

# APPLIED EVIDENCE

New research findings that are changing clinical practice

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## Complex regional pain syndrome underdiagnosed

CRPS type 1 is an under-recognized problem in limbs recovering from fracture or immobilized post-stroke

### Practice recommendations

■ Complex regional pain syndrome (CRPS) type 1 may be diagnosed by history and physical exam with no further testing (B). Several different diagnostic criteria have undergone validity testing: the 1993 IASP criteria, Bruehl's criteria, and Veldman's criteria; there is no compelling reason to recommend 1 set of criteria over the others (C).

■ Some cases of CRPS type 1 may be preventable. Some cases of CRPS type 1 in post-stroke upper extremity hemiplegia (also known as shoulder-hand syndrome) may be prevented by early inpatient rehabilitation (C) and avoidance of shoulder trauma to the affected arm (B). Some cases of post-fracture CRPS type 1 may be prevented with 500 mg vitamin C daily started upon diagnosis of fracture and continued through healing (B).

**D**o you have a patient recovering from a limb fracture who is complaining of pain and tenderness long after most patients with a similar injury would be symptom free? The problem may be an under-recognized one—complex regional pain syndrome (CRPS) type 1, also known as reflex sympathetic dystrophy. The problem is also encountered in immobilized limbs of post-stroke patients.

Persons with persistent post-traumatic pain eventually diagnosed with CRPS type

1 often undergo unnecessary testing resulting in inappropriate or delayed treatment.<sup>1</sup>

Signs and symptoms typical of CRPS type 1 can also occur transiently with a normally recovering immobilized limb,<sup>2,3</sup> so diagnosis of CRPS type 1 is based on increasing severity and duration of signs and symptoms (level of evidence [LOE]: 3; consensus guidelines)<sup>4</sup>:

- pain
- hyperalgesia/allodynia (pain or exaggerated response resulting from a normally painless or only slightly painful stimulus)
- joint stiffness
- swelling
- autonomic abnormalities (often sweating and temperature differences compared with the unaffected limb).

### ■ Diagnosis: Watch recovery course over first 9 weeks

Clinicians face a number of challenges in diagnosing CRPS type 1. No psychological or personality traits appear to predispose to CRPS type 1 (LOE: 2, lower-quality literature review).<sup>5</sup> Fracture types and severity of injury among persons who develop CRPS type 1 are not significantly different from persons who recover normally (LOE: 2, case control studies).<sup>6,7</sup> The key is to remain alert to deviation from the normal course of recovery.

Studies have shown that 9 weeks post-

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TABLE 1

## Diagnostic criteria for CRPS type 1\*

NAME	CRITERIA
IASP 1994 consensus criteria <sup>4</sup>	<p>Criteria 2, 3 and 4 are necessary for a diagnosis of CRPS type 1.<sup>10</sup></p> <ol style="list-style-type: none"> <li>1) Type 1 is a syndrome that develops after an initiating noxious event.</li> <li>2) Spontaneous occurrence of pain in the absence of an external stimulus, allodynia (pain due to a mechanical or thermal stimulus that normally does not provoke pain), or hyperalgesia (exaggerated response to a stimulus that is normally painful) that is not limited to the territory of a single peripheral nerve, and is disproportionate to the inciting event.</li> <li>3) There is or has been evidence of edema, skin blood flow abnormality, or abnormal sudomotor (sweating) activity in the region of the pain since the inciting event.</li> <li>4) This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.</li> </ol>
Bruehl's criteria: IASP-family <sup>11</sup>	<ol style="list-style-type: none"> <li>1) Continuing pain disproportionate to any inciting event.</li> <li>2) Patient must report at least 1 symptom in each of the 4 following categories: <ol style="list-style-type: none"> <li>a) sensory: reports of hyperesthesia</li> <li>b) vasomotor: reports of temperature asymmetry or skin color changes or skin color asymmetry</li> <li>c) sudomotor/edema: reports of edema or sweating changes or sweating asymmetry</li> <li>d) motor/trophic: reports of decreased range of motion or motor dysfunction (weakness, tremor, dystonia) or trophic changes (hair, nail, skin)</li> </ol> </li> <li>3) Must display at least 1 sign in 2 or more of the following categories: <ol style="list-style-type: none"> <li>e) sensory: evidence of hyperalgesia (to pinprick) or allodynia (to light touch)</li> <li>f) vasomotor: evidence of temperature asymmetry or skin color changes or asymmetry</li> <li>g) sudomotor/edema: evidence of edema or sweating changes or sweating asymmetry</li> <li>h) motor/trophic: evidence of decreased range of motion or motor dysfunction (weakness, tremor, dystonia) or trophic changes (hair, nail, skin)</li> </ol> </li> </ol>
Veldman's criteria <sup>13</sup>	<ol style="list-style-type: none"> <li>1) Presence of 4 out of 5 symptoms: <ol style="list-style-type: none"> <li>a) Diffuse pain during exercise</li> <li>b) Temperature differences between affected and unaffected extremity</li> <li>c) Color differences between affected and unaffected extremity</li> <li>d) Volume differences between affected and unaffected extremity</li> <li>e) Limitations in active range of movement of the affected extremity</li> </ol> </li> <li>2) Occurrence or increase of symptoms during or after use</li> <li>3) Symptoms in an area larger than the area of the primary injury</li> </ol>

\*IASP definition of CRPS 1: A variety of painful conditions following injury which appears regionally having a distal predominance of abnormal findings, exceeding in both magnitude and duration the expected clinical course of the inciting event and often resulting in significant impairment of motor function, and showing variable progression over time. (All 3 criteria sets use this definition.)

injury, persons with persistent pain, tenderness, swelling, joint stiffness (fingers and wrist), and sweating or temperature changes in the injured limb may have CRPS type 1 (LOE: 2, case series and case control studies).<sup>6,8</sup> In a prospective case series (n=109), no new cases of CRPS type 1 developed beyond 9 weeks (LOE: 2, case series).<sup>8</sup>

### Diagnostic criteria: No consensus

No one test identifies all persons with CRPS type 1. There is no objective

gold standard for diagnosis.<sup>9</sup> Instead, researchers and clinicians must rely on clinically derived diagnostic criteria. Unfortunately, despite the development of diagnostic criteria by the IASP in 1994 (TABLE 1),<sup>4</sup> experts have not reached consensus on the best method of diagnosis, and several different sets of diagnostic criteria are used.<sup>7,10</sup>

**Initial IASP criteria.** Of these, the 1994 IASP consensus-based diagnostic criteria appear to be most widely used in the literature. These criteria were intended as a start-

### CRPS underdiagnosed

The diagnosis of CRPS type I is often missed,<sup>1,29,30</sup> so it is likely that the diagnosis rate per population of 0.02% reported in a recent population based study is an underestimate of the actual prevalence.<sup>31</sup> After distal radial fracture, rates of CRPS type I have varied widely in reports, from 0.9%<sup>32</sup> to 15%<sup>33</sup> to 28%.<sup>34</sup> After tibial shaft fracture, Sarangi et al<sup>35</sup> reported that 30% of persons developed CRPS type I.

In cases of post-stroke hemiplegia, CRPS type I has been reported in the paralyzed arm at rates between 25%<sup>36</sup> and 40%.<sup>37</sup> However, in a more recent study among stroke patients in the US who underwent early inpatient rehabilitation, Petchkrua et al reported a lower incidence of about 2%.<sup>38</sup> Impairment can be severe among persons with persistent CRPS type 1. A prospective study revealed that activities of daily living were significantly impaired in 62% of persons with chronic CRPS type 1.<sup>39</sup>

ing point, requiring validation through future clinical research.<sup>4,11</sup> In further studies using controls with neuropathic conditions, IASP criteria have demonstrated low specificity (TABLE 2).<sup>11,12</sup>

**Criteria refinements.** Derived from 1 of these studies, Bruhl's criteria were subsequently developed to improve the IASP criteria (TABLE 1).<sup>11</sup> Several other sets of diagnostic criteria exist, but only Veldman's criteria (TABLE 1),<sup>13</sup> which have been adopted as the standard in the Netherlands, have undergone further study.<sup>14</sup> Studies of Bruhl's and IASP criteria have measured specificity and sensitivity, and along with Veldman's criteria, interobserver reliability (TABLE 2).<sup>11,12,14,15</sup> However, these numbers must be interpreted with care due to the absence of an objective and independent gold standard.

The absence of an objective gold standard does not mean CRPS type 1 is not a "real" disorder.<sup>12</sup> In developing diagnostic criteria for CRPS, the IASP turned to models developed for other conditions without objectively measurable findings: the International Headache Society (IHS) classification and the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). These descriptive systems are based largely on history

and self-reported symptoms rather than on clinical signs and laboratory tests. The accuracy of these types of diagnostic criteria is refined over time, through repeated, controlled validation studies using the best means available.<sup>11</sup>

**Specificity of criteria.** Specificity has been tested using controls with neuropathic conditions.<sup>11,12</sup> In these studies, nonblinded clinicians applied CRPS type 1 diagnostic criteria, except the exclusion criterion, to patients who had either CRPS type 1 or neuropathic pain from other causes. Many persons with peripheral neuropathy met criteria for CRPS type 1. However, as stated in the IASP criteria, the diagnosis of CRPS type 1 is not considered until common causes of neuropathic pain and post-traumatic limb pain have been excluded.<sup>4</sup> As long as the primary care provider considers and rules out other causes of pain, the clinically relevant specificity of these criteria is likely much higher.

**Sensitivity of criteria varies.** The sensitivity in these studies is based on a non-independent reference standard. Patients with CRPS type 1 were chosen for these studies using clinical criteria, and these criteria were reapplied by study clinicians to determine sensitivity.<sup>11,12</sup> This method does not allow any determination of whether cases of CRPS type 1 might be missed by the criteria. Sensitivity measured in this way more closely resembles interobserver reliability—the likelihood that different clinicians using the same diagnostic criteria will reach the same diagnosis—and it appears quite good, especially for IASP criteria, in these 2 studies.<sup>11,12</sup>

However, when interobserver reliability has been directly studied, albeit in small studies of 3 and 6 observers, only Veldman's criteria achieve good reliability; IASP and Bruhl's criteria appear unreliable (TABLE 3).<sup>15,16</sup> However, IASP and Bruhl's criteria do fall within the range of reliability of other clinical assessments including medical fitness for a job and shoulder disorders.<sup>15</sup>

### FAST TRACK

**No single test identifies all persons with CRPS type 1; there is no objective gold standard for diagnosis**

**TABLE 2****Accuracy of diagnostic criteria for CRPS type 1**

CRITERIA TESTED	STUDY OF ACCURACY	STUDY QUALITY	CONTROL GROUP	SN	SP	LR+	LR-	PV+	PV-
IASP	Bruehl et al, 1999 <sup>11</sup>	3 (non-indep. ref. standard)	Patients with diabetic neuropathy, polyneuropathy, postherpetic neuralgia, and radiculopathy	98%	36%	1.5	0.1	0.21	0.99
IASP	Galer et al, 1998 <sup>12</sup>	3 (non-indep. ref. standard)	Patients with diabetic neuropathy	100%	55%	2.2	0	0.28	1.0
Bruehl's	Bruehl et al, 1999 <sup>11</sup>	3 (non-indep. ref. standard)	Patients with diabetic neuropathy, polyneuropathy, postherpetic neuralgia and radiculopathy	70%	94%	12	0.3	0.67	0.94

Sn, sensitivity; Sp, specificity; LR+, positive likelihood ratio; LR-, negative likelihood ratio; PV+, positive predictive value (probability of disease given a positive test); PV-, negative predictive value (probability of disease given a negative test). PV+ and PV- assume baseline likelihood of disease of 15%.

**TABLE 3****Interobserver reliability of diagnostic criteria for CRPS type 1**

DIAGNOSTIC CRITERIA TESTED	STUDY QUALITY	STUDY SIZE	INTEROBSERVER RELIABILITY
IASP <sup>15</sup>	2 (small cohort study)	6 diagnosticians	Poor
Bruehl's <sup>15</sup>	2 (small cohort study)	6 diagnosticians	Borderline moderate
Veldman's <sup>16</sup>	2 (small cohort study)	3 diagnosticians	Good

**Factors undermining objective evaluation**

Despite clinically based diagnostic criteria, researchers and physicians continue to use office, laboratory, and radiographic tests to diagnose CRPS type 1,<sup>1,10</sup> perhaps in an attempt to provide a more objective basis for the diagnosis. However, the evaluation of these methods has been plagued by difficulties.

First, because current clinical diagnostic criteria are not yet optimized or even standardized in the literature, there is no gold standard by which to measure the accuracy of these tests.

Second, patients in different studies have been diagnosed with CRPS type 1 by varying criteria.

Third, CRPS type 1 presents differently in different people, and symptoms and signs vary over time in the same person. As a result, the sets of diagnostic criteria have been designed with various clinical findings, and CRPS patients may meet only a few at any one time.

For example, if a group of CRPS type 1 patients were tested for sweating abnormalities, only 24% at best might be expected to test positive (see **TABLE 4** for representative frequency of symptoms and signs),<sup>17</sup> resulting in an apparent sensitivity of 24% for sweating abnormalities. This is why it is important for clinicians to consider patients' report of typical signs even when these signs are not present on exam when making a diagnosis of CRPS type 1.

**FAST TRACK**

**It is important to consider patients' report of typical signs even when these signs are not present on examination**

TABLE 4

Frequency of symptoms and clinically observed signs in CRPS type 1

VARIABLES	SIGNS (%)	SYMPTOMS (%)
Allodynia	74	—
Decreased range of motion	70	80
Color changes	66	87
Hyperalgesia	63	—
Temperature asymmetry	56	79
Edema	56	80
Weakness	56	75
Sweating changes	24	53
Skin changes	20	24
Dystonia	14	20
Nail changes	9	21
Hair changes	9	19
Tremor	9	24
Hyperesthesia	—	65
“Burning” pain	—	81

By exam or report in patients meeting IASP criteria for CRPS, adapted from Harden et al, 1999.<sup>17</sup>

**Diagnostic instrumentation adds little**

Some investigators have tried using instruments to measure the clinically apparent signs included in diagnostic criteria—volumetry to measure edema, thermometry to measure skin temperature differences, and resting sweat output (RSO) to measure sweating.

**Confounding nature of CRPS 1.** The value of these tests is limited by factors such as the duration of CRPS type 1, time of day, relaxation of the subject, ambient temperature, body temperature, and exact placement of the measuring device,<sup>18,19</sup> so it is not clear that objective measurement is practical or adds precision. In fact, in a study comparing testing to clinical diagnosis, instrumentation added little to the

overall accuracy of diagnosing CRPS type 1 (LOE: 2, prospective cohort study).<sup>14</sup>

**Sympathetic nerve block unhelpful.**

Other investigators have focused on testing to improve or replace clinical diagnostic criteria. Although at one time a response to sympathetic block was considered diagnostic for CRPS type 1,<sup>4</sup> subsequent studies have demonstrated there is a significant placebo response to sympathetic block, that many persons with CRPS type 1 do not respond, and that some persons with other neuropathic pain conditions do respond. A negative or positive response to sympathetic block cannot rule CRPS type 1 in or out (LOE: 2, systematic reviews with only a few high-quality studies).<sup>20-22</sup>

**Radiographic findings add nothing.**

Bone scanning (scintigraphy) and radiography have been used frequently in the diagnosis of CRPS type 1. Although 3-phase scintigraphy looking for different uptake of radioisotope between affected and unaffected limbs has been touted as an objective and definitive test for CRPS type 1,<sup>23</sup> this method also suffers from the subjective interpretation of the radiologist and poor interobserver reliability.<sup>24</sup> Researchers disagree on whether the typical appearance on scintigraphy is periarticular cuffing<sup>25,26</sup> or diffuse uptake of radioisotope,<sup>27</sup> and about whether delayed phase scintigraphy is adequate<sup>26</sup> or whether 3-phase scintigraphy is necessary.<sup>27</sup>

To make the interpretation of these scans more objective, quantitative analysis of bone scans has been undertaken; however, subjective interpretation was required to decide where to measure the uptake and what degree of difference between affected and unaffected limbs was considered positive for CRPS type 1.<sup>27</sup>

In 1 study, without mention of whether the radiologist was blinded but using an appropriate post-traumatic control group, sensitivity of 80% and specificity of 80% were reported (LOE: 2, case-control design).<sup>27</sup> In a cohort of persons with upper extremity pain, also without mention of blinding, sensitivity of 73% and specificity of 86% were reported



(LOE: 2, cohort design).<sup>25</sup> Using normal controls, not a clinically relevant comparison, sensitivity of 97% and specificity of 86% using bone scans have been reported (LOE: 2, case control design).<sup>26</sup>

Despite the reasonable sensitivity and specificity of the bone scans in these studies, clinical assessment was used as the gold standard for diagnosis and the bone scans did not add any degree of accuracy to that clinical assessment. Based on these studies, clinicians using a bone scan to rule in or rule out CRPS type 1 instead of using a clinical assessment risk missing up to 27% of cases and over-diagnosing 20% of cases.

Older literature suggested that osteopenia/porosis demonstrated on plain radiography or dual energy x-ray absorptiometry (DEXA) scanning was important for the diagnosis of CRPS type 1, but more recent studies have revealed sensitivity for plain radiography as low as 23% (LOE: 2, exploratory cohort study with good reference standards)<sup>13</sup> and for DEXA a sensitivity of 76% (LOE: 2, case-control design).<sup>28</sup> No studies were identified that used a control group post-trauma, so an adequate assessment of specificity has not been made.

## ■ Applying the evidence in practice

CRPS type 1 is often relegated to specialists. But, in fact, no special equipment or testing is required for the diagnosis of CRPS type 1, and the best treatments appear to be non-invasive and completely within the realm of family medicine.

With more attention to deviations from the normal course of recovery from trauma, the family physician will begin to recognize more cases of CRPS type 1 and can have full confidence that the treatments prescribed and monitored are in fact the treatments of choice.

### Preventing CRPS 1

For persons with hemiplegia, and of course early inpatient rehabilitation of post-stroke patients with upper extremity hemiplegia. Give 500 mg of vitamin C daily to post-

## Pathophysiology unclear

Researchers have been unable to identify the underlying pathophysiology for CRPS type 1, perhaps in part because patients with different pathophysiologies may present with similar clinical findings.<sup>9</sup> Recent discovery of an HLA linkage suggests that there may be a genetic predisposition to CRPS type 1.<sup>40</sup>

By definition, in CRPS type 1 no major nerve damage can be detected, but there may be damage to nerve fibers too small to detect on electromyograph. Research suggests that injured peripheral C-fibers and A-delta pain fibers immediately flood the central nervous system (CNS) with neurochemicals via the dorsal root ganglion and central pain projecting neurons of the CNS. The CNS is pathologically altered and sends signals to the injured area that serve to maintain the clinical signs and symptoms of CRPS type 1: peripheral pain and sensory changes, local sympathetic changes in blood vessels and sweat glands, and local motor changes.<sup>9</sup> Abnormal sympathetic activity can be clearly demonstrated, but there is no evidence to suggest that this is the cause of CRPS type 1.<sup>41</sup>

fracture patients in the hope of preventing CRPS type 1 (SOR: B).

### Base evaluation on history and physical exam

More often, the family physician will be in the position of evaluating persistent post-traumatic pain. Given the absence of compelling evidence in the literature, rely on your experience to guide the work up.

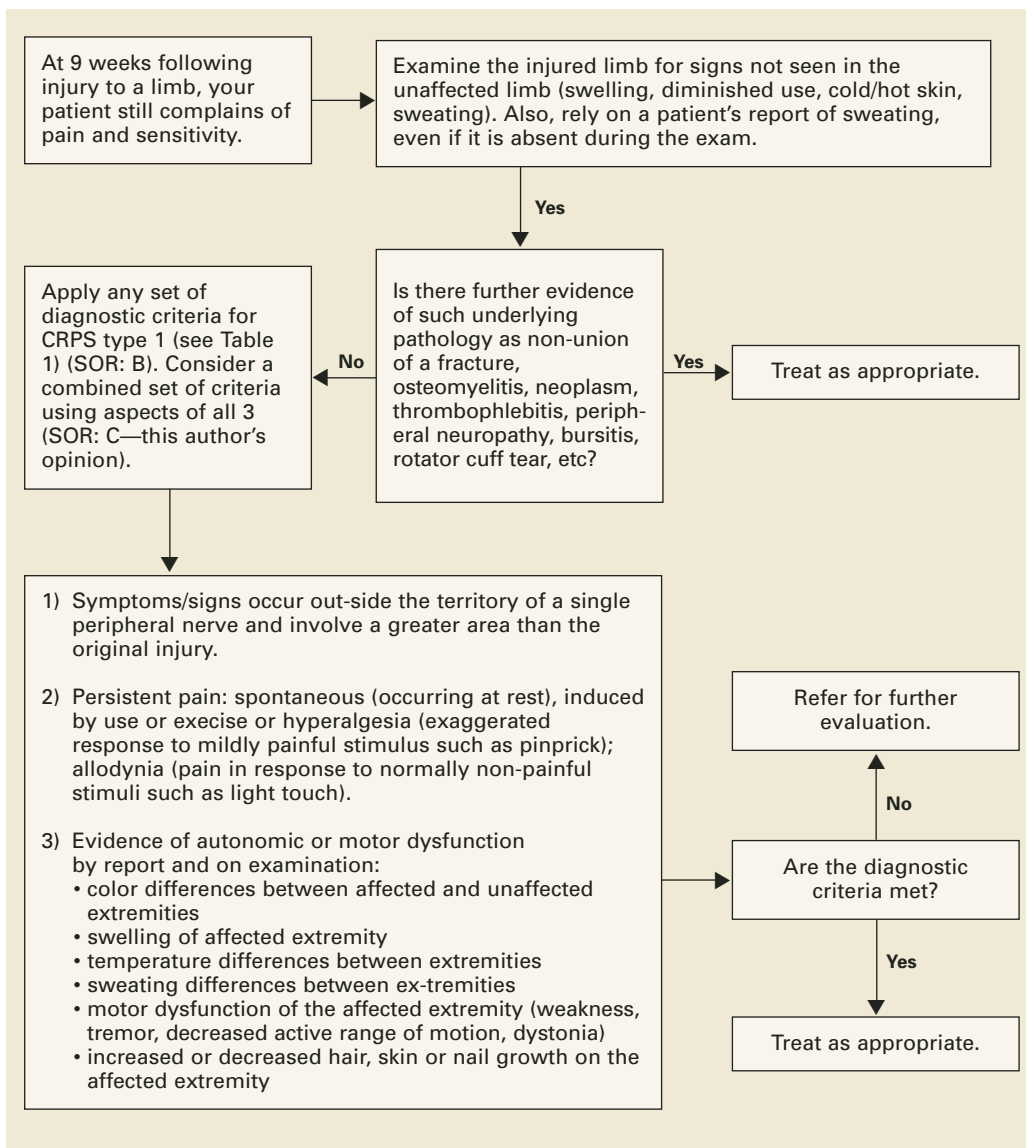
To diagnose CRPS type 1, first rule out other diseases (FIGURE).<sup>4</sup> The frequency with which other conditions occur in persons at risk for CRPS type 1 is not known because the research concerning CRPS type 1 has been undertaken in specialty care clinics; primary care physicians had already done the work of excluding many other disorders.

**Physical diagnosis.** The differential diagnosis for limb pain is extensive and includes fracture non-union, tendonitis, diabetic neuropathy,<sup>4</sup> osteomyelitis or cellulitis,<sup>13</sup> polyneuropathy, radiculopathy,<sup>11</sup> phlebothrombosis,<sup>13</sup> and Raynaud's

### FAST TRACK

**Give 500 mg of vitamin C daily to post-fracture patients in the hope of preventing CRPS type 1**

**FIGURE** Diagnosing CRPS type 1



**FAST TRACK**

**Plain radiography or bone scanning may identify a poorly healed fracture or bony lesions; WBC may identify infection or autoimmune disorders**

disease.<sup>13</sup> Physical exam will reveal signs of infection, focal tenderness consistent with tendonitis, erythema suggestive of cellulitis, a distribution of pain following a nerve suggestive of radiculopathy or carpal tunnel syndrome, or the stocking-glove distribution diabetic neuropathy.

**Auxiliary testing.** Limited testing may be helpful. Plain radiography or bone scanning may identify a poorly healed fracture or other bony lesions. A white blood cell count and inflammatory markers may identify infection or autoimmune disorders.

**Using the diagnostic criteria.** Once other disorders have been ruled out, evidence does support the diagnosis of CRPS type 1 based on history and physical exam without further testing (SOR: B). In the absence of clear evidence supporting 1 set of criteria over the others, clinicians may use IASP, Bruehl's, or Veldman's clinical criteria for diagnosis (SOR: C). While the IASP criteria are nonspecific and possibly not as reproducible as Bruehl's or Veldman's criteria, they are cited more widely the literature

including treatment trials. The criteria (FIGURE) can also be combined to encompass their complementary aspects (SOR: C, this author's opinion). ■

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#### CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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### Subtypes of complex regional pain syndrome

CRPS has historically been described as comprising 2 distinct subtypes: type 1, also known as reflex sympathetic dystrophy, in which nerve damage is not detectable, and type 2, also known as causalgia, in which nerve damage can be detected by electromyograph (EMG) but pain is not confined to the distribution of that nerve.<sup>4</sup> However, the clinical relevance of distinguishing the 2 types of CRPS has not been proven. Although the mechanism of pain is hypothesized to be different, thus far the 2 syndromes appear to be clinically similar (LOE: 2, case-control study).<sup>11</sup> Many, but not all, recent articles on treatment of CRPS combine types 1 and 2 in their subject populations. Yet, because CRPS types 1 and 2 have not yet been officially merged and because some researchers continue to make the distinction in studies, this paper will focus on CRPS type 1.

The nature of, diagnostic criteria for, and even the naming of CRPS have been controversial. In 1995 the International Association for the Study of Pain (IASP) recommended abandoning the commonly used term *reflex sympathetic dystrophy* because: 1) the existence of a “reflex” is questionable, 2) “sympathetic” or autonomic changes may not be causative, and 3) “dystrophy” is rare.<sup>4</sup> Despite this recommendation, a review of the literature 5 years later revealed that the terms *reflex sympathetic dystrophy* and *causalgia* are still commonly used, along with *algodystrophy*, *shoulder-hand syndrome*, *Sudeck's atrophy*, and *transient osteoporosis*.<sup>42</sup>



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