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Complex regional pain syndrome – False hopes and miscommunications

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ABSTRACT

Complex regional pain syndrome (CRPS) has been considered to be an autoimmune disease and there have been clinical trials with intravenous immunoglobulin. Often the etiology of the so-called CRPS diagnosis cannot be discerned and there are no validated instruments that provide functional metrics. The term complex regional pain syndrome (CRPS), coined in 1994 to describe patients in whom the pain is out of proportion to the injury, was actually a diagnosis proposed during the American Civil War, but was originally known as causalgia. Physicians have long observed similar sensitivity and inflammatory symptoms following periods of immobilization and disuse, which generally resolve within a few months of remobilization. Following the original description, persistent disproportionate pain would come to be known under many other names until researchers theorized that it was related to dysfunction in the sympathetic nervous system, after which it acquired the moniker, Reflex Sympathetic Dystrophy ("RSD"). In the latter quarter of the twentieth century, after researchers failed to prove the connection between the pain and the sympathetic nervous system, a small cadre of physicians–without rigorous science—invented CRPS. This new descriptor, CRPS, has become not only a diagnosis without objective data but with proposed criteria involving ambiguous signs and symptoms with low specificity. It has led to patients being treated erroneously with sympatholytic drugs, with or without pharmaceutical or surgical blockade of the sympathetic nervous system, unwarranted use of ketamine infusions, inappropriate use of narcotics and nerve stimulation. Intravenous immunoglobulin infusions have not been effective in the treatment of chronic pain. The indiscriminate use of pain medications to treat subjective symptoms of unclear diagnoses can be a risk factor for opioid and analgesic misuse or abuse.

1. Introduction

Historically, the medical profession has been generally ineffective in treating patients with pain. One of the more common conditions associated with chronic pain is fibromyalgia, a syndrome of unknown etiology whose existence as a real disease with a true pathophysiology is itself dubious. While the discovery of analgesics has brought notable improvements in reducing pain complaints, many medications are addictive, or may have other significant adverse effects. The risk of adverse effects is magnified when several physicians prescribe a patient with a combination (or cocktail) of pain and mood-altering medications, or if patients mix pain medications with alcohol. Many patients convert mental distress into physical symptoms, but treatment of these symptoms is unlikely to improve the underlying condition. Indeed, pain organizations have long defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." [1] Moreover, they have long acknowledged that "pain in the absence of tissue damage or any likely pathophysiological cause [usually … happens for psychological reasons.]" [1] Due to the stigma of mental illnesses, patients may search for physical causes of their pain; rather than seeking appropriate psychiatric treatment. Striking a balance between addressing subjective complaints but avoiding inaccurate labeling of patients has been fraught with challenges, and these challenges are not simply limited to the scientific arena, but are impacted by social norms, financial considerations and regulatory factors. [2]

Abbreviations: CRPS, Complex Regional Pain Syndrome; IASP, International Association for the Study of Pain; PANDAS, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections; PHN, Post herpetic neuropathy; RSD, Reflex Sympathetic Dystrophy; RTFM, Rodent Tibial Fracture Model; TRV, Traumatic arterial vasospasm

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Fig. 1. Characteristics of pain. Many factors may contribute to pain, and affect the severity, distribution and quality of pain.

The clinical evaluation of pain is difficult because of the subjective nature of the symptom (Fig. 1). However, there are guiding principles that must be followed when diagnosing and treating pain. First and foremost, if there is pain, an etiology must be sought. Once found, the pain complaints should be proportionate to the diagnosed injury or disease. Biologically, greater tissue destruction and nerve damage causes more pain that minor injuries, depending on the location and density of sensory proprioceptive nerve endings. Not determining the cause of disproportionate pain and simply treating the symptoms may lead to disastrous results, such as delayed diagnosis or erroneous diagnosis due to potential masking of the pain, or denial of appropriate curative treatment. Sometimes such events may have adverse outcomes. On the other hand, provided that an underlying physical or psychiatric etiology cannot be found, or the disease cannot be cured, palliative treatment may be appropriate to improve quality of life. It is estimated that one third of the population of the world is plagued by either chronic or recurrent pain [3]. Chronic pain affects approximately 50% of older individuals who are community dwelling, and 80% of those who live in nursing homes [4].

2. Complex regional pain syndrome

The coining of the phrase "Complex Regional Pain Syndrome (CRPS)" occurred at an International Association for the Study of Pain (IASP) conference in 1993, when a panel congregated to develop criteria for CRPS [5]. Typical symptoms of CRPS include pain in a single extremity. The pain is usually characterized as a "burning" or may be described as resembling repeated electrical shocks. CRPS was classified into types 1 and 2 in 1994 [6]. Type 1 was described as occurring after trivial injury in which there is no nerve damage. In type 2, the injury may be more serious, such as a fracture or direct trauma, and nerve damage can be elicited. Type 2 is real in that it has a clear pathology along a specific nerve. Type I is the problem that physicians have seemingly defaulted to when faced with a lack of clear etiology and pathophysiology.

From the standpoint of "bedside-to-bench" research, many significant discoveries of pathogenesis have been made based on initial observations of clinical patterns. CRPS perhaps demonstrates the worst of "bedside-to-bench". The embracing of vague symptomatology that theoretically could be attributable to the sympathetic nervous system was the basis for the early descriptive name for CRPS type 1, namely Reflex Sympathetic Dystrophy (RSD), but no scientific studies were able to support such a theory.

In 2003, the Mayo Clinic conducted the only US population study of CRPS and found it to be extremely rare (5.5 per 100,000-person years); women outnumbered men [7]. More than 74% of patients in the Mayo study recovered with minimal or no treatment. While a 2007 Netherlands study, using less rigorous diagnostic criteria, found a higher incidence of CRPS (26.2 per 100,000 person/years), it was still remarkably rare [8]. The peak age was between 61 and 70 years, consistent with the onset of chronic pain associated with aging in the general population. Mean age at diagnosis was 52.7 years. A higher risk was found for postmenopausal women.

Rarely, CRPS has also been reported in children. In one study from the United Kingdom, the incidence was 1.16 per 100,000 children between the ages of 5 and 15. Only 26 cases were found, reported over a period between Nov 1, 2011 and Oct 31, 2015, and were predominantly (73%) female. Most cases had single site involvement and legs were more frequently involved than arms [9]. The mean interval between symptom onset and diagnosis was 2 months. Studies report almost

100% recovery in children and adolescents with extremely aggressive physical therapy, forced movement of the affected limb, and cognitive behavior therapy. For example, Sherry et al. [10] achieved a 92% success rate with an intensive exercise program without the use of medication or more intensive procedures.

Because of the reported rarity of CRPS, quality scientific studies using appropriate sample sizes do not exist and are unlikely to ever exist. For example, on a statistical basis using the Mayo Clinic's numbers, a researcher would have to enroll, examine, and follow 400,000 patients for 5 years to see 100 cases of CRPS develop among the cohort. Moreover, given its reported resolution rate of 74%, only 26 of those patients would develop chronic CRPS. On a national scale, this would mean that there should be less than 21,170 cases of chronic CRPS in the entire country during a five-year period. Based upon the Mayo Clinic's study, only 390 chronic CRPS patients would be expected over a five-year period within a major metropolitan area (6,000,000 population). Despite its epidemiological rarity, there are many “CRPS experts” aggressively diagnosing this syndrome and reporting hundreds of patients in a single practice. Nonetheless, the epidemiology suggests that most physicians will never encounter a significant number of CRPS patients.

As reported by Mallis-Gagon in 2014, among patients referred to a Major Metropolitan Tertiary Care Pain Clinic with a diagnosis of CRPS, less than 28% actually had the diagnosis, and more than 50% actually had other confirmable diagnostic entities [11]. Moreover, the same study showed that upon observation in an in-patient setting, it was determined that almost 20% of “CRPS” patients had a primary psychiatric conversion disorder or were self-inducing symptoms and signs. Therefore, reported incidence from population studies that do not include extensive in-patient observation and careful work up for other conditions may be grossly overstated.

In contrast to its extreme rarity in the clinical or research setting, CRPS appears frequently in the medical-legal context. While Governmental statistics from the U.S. Department of Labor and the CDC suggest that less than 10% of all accidents are work related, multiple CRPS studies where compensation status is indicated report that anywhere from 54 to 81% of patients with CRPS were receiving workmen's compensation, a disparity that cannot be explained statistically [12]. In light of the Netherlands' generous “no fault” national disability program, which pays 75% of a worker's daily wage, the greater reported Dutch incidence over the Mayo study could also be related to financial incentives [13]. In addition to workplace accidents, CRPS is reported frequently in personal injury suits, often after extremely minor accidents that do not involve a fracture or major tissue damage [14].

2.1. Inciting events

It has been proposed that CRPS occurs following a particular inciting event, usually trauma. In both the Mayo [7] and Netherlands [8] population studies, the most common inciting traumatic events were fractures and sprains; conditions that generally involve extended periods of immobility post-injury [7,8]. In the Mayo study, a fracture (46%) or sprain (12%), made up the majority of cases (58%). In the Netherlands study, fractures (44%) and sprains (17.6%) represented 61% of all cases. An additional 12.2% of cases followed elective surgery, usually of the hand or wrist, which would likely also involve some post-surgical period of immobility. Terkelsen, et al., reported that casting of four-week duration produces transient CRPS symptoms in healthy controls, most likely attributed to immobility [15]. Significantly the Mayo Study reported that CRPS following fractures resolved in 91% of all cases of fractures and 78% of sprains. Therefore, it is unclear whether most of the traumatically induced CRPS cases reported in population studies belong to a distinct clinical entity, or are simply expected transient symptoms following extended periods of immobility due to casting, compression dressings, or surgical recovery.

2.2. Is it really post-immobilization syndrome?

While population incidences reported in the Mayo and Netherlands studies are cited in nearly every CRPS research paper, including its purported relation to fractures, these widely referenced studies contain no description of the type, area, or grade of fracture; the method used to reduce it, or the period of immobility. Nor does it explain whether recovery from the fracture was routine or protracted; or complicated by non-union. Diagnostically and prognostically, there are vast differences among various fractures; the term includes everything from a hairline fracture reduced with a short period in a compression boot to a severe open fracture with surrounding soft tissue damage, several surgeries, and protracted immobilization [16]. Likewise, there are significant differences among sprains, which can range from a minor Grade 1 inversion ankle sprain to a Grade 3 high ankle sprain [17,18]. The injury, treatment and expected period of immobilization are completely different, but all of these events are carelessly lumped together as purported inciting events.

Virtually every CRPS study, including the seminal Mayo and Netherlands population studies, abandon diagnosis-based classification of the inciting event, and report only upon whether a particular constellation of symptoms occurred afterwards–even though many of these symptoms and signs occur naturally following even a relatively short period of immobility—and can persist through protracted periods of recovery [19]. The absence of diagnosis-based classification of an event means that the current population studies provide no insight into what types of fracture/sprain events are likely to cause these symptoms, whether they are truly unusual given the inciting event and treatment, and whether it is a separate clinical entity, or simply protracted recovery from the initial event or immobility. Moreover, the population studies report that the rate of recovery from a fracture or sprain event is more favorable and more complete. Absent is an explanation as to why these post fracture/sprain symptoms, most of which completely recover within several months, deserve a separate clinical classification, or should be described as CRPS.

Adding credence to the theory that post fracture/immobilization inflammation may be a completely separate clinical entity from CRPS are animal studies that attempt to replicate the symptoms. In that regard, one specific animal model is the Rodent Tibial Fracture Model (TFM), which involves causing a closed tibial fracture under general anesthesia followed by several weeks of casting. As noted in a recent review article, almost all of the RTFM rodents manifest CRPS-like symptoms for several weeks after the cast removal, and in virtually all cases, the symptoms spontaneously resolve within a few months of cast removal [20]. The authors noted that further research is required to “help clarify whether ‘acute’ and ‘chronic’ post traumatic CRPS describes the chronology of the same disorder, or describe very different disease processes that are initiated almost immediately at the time of injury. So far, the human epidemiological and rodent studies suggest that there is a common constellation of symptoms that develop after fracture, immobilization or disuse of a limb in virtually all cases, which resolves spontaneously within weeks to several months. Therefore, what is most frequently described as CRPS following immobilization may not be clinically significant, no less a separate clinical entity. Unfortunately, CRPS research has combined what may be ordinary symptoms of immobilization with very rare and unexplainable “chronic” pain following any number of events, which can then be used to overstate the incidence of the alleged condition.

2.3. Other alleged causes of CRPS

Because fracture/sprain events represent approximately 60% of claimed CRPS cases, and the terms are themselves extremely broad, attempts to categorize the remaining alleged inciting events comprising the other estimated 40% are even more imprecise; and in some cases, causes are not identified. For example, the Netherlands population

study reported a relatively high incidence (over 20%) of undefined causes, including “no inciting event” (10.8%), “others” (8.8%), and “unknown” (1.7%) [8]. A later 2010 study, also from the Netherlands, found that CRPS in 7% of all patients occurred spontaneously [21]. According to this 2010 de Rooij, study, “traumatic” CRPS had a mean duration of less than 6 months while “spontaneous” CRPS patients had mean duration of nearly 2 years, which is also consistent with the Mayo's (and animal) studies' findings of spontaneous and complete CRPS resolution that usually follows fractures and sprains [7]. The Mayo study broadly characterized the remaining minority incidences as stroke, crush injuries, and contusions, which again are medically imprecise terms, divorced of any formal specificity or classification. As reported by in Mallis-Gagnon's 2014 paper [11], upon in-patient observation, CRPS was determined to be self-induced in 15.4% of all patients, and 26.7% of all women meeting the criteria. Anecdotally, inciting events attributed to the onset of CRPS include strokes, cardiac events, spinal injuries/surgery, and viruses. Again, while CRPS papers consistently propose the condition as being related to trauma, the underlying research fails to substantiate a direct relationship between trauma and prolonged chronic CRPS, particularly because it can develop spontaneously. Instead, it suggests the development of transient symptoms following more traditional forms of trauma, i.e. sprains, fractures and surgery, and prolonged chronic symptoms following no trauma or trivial trauma. What is consistent among all the studies is that the chronicity and duration of the symptoms appears completely unrelated to the degree or nature of the initial injury.

While surgery is often included as a potential trigger for the development of CRPS symptoms, there does not appear to be any method to exclude any number of surgical (or post-surgical) complications causing neural or ischemic damage as being the actual cause of symptoms. At least one animal study conducted has shown that direct surgical trauma to a distal nerve can cause CRPS symptoms [22]. Likewise, tourniquets can produce ischemic damage manifested as CRPS-like symptoms in animal studies [23]. These animal studies present direct evidence that surgical team technique or error can cause specific nerve injuries that can produce symptoms attributed to CRPS. None of the studies attributing CRPS to “surgery,” however, account for potential bias against labeling the development of neural or ischemic complications as surgical team error. Moreover, the CRPS label can potentially harm efforts to advance or improve surgical standards, since the development of these symptoms is currently attributed to a “pain syndrome of unknown pathology” rather than differences in surgical technique, technical ability, or failure to mobilize the limb soon after surgery. The harm in propagating an unproven condition has led to an editorial questioning the syndrome's existence. In that editorial, del Pinal explains that in his surgical practice “lack of stable fixation, poor fixation, and poor fracture reduction are the main causes of incorrectly labeled CRPS I patients.”

Finally, there are anecdotal reports of trivial trauma such as cuts, bumps, contusions, bruises causing the development of CRPS, leading to permanent disability [24]. No population or epidemiological studies exist that provide the odds ratio for developing CRPS following minor trauma. Given that the reported incidence of non-traumatic CRPS in the Dutch studies ranges from 7 to 20%, it appears as though non-traumatic CRPS occurs at least as often as CRPS allegedly occurring following minor or trivial trauma [21]. Moreover, there is no pathologically recognized mechanism that has been validated scientifically to causally link the development of CRPS to minor trauma. Minor trauma is ubiquitous and commonplace, and there is no biological explanation for the development of permanent sequelae following such everyday events.

2.4. The invention of complex regional pain syndrome

As discussed above, CRPS replaced the condition previously known as RSD, but many other names have preceded CRPS, including causalgia, algodystrophy, Sudeck's dystrophy and shoulder-hand syndrome [25]. In fact, the name CRPS evolved from either RSD, or the diametrically opposed condition known as traumatic arterial vasospasm (TRV). The origin of RSD and TRV can be traced to the 1940s, when two Boston physicians described syndromes of pain whose clinical features were similar, but whose proposed etiology were significantly different. In the case of RSD, it was proposed by J.A. Evans that a “stimulation of the sympathetic” was the cause of pain, the preceding trigger being linked to various trauma to the extremities, while in the case of TRV, P.S. Foisie proposed that it was subacute but undetectable arterial vasospasms that cause the pain in the extremities after soft tissue injury. In either case, the proposed etiologies for the onset of pain were never definitively supported by scientific studies; therein lies the problem with CRPS.

2.5. Attempts to create a historical pedigree

It is interesting to note how once CRPS was invented, the quest to discover the earliest reports began in earnest. Previous descriptions of symptoms that meet the general description of CRPS have been described as early as the 19th century, and perhaps even before that [26]. Searches in the archives of medical history identify Ambroise Pare's report of King Charles IX's contractures and joint pain following a blood-letting procedure in the 17th century as possibly the earliest reports of a pain syndrome resembling CRPS [27,28]. Hunter, in 1766, described pain in the joints following injury and the “father of neurology” Silas Mitchell described in vivid detail the occurrence of pain that was out of proportion with the injuries sustained during the American Civil war [29,30]. At the time, Mitchell called this condition “causalgia”. At the turn of the previous century, Sudeck described complications of limb trauma that included pain, loss of motor function and swelling. This condition was later named Sudeck's atrophy [31]. A multitude of names followed (Table 1), and it is conceivable that at the time each condition was described, there was no consensus that each was referring to the same condition. In fact, even now, whether or not they are all the same is debatable, given the vague nature of the current diagnostic criteria. Despite the fact that the only consistent history is a description of a pain syndrome lacking any reliable criteria, CRPS is often rationalized and validated as being related to a well described medical syndrome consistently described for centuries. In fact, there is no empirical evidence that CRPS bears any relationship with these historical descriptions, aside from complaints of disproportionate pain and clinical signs of disuse.

2.6. “Forget What We Said About the Sympathetic Nervous System, We'll Just Describe It”

The first reports that proposed that post traumatic pain may be related to the sympathetic nervous system appeared in 1916 [32]. As mentioned above, Evans coined the term RSD in 1946 [33–35], basing the name on the idea of a sympathetic coupling hypothesis proposed by

Table 1
CRPS synonyms and related terms.

Reflex Sympathetic dystrophy (RSD)
Sudeck's atrophy
Causalgia
Minor causalgia
Post-traumatic pain syndrome
Post-traumatic painful arthrosis
Shoulder-hand syndrome
Chronic traumatic edema
Peripheral trophoneurosis
Algodystrophy
Sympathalgia
Sympathetically maintained pain

Livingston [36]. Roberts in 1986 became a strong proponent of the proposal that the sympathetic nervous system was the driving force behind such pain [37], and that blocking the sympathetic nervous system would alleviate the pain [33]. In no small part, the alleged positive response to such blocks allegedly "proved" the role of the sympathetic nervous system in maintaining this pain response. Unfortunately, it was noted that many people did not respond to this form of therapy. By the mid-1990s, the role of the sympathetic nervous system as a primary mechanism for CRPS gradually fell out of favor [38]. It was out of this failure to establish the sympathetic nervous system's role in producing CRPS's symptoms that ongoing efforts to identify the biological mechanism were abandoned in favor of a descriptive construct. The implications of the RSD failure and its implications cannot be understated. Following the failure of the RSD neurological construct, researchers set out to reinvent a separate clinical construct based upon symptoms apart from any biological or pathological theory. Basically, it involved inviting many of the same "RSD experts" to conferences to meet and reach a consensus on how the newly defined entity would be identified. Because RSD failed as a separate neurological diagnosis, the new entity evolved as a separate descriptive pain syndrome and research conducted under the umbrella of pain management.

2.7. Conference based medicine

In the early 1990s, the International Association for the Study of Pain ("IASP") Task Force of Taxonomy contributed to the invention of CRPS, abandoning all attempts to identify its pathology in favor of a purely descriptive syndrome [39]. Coincidentally, during this same time, pain management, as a field, began aggressively promoting the idea of pain as a separate disease rather than a symptom of an underlying pathology [40]. Pain organizations such as the American Pain Society, prompted by poor quality evidence, promoted pain as the "Fifth Vital Sign; and advocacy ultimately led to changes in the Joint Commissions Pain Standards [41,42]. Despite mounting evidence of an emerging opiate epidemic over the next decade, pain organizations like the IASP continued to recommend assessment of pain based principally on a patient's self-report of symptoms and declared the alleviation of pain with opiates as a human right [43,44]. Although the research supporting such concepts were either absent, biased, or woefully unscientific, pain organizations through advocacy and politics were largely successful over several decades in implementing changes in clinical practice and gaining wide recognition for complaint-based diagnoses and treatment. The concept of CRPS has been further sustained and perpetuated by the re-convergence of the same group of "experts" at their yearly congresses. Recently, the Joint Commission recognized that unscientific promotion of symptom-based medicine played a significant role in the opiate crisis, which currently is a leading cause of US deaths [45]. Likewise, the notion that pain is a separate vital sign has been widely discredited and is no longer standard of care.

In 1993, the IASP sponsored a conference in Orlando, FL to replace the failed RSD concept. The attendees agreed upon a new name, Complex Regional Pain Syndrome ("CRPS"), which was admittedly descriptive rather that pathological; and proposed the diagnostic criteria shown in Table 2a. These so called "Orlando Criteria" included the presence of noxious stimuli, disproportionate pain, accompanying signs such as edema or vasomotor activity, and exclusion of other causes of pain. Researchers utilized component factor analysis to develop groups of factors that were believed to improve specificity. This theoretically entailed grouping signs into factor groups based on the presumption that they share a common pathophysiology, for example, in Factor 1, hyperalgesia, hyperesthesia and allodynia are group together and in factor 3, edema and sweating are grouped together, to facilitate the distinction between CRPS and non-CRPS related pain syndromes [46]. The problems with factor analysis when the factors are subjective or poorly defined are that 1. erroneous assumptions are made, intentionally or not, to arrive at a conclusion that favors the initial hypothesis (a form of circular logic), and 2. this is not an exact science, and the results are subject to widely diverse interpretation.

Table 2a
The original IAPS Orlando criteria for the diagnosis of CRPS. (adapted from [2])

- Identification of a preceding noxious event or cause of immobilization
- Ongoing pain, allodynia, hyperalgesia
- The pain is disproportionate to the inciting event
- Associated signs – edema, changes in skin perfusion, abnormal sudomotor activity in the pain region
- CRPS is a diagnosis of exclusion, and other conditions that may account for the pain must be considered first.

2.8. Failed efforts to validate the newly created diagnosis

After the 1993 IASP Orlando conference where attendees invented CRPS, a smaller group of researchers then conducted various validation studies on the proposed diagnostic criteria. Initial attempts to preliminarily validate the so-called Orlando Criteria with relatively small sample sizes showed that these criteria were prone to very high levels of false diagnosis [47]. The 1998 Galer validation study showed that even though diabetic neuropathy would be an easy diagnosis to exclude or include in the differential diagnosis of pain, when the diagnosis of diabetic neuropathy was hidden during validation trials, there were a large percentage of subjects (37%) with diabetic neuropathy that would be misdiagnosed as CRPS [47]. The preliminary Galer study, conducted at the University of Washington and evaluated by the lead author, included 18 CRPS patients and a control group of 30 diabetic neuropathy patients. The following year, in another external validation paper published by essentially the same group of researchers [48], the study physicians incorrectly diagnosed various neuropathic pain disorders as CRPS in nearly 60% of the controls, an unacceptably high false positive rate. Moreover, the population sample in the Bruehl 1999 study was extremely small and appeared biased heavily in favor of finding CRPS [48]. In that respect, the 160 patient multi-site study involved 117 "CRPS" patients, 98% of whom the study physicians deemed to have CRPS under criteria they themselves identified as lacking specificity, but only 43 controls, 25 of whom were incorrectly diagnosed as having CRPS during the validation study. In other words, less than 18 patients were diagnosed as having something other than CRPS by so-called "CRPS experts" across the world. Moreover, the 1999 Bruehl study does not indicate which of the neuropathic pain syndromes, which included diabetic neuropathy (44.2%), polyneuropathy (14%), post herpetic neuropathy (PHN) (20%), or radiculopathy (20.9%) were incorrectly diagnosed. The study did not resolve whether the prior difficulty observed by Galer, misdiagnosing diabetic neuropathy as CRPS, was repeated; nor did it identify the control conditions that would lead to an incorrect diagnosis.

In the 1999 Bruehl study [48], only 19 patients of the in the control group had a diagnosis of diabetic neuropathy, and there was no indication that any of the so-called CRPS group were evaluated for diabetes or other metabolic diseases with appropriate laboratory studies. More importantly, since CRPS purportedly involves autonomic changes in addition to pain, it is unclear what "control" value the inclusion of polyneuropathy or radiculopathy satisfied since these clinical entities generally do not involve autonomic symptoms. Undaunted by a validation study showing that CRPS "experts" were less likely to distinguish various forms of neuropathic pain from CRPS than a chimpanzee with a coin, a second meeting was held in Budapest, Hungary to establish consensus based diagnostic criteria.

2.9. Try again? the budapest criteria

The Budapest group, consisting of 27 CRPS advocates, met in 2003

Table 2b
Component factor analysis for IAPS Orlando criteria for diagnosing CRPS. (adapted from [60])

Factors that are composed of several clinical signs or symptoms are used in the criteria rather than individual signs or symptoms
Factor 1 – Hyperalgesia, Hyperesthesia, Allodynia
Factor 2 – Temperature asymmetry, Signs of color change, Symptoms of color change
Factor 3 – Signs of edema, Sweating asymmetry, Symptoms of edema
Factor 4 – Decreased range of motion signs, Decreased range of motion symptoms, Motor dysfunction signs, Motor dysfunction symptoms, Trophic symptoms, Trophic signs

to modify the "Orlando criteria" in an attempt to improve sensitivity and specificity [49]. These modified criteria are shown in Table 2b. As agreed by conference participants, the process for diagnosing CRPS would involve the identification of signs and symptoms in four categories each. However, it was deemed that specificity would be more important for use in research, whereas sensitivity would be more critical in the clinical setting. The reasons for this were that research criteria needed to be more stringent; however, this is a fallacy. Why would making the correct diagnosis be different from research or clinical practice? Accurate diagnosis is important in the clinical setting as well.

The way the criteria are laid out for both research and clinical use, the presence of continuing pain and no other diagnosis to explain the pain are required. But then within the symptoms categories, one symptom in each of three categories are needed to make the diagnosis for clinical use, whereas one symptom in all four symptom categories are needed for research use. In addition, in both research and clinical criteria, one sign in each of two of four sign categories were required. The Budapest criteria, adopted in 2007, required a symptom in three of the four symptom categories and two of four signs [48,49]. The researchers hypothesized, based upon further statistical analysis of the 1999 group, that the effect of the Budapest criteria (using two of four signs and three of four symptom categories) would decrease the sensitivity from 0.94 to 0.85 and increase the specificity of diagnosis of easily distinguishable neuropathies from 0.36 to 0.69.

2.10. The budapest criteria sham validation

Unlike the prior external efforts to validate proposed criteria, which included a small control group that included primarily diabetic neuropathy and post herpetic neuralgia (PHN) patients, conditions that can at least include autonomic symptoms, the 47-person control group for the Budapest validation study included only 15% diabetic neuropathy patients (7 patients) and no PHN patients [49]. Although specificity, the ability to distinguish CRPS from controls, was the prior defect in earlier proposed diagnostic criteria, the Harden 2010 study group inexplicably included "113 CRPS patients" and only 47 controls [50]. The lead authors of the purported validation study [49,50] were essentially the same group who had failed to validate the prior incarnation of the diagnostic criteria, and thus were aware of the difficulties of distinguishing between diabetic neuropathy and CRPS. Nonetheless, their selected control group for the Harden/Bruehl 2010 study included peripheral neuropathy isolated to a single extremity (45%), radiculopathy (30%), and carpal or tarsal tunnel syndrome (10%). In other words, 85% of the control group included easily diagnosable neuropathic conditions that present in a specific dermatome with no autonomic symptoms.

Given that CRPS-I is supposed to involve pain that is not confined to a specific neural dermatome, these conditions should be easily excluded by the patient's own description of their pain distribution. In the Harden/Bruehl 2010 validation study [50], the statistical odds for the exercise, CPRS or non-CRPS, was 50%; and the study contained less than half as many controls as the CRPS group. Moreover, the CRPS group was diagnosed according to the IASP criteria, which the researchers had already proven had only a 40% specificity; accordingly, there was an excellent chance that a significant percentage of the CRPS patient group had another uncomplicated medical condition that had been misdiagnosed. Thus, the Budapest validation study showed that over 30% of the time, a physician utilizing the proposed clinical criteria would incorrectly identify a patient with an uncomplicated neuropathy as having CRPS; and confirm a diagnosis of CRPS 99% of the time utilizing existing criteria that only had a specificity of only 40%. The study does not cite how many of the seven diabetic neuropathy patients were incorrectly diagnosed as having CRPS. Moreover, if more stringent research decision rules are used, the sensitivity decreases to 0.78 and the specificity to 0.79, which is still remarkably inaccurate given the structure of the study [48,49,51]. More importantly, none of the subsequent validation studies addressed the diabetic neuropathy false positives noted in the initial Galer study; or the lack of specificity in the criteria used to identify the CRPS group.

Given that diabetic neuropathy is one of the most common medical neuropathies and easily available for a large control group, and CRPS patients are reportedly rare (which is why multiple sites around the world were required to assemble the sample in the Harden/Bruehl 2010 validation study), it is hard not to infer that diabetic neuropathy was intentionally excluded from subsequent validation studies and replaced with relatively isolated neuropathies with no autonomic qualities in order to improve the specificity of the proposed criteria. Aside from the math, which appears to be correct, the Bruehl/Harden 1999 and Harden/Bruehl 2010 validation studies, including their tiny population sample, multiple sites, and heterogenous control group, share more in common with a high school science project than rigorous scientific research. According to these validation studies, if the patient does not already have a known neuropathic disorder, then they have CRPS, as defined by the study physicians—even though no validated diagnostic criteria exist. Moreover, while CRPS is considered to have a wide and vast differential diagnosis, there have been no validation studies to determine whether physicians could distinguish CRPS from a large group of diabetic neuropathies, or neuropathies due to infectious conditions such as HIV or Hepatitis C; nor have there been any validation studies involving controls of patients suffering from poor circulation or venous insufficiency, which in some cases can be related to cigarette smoking.

In addition, there have been no validation studies involving patients with known psychogenic pain, drug seeking patients, or psychiatric conditions, in order to determine whether the clinicians could distinguish CRPS from other conditions that produce similar symptoms. In a review article published by Hawley, et al., no evidence could be found to distinguish CRPS dystonia from psychogenic dystonia or somatoform disorder [52]. Without specific validation studies comparing CRPS to known conditions identified as part of its differential diagnosis, no claim can be made generally about the specificity of the Budapest criteria, aside from their ability to exclude, at a rate a little better than chance, relatively common neuropathic conditions easily diagnosable with cursory histories and clinical examinations. Despite the limited significance of the seminal validation of the Budapest criteria, its purported specificity is repeatedly cited in CRPS articles as having validated the diagnosis and accepted as gospel truth in pain management circles.

Ongoing issues with the diagnostic criteria include an ambiguous description of the individual signs and symptoms listed. For example, it is unclear of the meaning of temperature asymmetry, color change, or sweating asymmetry (see Table 2c). The vagueness of these signs confounds our ability to be objective about CRPS, and also affects the outcome of many studies that have been performed on CRPS. In fact, very few studies on CRPS, if any, can be considered level 1 or even level 2 grades of evidence [53–55].

Table 2c
Revised criteria for the diagnosis of CRPS.[a]

Continuous pain which is disproportionate to any inciting injury or event.
Symptoms (report one symptom in 3/4 categories for clinical decision rule, 4/4 categories for research decision rule)
Sensory
Vasomotor
Sudomotor/edema
Motor/Trophic
Signs[a] (at least one sign in 2/4 or more of the following categories)
Sensory
Vasomotor
Sudomotor/edema
Motor/Trophic
No other diagnosis that better explains the symptoms

[a] Signs must be directly observed by the evaluator, not simply reported.

3. Discussion and conclusions

3.1. Psychosocial effects of creating syndromes and labeling of conditions

Because diagnoses such as CRPS are not scientifically based, the vague and inconsistent set of criteria means that the criteria are too easily met. Then there is invariably a subset of physicians and care providers who readily or reluctantly accept the existence of such a dubious condition and from that point on the condition gains traction. Soon, there appears increasingly more studies confirming the existence of the condition, but this itself is a fallacy, because these studies are based on the false premise that the condition actually exists. For example, it had been previously reported that 21% of patients undergoing total knee arthroplasty develop CRPS. In a study of 100 patients who were diagnosed as having CRPS after total knee arthroplasty, it was found that none of the patients actually had CRPS even using the current Budapest diagnostic criteria. Indeed, some had neuropathic pain, but did not fulfill the criteria of CRPS. The paper points out that misdiagnosis can have grave consequences as patients may not receive the correct medications or treatment (Table 3) [56].

Very often symptoms or a group of symptoms can occur where there is no distinct etiology. An example can be found in patients who have manifestations of histamine release such as hives, diarrhea and or headache. These patients go from one doctor to another trying to discern what they have, until one doctor brings up the term “mast cell activation syndrome”. All of a sudden there is now a name for what they have, and they can begin the next phase of their search, such as to find a doctor who treats this. But in fact, they are no closer to the truth, because for many of them, there is no evidence of excessive mast cell activity. The same thing can be said about CRPS. Once a patient is labeled, it become a disease they own, and the disease becomes the patient's identity. This is not a healthy situation.

The unintended consequence of creating a new condition based on controversial and vague criteria is akin to attempting to unscientifically “profile” a suspected serial killer based upon alleged common psychological characteristics of other criminals. The pseudoscientific name (and diagnostic process) takes on a life of its own, and people who are frustrated with a lack of information about their condition flock to these types of diagnoses, and they keep searching until they find a physician willing to provide a label for their symptoms. The same thing has happened with the false association of MMR vaccines with autism, the unsubstantiated association of “toxic mold syndrome” (another non-existent entity) and a plethora of vague, subjective symptoms leading to diseases such as sick building syndrome (SBS), and the unconfirmed relationship between Streptococcal infections and obsessive-compulsive behavior in the dubious condition known as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS). The popularity of these concepts, if even only for a short time, demonstrates how difficult it is to dispel untruths even when there is no scientific evidence for them. It should be noted that providing an acronym for the condition, as in CRPS, tends to provide the validation the “condition” requires to propagate, much like the branding of a product promotes sales in the marketing world.

There are publications claiming that CRPS can spread, like some sort of infectious disease. Yet there is no biologic or medically plausible explanation for this and it leads to even further drug and procedure abuse [57]. There are a number of potential harmful consequences of creating a false condition. One is that treatment may not be appropriate for the condition. Indeed, in the case of CRPS, patients who claim to have CRPS all of a sudden become legitimate candidates for overuse of pain medications, including addictive drugs such as opioids or even marijuana.

4. Challenges

Scientific, relevant evidence is essential in clinical care, policy-making, dispute resolution, and compensation decisions. Because pain management is currently the discipline focusing on CRPS research and treatment, the field's involvement in promulgating clinical guidelines across multiple disciplines related to opiate use that have not withstood rigorous scientific examination must be considered in the context of inventing new pain syndromes that purportedly require analgesics and invasive treatment. Simply put, the track record for the theory that pain is a separate disease apart from some confirmable biological diagnosis is poor. Currently, CRPS is a theoretical pain syndrome with: 1) developing diagnostic criteria that have not been vigorously validated; 2) no objective “gold standard” test scientifically confirming the diagnosis;

Table 3
Medications used in pain management and CRPS.

Medication class	Examples	Mechanism of action	Effectiveness in treating neuropathic pain	Theoretically appropriate for CRPS	Potential for misuse
Corticosteroids	Prednisone	Anti-inflammatory	No	No	Medium
NSAIDS	Aspirin, Ibuprofen	Anti-inflammatory	No	No	Medium
Antidepressants	Amitriptyline	enhancement of noradrenergic and serotonergic descending inhibitory pathways, also sodium channel blocking effects	Yes	Yes	High
Calcium-regulating agents	Gabapentin, pregabalin		Yes	Yes	Medium
Sodium channel blockers	Mexiletine, lidocaine		Yes	Yes	Low
NMDA receptor antagonists	Ketamine	Blocking NMDA receptors in the dorsal horn	Yes	Yes/No	Low
Opioids	Morphine		No	No	High
Botulinum toxin		Cleavage of the SNARE complex	Yes	Yes	Low
Bisphosphonates	Alendronate	Poorly understood	Unknown	Controversial	Low
Cannabis	Tetrahydrocannabinol	Via cannabinoid receptors	No	No	High
Intravenous immunoglobulin	Various brands of IVIg	Anti-inflammatory	No	No	Low

*NSAIDS = Non-steroidal anti-inflammatory drugs, NMDA – *N*-methyl-D-aspartate, IVIg = intravenous immunoglobulin.

3) no generally accepted clinical treatment scientifically proven to improve patient function; and 4) no generally accepted etiology or biological cause. Despite the scientific uncertainty, physicians are currently subjecting their patients to invasive procedures (spinal cord stimulation), psychoactive medications (ketamine), intravenous immunoglobulin and addictive pain medications, none of which, according to a recent Cochrane Review, are supported by high quality evidence [58]. A disabling condition defined by ambiguous clinical symptoms and signs that allegedly result spontaneously, after minimal injury, or following medical and surgical procedures poses significant implications. There is no evidence that CRPS is an autoimmune disease, and the use of intravenous immunoglobulin has not been efficacious in the treatment of CRPS. Absent a recognizable pathology for CRPS, physicians are necessarily treating symptoms, often with invasive treatment that does not improve functional outcomes. Moreover, CRPS treatment has been universally ineffective for restoring patient function with results measurable only in reductions of subjective visual analogue pain scores. CRPS is supposed to be diagnosed only after a thorough differential diagnosis and consideration of other conditions to prevent overdiagnosis [59]. But aside from collecting signs and symptoms, there have been no clinical protocols established for excluding other medical causes that better explain the symptoms; nor are there validation studies demonstrating that CRPS can be reliably distinguished from common conditions such as diabetic neuropathy, postherpetic neuralgia, or psychogenic dystonia.

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