based neurologists fared even worse. One flatly stated that she did not diagnose or treat CRPS. Another neurologist seemed unaware of the possibility of continuous or mirror-image spread, or the development of motor symptoms. The third remained noncommittal about the diagnosis at all, though to be fair, at the time I was evaluated, my symptoms were reasonably well-controlled with multiple medications. It was only after I traveled out of country to see a world-renowned US neurologist specializing in CRPS that the full range of my neurological symptoms were appropriately recognized. Clearly, more education about spread of CRPS and motor involvement needs to be directed towards practicing physicians treating this condition.

b. Awareness of Treatment Options

There were treatment options that I later found to be helpful, that were not offered by my initial pain specialists.

The rationale for using NMDA receptor antagonists is based on the observation that there is over expression of NMDA receptors in animal models of neuropathic pain syndromes. Memantine is a centrally acting, oral NMDA receptor antagonist that has shown efficacy in the treatment of CRPS. (Sinis et al. 2006, 2007). At a time when my symptoms continued to progress despite conventional and some experimental treatments, including a 4 day continuous ketamine infusion (see below), I was discouraged, and physically weak. A friend from residency, now an intensivist working in Montréal, insisted that I come to see the smart and innovative pain specialists at her teaching hospital. She knew of their expertise in treating CRPS since they had approached her for the use of an ICU bed for a CRPS patient, who, having failed all other treatments, was being considered for five day ketamine-induced coma. Having exhausted all treatment possibilities in Toronto, I got an appointment with the pain specialist in Montréal in a few weeks. He started me on memantine, to reduce the glial cell activation that contributes to CRPS. (Memantine is normally used for neuroprotection in Alzheimer's). Improvement was slow but definite. However, after several months of good control, my symptoms again progressed.

Ketamine is another NMDA receptor antagonist, used to quiet overactive glial cells that contribute to neuroinflammation, that has shown efficacy in treating CRPS (Schwartzman et al. 2009; Goldberg et al. 2005; Kiefer et al. 2008; Villanueva-Perez et al. 2007). It is most often used intravenously, but can be used orally or topically. Oral ketamine, administered at bedtime, was added to my treatment regime. Not only did this help control symptoms, but there were far fewer side effects compared to intravenous ketamine that I had previously been given, apparently due to the large first pass effect and the production of active metabolites by the liver, when administered orally (Hocking and Cousins 2003; Legge et al. 2006). Although often administered in divided doses throughout the day, we elected to consolidate the ketamine to a single bedtime dose in order to avoid daytime sedation, which would otherwise interfere with my ability to function at work.

Still, after a few months, tremors returned, and baclofen was added to control them. Again, to avoid daytime sedation, I take this as a single evening dose.

On the basis of genetic studies, it was thought that TLR-4 might be important for initiating the microglial activation that contributes to neuropathic pain following nerve injury. Anti-TLR 4 agents, including low-dose naltrexone, reverses neuropathic pain in animal models (Hutchinson et al. 2008).

Low-dose naltrexone, was added to my regime. Again, there was initial slow improvement, followed by eventual progression of my symptoms.

In the last year, since I have been traveling to Montréal for treatment, my symptoms have been fairly well controlled, and there has been only a slight increase in my requirements for oral corticosteroids. In hindsight, my greatest regret is that I did not see this particular pain specialist early in the course of my CRPS. Had this very knowledgeable and experienced physician been in charge of my care from the outset, I believe I would have had a much better outcome, as I believe that some of the medications he suggested might have prevented spread of my CRPS. None of these options were ever considered by either of the university-based pain specialists I have seen in Toronto.

The above treatments were clearly effective for me, and likely would be effective for other patients. They seem to have minimal side effects, and it would seem reasonable that pain care specialists elsewhere should become familiar with their use. Yet none of the specialists I had seen in Toronto were familiar with their use, despite descriptions in the medical literature.

To this end, better education and communication about CRPS treatments, perhaps including a CRPS telemedicine clinic, sponsored by patient organizations, might be helpful to both pain care specialists and CRPS patients alike. Other forums for sharing clinical experience would also clearly be helpful.

Barriers to accessing specific treatments: ketamine infusions

Ketamine infusions, administered according to various protocols, are promising new treatments for CRPS (Harden 2006; Netherlands Society of Rehabilitation Specialists and Netherlands Society of Anaesthesiologists 2006; Schwartzman et al. 2009; Goldberg et al. 2005; Kiefer et al. 2008; Villanueva-Perez et al. 2007). Unfortunately, they are not widely available. None of the university-affiliated teaching hospitals specialty pain clinics in Toronto were using this treatment modality; it was only through my own concerted efforts that I found a pain specialist who was interested in initiating ketamine treatments, and I became the first patient to receive them.

There were however significant barriers to initiating and maintaining the treatment regime, and it took determination and concerted effort on the part of my new pain specialist to arrange my infusions. Ketamine infusions must be administered in a setting where the patient can be monitored closely. This meant having a bed in the medical day care unit, however hospital administration was reluctant to approve the allocation for the purpose of ketamine infusions, and my pain specialist struggled to justify proceeding. Sometimes, a bed was not available, as patients were scheduled for other procedures, and my treatment protocol would be put on hold. There were challenges with physician supervision as well. The pain care specialist team was on staff at two amalgamated, but geographically separate hospitals, and were present on-site at the hospital where the ketamine infusions were to be administered only two days a week. As a result, it was not possible to follow the recommended protocol of daily ketamine infusions, five days a week for two weeks (Schwartzman et al. 2009; Goldberg et al. 2005). I would usually receive one infusion per week, at most two, and at one point, had a hiatus and treatment of approximately 6 weeks duration. Additional problems arose with the availability of nursing staff during the ketamine treatments. Typically, the medical day care nurse worked from approximately 8 AM to 3:30 PM, which did not allow for sufficient recovery from ketamine induced nausea and vomiting post-infusion before I had to be discharged home.

Although my condition stabilized somewhat during this treatment interval which lasted for several months, I did not improve sufficiently to taper my oral corticosteroids, and I was deemed to be a treatment failure. Both the pain specialist and the hospital administration declined to give me further ketamine treatments. However, the US specialist I had consulted by telephone did not consider me a treatment failure; he felt the patchy, intermittent ketamine infusions were entirely inadequate. Yet this major teaching hospital could not offer me the proven treatment protocol. This clearly demonstrates how difficult it is to access this treatment modality.

It was through consultation with the US specialist that I determined the next steps in my treatment. He felt my best option would be an adequate trial of ketamine infusions. However, traveling to the United States for this treatment would have been prohibitively expensive; $30,000 US for the treatment alone. Ketamine infusions do not require a lot of special equipment or expertise; technically it should have been feasible to administer this in Canada. I felt sure there had to be a way to arrange this in my own country.

A solution occurred to me. In a small town in central Ontario where I act as an itinerant consultant, one of the family physicians who had worked in the same group practice had left to provide pain and anaesthesia services to the community. He agreed to supervise a five day, 24-hour a day subanaesthetic ketamine infusion, with the assistance of one of the local internists in charge of the ICU. These kind and competent physicians collaborated intimately with the US specialist, who supplied detailed treatment protocols (Goldberg et al. 2010). In this small community hospital, there was less administrative bureaucracy, and it was possible to arrange my treatment, thanks to the extraordinary efforts of these two local physicians. The physicians and nursing staff

were unbelievably supportive and caring, and I was overwhelmed by their generosity of spirit. I appreciated how doubly lucky I was; I was receiving superb care, but I also understood that an ordinary patient would not likely have had the resources, contacts, or confidence to arrange the procedure. Clearly, these effective treatments should be available to all patients who need them.

There were few minor problems that did interfere with the treatment. Due to an understandable lack of familiarity with the treatment protocol, there was a delay of several hours in initiating the infusion the first day of treatment. On the fourth night of treatment, ketamine-associated hallucinations became severe, and the infusion was temporarily discontinued. Additional experience and confidence with the use of ketamine might have allowed continued treatment through this complication. Finally, resources were still an issue, so my infusion was tapered and discontinued after four days of treatment. Overall, I received approximately 3 days of full dose ketamine infusion, with an initial half day of dose escalation, and a final half day of dose reduction, instead of the recommended five days of full dose ketamine. Thus, in spite of the impressive efforts of my treating physicians, there were still barriers to following recommended treatment protocols. The infusion certainly ameliorated many of my symptoms, but was not helpful enough to allow me to reduce my oral corticosteroids subsequently. Whether the additional recommended two days of full dose ketamine infusion would have been effective is unclear, but it is certainly possible.

Improved outcomes would be likely if hospital administration and pain specialists fully committed to using this treatment modality. Appropriate allocation of resources would allow proven treatment protocols to be followed (i.e., daily infusions, five days a week for two weeks, or five days of full dose continuous ketamine). Availability of staff for sufficient recovery post-infusion would significantly diminish patient and family caregiver distress.

Barriers to accessing specific treatments: intravenous immunoglobulin treatment

Through review of the medical literature, I became aware that treatment with intravenous immunoglobulins (IVIG) was reported to be helpful in some cases of CRPS (Goebel 2010; Goebel et al. 2010). There are multiple mechanisms by which IVIG can reduce inflammatory or autoimmune processes, including Fc receptor blockade, inhibition of complement deposition, enhancement of regulatory T cells, inhibition or neutralization of cytokines and growth factors, accelerated clearance of autoantibodies, modulation of adhesion molecules and cell receptors, and activation of regulatory macrophages through the FcγRIIb receptor (Ballow 2011). The US specialist agreed that since my symptoms were exquisitely responsive to oral corticosteroids there was a good chance that I would be in the 30 % of CRPS patients who, in his experience, responded to IVIG. Once again, travel to the United States for treatment would have been prohibitively expensive, and it should have been relatively easy to arrange this treatment in Canada. This turned out to be far more challenging than I had anticipated. In one of the teaching hospitals where I am on staff, I often supervise the administration of IVIG to patients with humoral immune deficiency and autoimmune conditions., However, it was not possible for me to receive my IVIG treatments there, due to lack of availability of bed space, or a physician to supervise infusions on five consecutive days. My colleagues did not feel comfortable treating a condition with which they had no experience. My pain specialist in Montréal was certainly open to the idea, but since his background was in anaesthesia, he had no experience with IVIG, and understandably did not feel comfortable using this treatment himself.

It seemed reasonable to think that a neurologist might treat this neuroinflammatory disorder and be able to offer me this IVIG, which they use for Guillain Barre syndrome and chronic inflammatory demyelinating polyneuropathy. Yet this turned out to be a very frustrating experience. Despite calling ahead, and explaining that the sole purpose of my visit would be to obtain IVIG for CRPS, the first academically-based neurologist I saw flatly stated that she did not treat CRPS. She agreed to supervise my treatment under the direction of the US specialist if an MRI scan of my brain to rule out other pathology. As a non-urgent case, it was several months before the procedure and return visit to see the neurologist, but she then told me she did not feel comfortable supervising IVIG infusions; a waste of 6 months time. My family physician then contacted one of the neurologists at our own hospital. It was several months before I was seen, only to be told that he had reviewed the literature and did not feel that there was sufficient evidence of efficacy to justify the use of IVIG in CRPS. I left frustrated at the lack of progress after several more months.

I continued to explore other opportunities to arrange IVIG treatment. A neurologist at our university had expertise in using IVIG for chronic inflammatory demyelinating polyneuropathy and was setting up a study to assess the efficacy of subcutaneous immunoglobulins in chronic neuropathic pain states, including CRPS. After an assessment, I was informed that the neurologist did not have funding, but hoped that this would occur within the next 6 to 12 months. However, my pain was too well-controlled for me to qualify for this study; it would be necessary for me to reduce my oral corticosteroids so that my pain scores would increase. If I did qualify, there was an equal chance that I might receive placebo

rather than active treatment. She declined to treat me empirically with IVIG, despite the recommendation of the US specialist. I did not believe the trial would be the right course of action for me; I knew that in the past if my pain got out of control, it was very hard to get it back under control, and this usually meant a further escalation in the use of oral corticosteroids. In addition, I knew that if I tapered my corticosteroids, my motor symptoms would also return, and I would become nonfunctional, unable to work, feed or dress myself. I could not risk that I would receive a placebo under those circumstances. My family physician agreed.

A colleague in my own division came to my assistance. He approached a hematologist at our hospital who was familiar with the use of IVIG, and who agreed to supervise my treatment if it was directed by a treating physician with expertise in CRPS. Although the US specialist had reviewed the details of my case by telephone and e-mail, I would formally have to become his patient. Once again, there was a cancellation, and I was able to fly to the US to see the specialist there within a few weeks.

The US specialist did not doubt the diagnosis of CRPS. Although most of my symptoms were well controlled by the medications prescribed by my pain specialist in Montréal, the US specialist detected subtle abnormalities, including slight motor weakness and muscle wasting, more prominent on the left side, generalized hyperreflexia and autonomic dysregulation of blood vessel tone throughout my body. He reaffirmed his previously stated opinion that I would be a good candidate for IVIG treatment, and agreed to send his recommendations and the appropriate treatment protocols to my other physicians. My IVIG treatments began at one of my own hospitals here in Toronto a month later, well over a year after the US specialist had first recommended that I receive it.

This sequence of events again illustrates the difficulty of obtaining certain treatments for CRPS. This results in part from the fact that many neurologists seem to have long since given up on treating the condition; they merely refer CRPS patients to pain clinics, which are typically staffed by individuals trained in anaesthesia, individuals who have no experience in the use of IVIG, and who are therefore understandably reluctant to consider its use. To be fair, there is limited evidence for the efficacy of IVIG in the treatment of CRPS, but, given the current evidence of underlying inflammatory and autoimmune components of CRPS, there is certainly a rational basis for its use in this condition, and further studies are warranted. It took persistence from my family physician and me, and the assistance of my colleagues to finally arrange this treatment. I would be surprised if an average patient or family physician would have had the confidence or resources to persist against the many obstacles that we faced.

What went right

Several things have contributed to my having a relatively good outcome. First and foremost, I have a conscientious and supportive family physician. Not only did she help confirm the diagnosis, but she was instrumental in my achieving initial remission by promptly initiating treatment once the diagnosis was made. This was successful due to a second factor that supported a good outcome: the existence of online treatment guidelines for CRPS, which she did not hesitate to access or discuss with me. My family physician also deserves credit for supporting me in seeking additional opinions from various specialists, as initial treatment options were inappropriate or unsuccessful.

My training as an academic physician also undoubtedly contributed to my ability to stablize my condition. As initial treatments began to fail, I was able to access the medical literature to better assess the appropriateness of my treatment, and to seek out possible additional treatments not offered by my initial consultants. I spent days reading and reviewing the medical literature once again. Even with my background in science and medicine, I found the information overwhelming and somewhat confusing. There were so many different aspects to pathology and treatment; it was hard to find a common theme. However, two important things came of my efforts. First, there were a few names that repeatedly came up as authors in the papers about CRPS research and treatment. One was the US specialist I eventually consulted. His work spanned many different aspects of CRPS, and he had a long career in the field. On the website of his academic institution, it was possible to verify that he had the appropriate credentials and breadth of experience to have significant expertise in treating CRPS.

The second important discovery was learning about the Reflex Sympathetic Dystrophy Syndrome Association (RSDSA), an organization devoted to improving diagnosis and treatment of CRPS patients through research and education. There was an excellent bibliography of relevant papers, hand-picked by their consulting experts, grouped into topics, all with full-text versions easily accessible on their website. This was a great help in organizing my concepts about CRPS, and helping me decide how to proceed further.

It was through a friend and colleague that I identified both the pain specialist in my city of residence who treated me with intermittent out-patient ketamine infusions, and the pain specialist in Montreal who now prescribes various medications that successfully control my symptoms and is largely in charge of my ongoing care. It was through colleagues that I was able to arrange a five day inpatient ketamine treatment, and later, IVIG treatments, both under the guidance the US specialist.

My access to these resources ultimately contributed to my relatively good treatment outcome. Most of these would not be available to the average non-physician patient.

Treatment: future possibilities

Despite the availability of various options for the treatment of CRPS, they are still not uniformly effective, and many have significant side effects. Better treatments are clearly needed, and will only come from further research into the underlying pathogenesis of this condition. Over the last several years, two important themes have emerged. First, glial cells become overactive, and secrete pro-inflammatory mediators that likely contribute to the pain, motor, vascular, and autonomic symptoms of CRPS. Second, there is increasing recognition that autoimmunity may play a significant role in the majority of CRPS patients. Together, these observations support the concept that CRPS is a neuro-inflammatory condition. Effective treatments will need to address this aberrant physiologic response.

Although intravenous ketamine, an NMDA receptor antagonist, appears to be effective in treating CRPS, it has significant side effects (nausea, vomiting, and hallucinations), and since administration must take place under carefully monitored conditions, it is not readily available to most patients. Oral administration, while helpful, is likely less effective, and physicians may be reluctant to prescribe it because of the perception of the risk of addiction, although I do not feel this has been relevant in my own care, and I believe more patients might benefit from its use. Alternate NMDA receptor antagonists, having fewer side effects, would be desirable.

Other options to reduce neuroinflammation should be developed. One potential treatment is IL-10 gene therapy (Soderquist et al. 2010). IL-10 is an anti-inflammatory cytokine that appears to reduce the neuroinflammation associated with neuropathic pain. Further studies of its use of CRPS are planned.

Additional treatment options might be suggested by tapping into pre-existing expertise in treating autoimmune and inflammatory disorders. Rheumatologists have extensive experience in treating such conditions, and the last several years have seen the development of numerous new agents. Their experience might well be applied to the treatment of CRPS, if they could be encouraged to take an interest. In my own experience, most rheumatologists do not treat CRPS, however there may now be a good reason for this situation to change, given our new insight into the inflammatory and possible autoimmune nature of CRPS.

Financial, occupational, and psychosocial aspects of CRPS

Although I have a reasonable income and live in a country with government-sponsored healthcare, I was not immune to the negative financial impact of living with a chronic condition like CRPS. It has been necessary to take considerable time off work for seemingly endless appointments, treatments and their complications, and sometimes the condition itself, despite usually good symptom control. Now that I travel out of province to see my pain specialist, even simple appointments mean taking a day and a half off work. My government-sponsored healthcare did not cover the costs when I traveled to the United States to seek expert medical advice. I was lucky to have the financial resources to do this, but many patients would not have the same option, which would limit their access to appropriate care. My drug plan does not cover all of my medications, particularly the more expensive biologic agents, as they are being used "off-label" to treat my CRPS. And although I carry private disability insurance, it has not fully covered the loss of income I have experienced from my CRPS. Concern over these financial matters adds to the stress of dealing with CRPS, which can exacerbate the condition. For patients with lower incomes, patients not covered by disability insurance, and certainly patients living in countries without healthcare coverage, these concerns would be overwhelming. Although important to address, solutions to these financial concerns are beyond the scope of this article.

CRPS patients and their family members often experience a negative impact on their careers, due to time taken away from work for the condition or for caregiving. This is certainly true of individuals in different fields, but for those in healthcare-related academic disciplines, there may be a unique solution; ironically, one that arises from the challenges in accessing expert medical care. The enormous amount of time it takes to research and arrange expert medical care can leave little time for other academic pursuits. Independently, many of the individuals in healthcare or the biological sciences, who are now affiliated with the RSDSA, have refocused their academic interests on CRPS as a result of having the condition themselves, or having an affected family member. This redirection of professional effort effectively dovetails personal and academic interests. Hopefully, this strategy will assist all patients with CRPS, as the academic individuals personally affected by CRPS are highly motivated towards improving the diagnosis and treatment of this condition.

The symptoms of CRPS can be frightening; severe pain, dramatic color changes in a limb, bizarre motor symptoms, even loss of motor control. These fears are compounded when there is the frequently experienced delay in diagnosis, lack of immediate access to expert medical care, or treatment failure. The stress of dealing with this often severe and disabling condition can take a significant emotional toll on the patient and their family. Since no one single treatment strategy will work for all patients, it can be difficult and confusing trying to decide which treatment might be helpful. Even if a treatment choice is clear, it is not always easy to

access it, In the future, hopefully these issues can be overcome with more prompt diagnosis, access to expert medical care and better treatments. Organizations such as the RSDSA can be of enormous benefit in this regard. Not only may patients find their website while searching the internet for a diagnosis, but they will find good information about treatment options, and can get assistance in finding physicians with expertise in treating the condition. Learning about other patients' positive outcomes, and knowing that many scientists and clinicians are working to find better treatments, can be of significant emotional benefit as well.

As a physician, I was lucky to have access to a unique and wonderfully helpful resource: my colleagues. Always supportive, they shared their experience and expertise, and helped me sort out my various treatment options when expert medical care was lacking, for which I am very grateful.

The importance of condition-focused organizations

The positive impact of condition-focused organizations, particularly those for uncommon **or** rare disorders, cannot be over-emphasized. For example, in my own field, I have worked with organizations focused on anaphylaxis and hereditary angioedema. Anaphylaxis Canada is an organization that promotes awareness and education regarding the condition and its treatment, maintains patient support groups, has successfully lobbied for better food labeling, has developed a system to notify registered members about important food recalls, has supported the development and distribution of guidelines for the care of affected children in schools and other settings, has successfully supported the passing of provincial legislation mandating the application of these guidelines, and actively supports research into the condition, not only by raising and providing funds , but also by maintaining a registry of members who agree to be contacted when opportunities to participate in research arise. As with CRPS, there is often limited or delayed access to expert medical care. Anaphylaxis Canada supports an excellent website, reviewing the basic aspects of the condition and its treatment to help fill these gaps. As recently as 15 years ago, parents would report difficulty convincing teachers that their child's food allergy was real and potentially fatal, and that the use of epinephrine autoinjectors to treat reactions was critical. Today, legislation mandates that all teachers undergo training to recognize and treat anaphylaxis, and there is now widespread public awareness of the condition. To accomplish these impressive results, Anaphylaxis Canada has collaborated with the physician specialist organization, The Canadian Society of Allergy and Clinical Immunology, with food service and pharmaceutical industries, and government agencies. Similar organizations, such as the Food Allergy Network in the United States, exist in other countries. The Canadian Hereditary Angioedema Network is a patient-based group dedicated to working with physicians, scientists, nurses, the pharmaceutical industry, and government agencies to improve care for patients with this rare disorder. They have helped bring together the above mentioned stakeholders for recent international meetings to develop guidelines for the diagnosis and treatment of hereditary angioedema. They facilitate cooperation between patients, clinicians and their specialist organizations, basic scientists, government agencies and the pharmaceutical industries, helping to shape and develop research protocols for emerging treatments. These meetings provide a forum where patients can directly interact with industry; patients have the opportunity to point out valid concerns or issues the industry might not considered, so that these issues can be incorporated into the design of research protocols from the outset, saving time and money. Participating in the design of trials for new treatments invests patients in the process, and increases their willingness to participate in those trials. Similar impressive results leading to new treatments which have arisen from cooperation between patients, clinicians, scientists and industry have been documented for lymphangioleiomyomatosis (Ingelfinger and Drazen 2011).

The mission of the RSDSA "is to promote public and professional awareness of CRPS and to educate those afflicted with the syndrome, their families, friends, insurance and healthcare providers on the disabling pain it causes". They "encourage individuals with CRPS to offer each other emotional support within affiliate groups, and are committed to raising funds for research into the cause and cure of CRPS." Many of the resources they offer have been documented elsewhere in this article. In addition, in recent years they have sponsored translational workshops including "Activated Glia: Targets for the Treatment of Neuropathic Pain" in 2010, and "Imaging Neuroinflammation and Neuropathic Pain" in 2011. These workshops have facilitated collaborative research between interested clinicians and scientists, bringing in other stakeholders including patients, pharmaceutical Industries and others at the same time. Similar organizations exist in the United States and other countries.

While some of the issues faced by condition-specific organizations are unique to the disorder on which they are focused, there are clearly shared themes which emerge, and these organizations can look to each other to learn from each other's successes. Patients, physicians, basic scientists, and the pharmaceutical industries alike can all benefit from the services offered by these organizations. But no one will benefit if they are not aware of the existence of these organizations, so promoting awareness of their own existence is critical.

Conclusions

The physician as patient experience offers a unique perspective from which to re-evaluate the management of a particular condition.

Early diagnosis of CRPS needs to be improved. Increased awareness of the condition through improved education of medical students, residents, and practicing physicians would likely be helpful, however, specific targeting of fracture clinics to spark the initial consideration of the diagnosis might be an effective means to provide early diagnosis and improve the outcome for many CRPS patients. Existing resources that might support such efforts have been suggested.

There can be unacceptably long delays in accessing expert medical care at pain clinics, where waiting lists can be particularly long. Mechanisms should be put in place to ensure that all CRPS patients have prompt access to expert medical care, as this will likely improve outcomes.

Although several effective treatments for CRPS have been recognized in the past several years, not all pain specialists are familiar with their use. Significant barriers to the administration of some of these treatment modalities have been reviewed, as have been suggestions to overcome them. Increased awareness of the efficacy of these treatments will hopefully lead to increased willingness of pain specialists to provide them, and hospital administrations to support their use. Better education is needed so that the standard of care of CRPS can be raised to a uniform level for the benefit of all patients. Some of the difficulty in accessing good care for CRPS relates to the fact that this multifaceted condition spans many different disciplines, and some of the treatment options currently available may be outside the realm of expertise of a particular pain specialist. Physicians treating CRPS need encouragement to step outside the usual boundaries of their own specialty so that their patients may benefit from these effective treatment modalities. This could simply mean the willingness to collaborate with specialists in other disciplines, who have the pre-existing experience with the use of these treatment modalities.

Substantial evidence supports the concept of CRPS is a neuroinflammatory condition. This suggests that future treatments should be directed against neuroinflammation, and suggestions as to how to best accomplish this have been reviewed.

Existing resources, especially the RSDSA, that have been helpful to the author as a physician and as a patient, have been reviewed. Improved awareness of these resources would be of benefit to other treating physicians as well as their patients.

Conflict of interest The author has no relevant conflict of interests to declare

References

Ballow M (2011) The IgG molecule as a biological immune response modifier: mechanisms of action of intravenous immune serum globulin in autoimmune and inflammatory disorders. J Allergy Clin Immunol 127(2):315–323

Bernateck M, Karst M, Gratz KF, Meyer GJ, Fischer MJ, Knapp WH, Koppert W, Brunkhorst T (2010) The first scintigraphic detection of tumor necrosis factor-alpha in patients with complex regional pain syndrome type. Anesth Analg 110(1):211–215

Bianchi C, Rossi S, Turi S, Brambilla A, Felisari G, Mascheri D (2006) Long-term functional outcome measures in corticosteroid-treated complex regional pain syndrome. Eura Medicophys 42(2):103–111

Cappello ZJ, Kasdan ML, Louis DS (2012) Meta-analysis of the imaging techniques for the diagnosis of complex regional pain syndrome Type I. J Hand Surg Am 37(2):288–296

De Bosscher K (2010) Selective glucocorticoid receptor modulators. J Steroid Biochem Mol Biol 120:96–104

Goebel A (2010) Immunoglobulin responsive chronic pain. J Clin Immunol 30(Suppl 1):S103–S108

Goebel A, Baranowski A, Maurer K, Ghiai A, McCabe C, Ambler G (2010) Intravenous immunoglobulin treatment of the complex regional pain syndrome: a randomized trial. Ann Intern Med 152(3):152–158

Goldberg ME, Domsky R, Scaringe D, Hirsh R, Dotson J, Sharaf I, Torjman MC, Schwartzman RJ (2005) Multi-day low dose ketamine infusion for the treatment of complex regional pain syndrome. Pain Physician 8(2):175–179

Goldberg ME, Torjman MC, Schwartzman RJ, Mager DE, Wainer IW (2010) Pharmacodynamic profiles of ketamine (R)- and (S)- with 5-day inpatient infusion for the treatment of complex regional pain syndrome. Pain Physician 13(4):379–387

Harden RN (ed) (2006) Complex regional pain syndrome: treatment guidelines. RSDSA Press, Milford CT

Hocking G, Cousins MJ (2003) Ketamine in chronic pain management: an evidence based review. Anesth Analg 97:1730–1739

Hutchinson MR, Zhang Y, Brown K, Coats BD, Shridhar M, Sholar PW, Patel SJ, Crysdale NY, Harrison JA, Maier SF, Rice KC, Watkins LR (2008) Non-stereoselective reversal of neuropathic pain by naloxone and naltrexone: involvement of toll-like receptor 4 (TLR4). Eur J Neurosci 28(1):20–29

Huygen FJ, Niehof S, Zijlstra FJ, van Hagen PM, van Daele PL (2004) Successful treatment of CRPS 1 with anti-TNF. J Pain Symptom Manage 27(2):101–103

Inchiosa MA Jr, Kizelshteyn G (2008) Treatment of complex regional pain syndrome type I with oral phenoxybenzamine: rationale and case reports. Pain Pract 8(2):125–132

Ingelfinger JR, Drazen JM (2011) Patient organizations and research on rare diseases. N Engl J Med 364:1670–1671

Jensen MP, Gammaitoni AR, Bolognese JA, Alon A, Smugar SS, Galer BS, Hewitt DJ (2011 Dec 7) The pain quality response profile of pregabalin in the treatment of neuropathic pain. Clin J Pain. [Epub ahead of print]

Kiefer RT, Rohr P, Ploppa A, Dieterich HJ, Grothusen J, Koffler S, Altemeyer KH, Unertl K, Schwartzman RJ (2008) Efficacy of ketamine in anesthetic dosage for the treatment of refractory complex regional pain syndrome: an open-label phase II study. Pain Med 9(8):1173–1201

Kohr D, Singh P, Tschernatsch M, Kaps M, Pouokam E, Diener M, Kummer W, Birklein F, Vincent A, Goebel A, Wallukat G, Blaes F (2011) Autoimmunity against the β(2) adrenergic receptor and muscarinic-2 receptor in complex regional pain syndrome. Pain 152(12):2690–2700

Kozin F, Ryan LM, Carerra GF, Soin JS, Wortmann RL (1981) The reflex sympathetic dystrophy syndrome (RSDS). III. Scintigraphic studies,

further evidence for the therapeutic efficacy of systemic corticosteroids, and proposed diagnostic criteria. Am J Med 70(1):23–30

Legge J, Ball N, Elliot DP (2006) The potential role of ketamine in hospice analgesia: a literature review. Consult Pharm 21:51–57

Maihöfner C, Seifert F, Markovic K (2010) Complex regional pain syndromes: new pathophysiological concepts and therapies. Eur J Neurol 17(5):649–660

McCabe CS, Haigh RC, Blake DR (2008) Mirror visual feedback for the treatment of complex regional pain syndrome (type 1). Curr Pain Headache Rep 12(2):103–107

Netherlands Society of Rehabilitation Specialists, Netherlands Society of Anaesthesiologists. Complex regional pain syndrome type I guidelines, 2006. (Available online http://www.rsds.org/clinical_guidelines.html)

Perez RS, Zuurmond WW, Bezemer PD, Kuik DJ, van Loenen AC, de Lange JJ, Zuidhof AJ (2003) The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study. Pain 102(3):297–307

Ribbers GM, Stam HJ (2001) Complex regional pain syndrome type I treated with topical capsaicin: a case report. Arch Phys Med Rehabil 82(6):851–852

Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M (2009) Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. Pain 147(1–3):107–115

Sinis N, Birbaumer N, Schwarz A, Gustin S, Unertl K, Schaller HE, Haerle M (2006) Memantine and Complex Regional Pain Syndrome (CRPS): effects of treatment and cortical reorganisation. Handchir Mikrochir Plast Chir 38(3):164–171

Sinis N, Birbaumer N, Gustin S, Schwarz A, Bredanger S, Becker ST, Unertl K, Schaller HE, Haerle M (2007) Memantine treatment of complex regional pain syndrome: a preliminary report of six cases. Clin J Pain 23(3):237–243

Soderquist RG, Sloane EM, Loram LC, Harrison JA, Dengler EC, Johnson SM, Amer LD, Young CS, Lewis MT, Poole S, Frank MG, Watkins LR, Milligan ED, Mahoney MJ (2010) Release of plasmid DNA-encoding IL-10 from PLGA microparticles facilitates long-term reversal of neuropathic pain following a single intrathecal administration. Pharm Res 27(5):841–857

van Rijn MA, Marinus J, Putter H, Bosselaar SR, Moseley GL, van Hilten JJ (2011) Spreading of complex regional pain syndrome: not a random process. J Neural Transm 118(9):1301–1309

Villanueva-Perez VL, Cerdá-Olmedo G, Samper JM, Mínguez A, Monsalve V, Bayona MJ, De Andrés JA (2007) Oral ketamine for the treatment of type I complex regional pain syndrome. Pain Pract 7(1):39–43

Zollinger PE, Tuinebreijer WE, Breederveld RS, Kreis RW (2007) Can vitamin C prevent complex regional pain syndrome in patients with wrist fractures? A randomized, controlled, multicenter dose–response study. J Bone Joint Surg Am 89(7):1424–1431