Complex regional pain syndrome: Which treatments show promise?

Anna Quisel, MD
Private practice, Wilmington, Del

James M. Gill, MD, MPH
Department of Family and Community Medicine, Christiana Care Health System Wilmington, DE; Department of Family Medicine and Department of Health Policy, Jefferson Medical College, Philadelphia, Pa

Peter Witherell, MD
Private practice in anesthesiology, Wilmington, Del

Practice recommendations

- Treatments for CRPS type 1 supported by evidence of efficacy and little likelihood for harm are: topical DMSO cream (**B**), IV bisphosphonates (**A**) and limited courses of oral corticosteroids (**B**). Despite some contradictory evidence, physical therapy and calcitonin (intranasal or intramuscular) are likely to benefit patients with CRPS type 1 (**B**).
- Due to modest benefits and the invasiveness of the therapies, epidural clonidine injection, intravenous regional sympathetic block with bretylium and spinal cord stimulation should be offered only after careful counseling (**B**).
- Therapies to avoid due to lack of efficacy, lack of evidence, or a high likelihood of adverse outcomes are IV regional sympathetic blocks with anything but bretylium, sympathetic ganglion blocks with local anesthetics, systemic IV sympathetic inhibition, acupuncture, and sympathectomy (**B**).

In last issue of the JOURNAL OF FAMILY PRACTICE, we discussed diagnosis of CRPS type 1 ("Complex regional pain syndrome underdiagnosed," 2005; 54: 524–532). Once other conditions have been ruled out, a primary care practitioner can diagnose CRPS type 1 right in the office using clinical findings and the patient's report of symptoms. Similarly, primary care practitioners can provide most of the best treatments for CRPS type 1. In fact, evidence indicates that no benefit has been proven from more invasive treatments such as sympathectomy which continue to be included in recommendations by experts.[1]

Evidence for intervention less than compelling

A review of the literature on treating CRPS type 1 raises a question: is there any evidence that treatment makes a difference in outcomes that matter to patients, such as returning to work, regaining functionality of the affected limb, or resolution of pain? The large discrepancy between the high rates of CRPS type 1 documented in prospective studies of post-traumatic patients and the low rates of diagnosis of CRPS type 1 in actual practice suggests that most cases of CRPS type 1 resolve without being diagnosed and treated. This is not proven because, unfortunately, the natural history of persons diagnosed in the first 9 weeks after injury is not known.[2]

Are there benefits to early treatment?

From the clinician's perspective, persons diagnosed with CRPS type 1 early appear more likely to respond to treatment. There is an "oft-quoted contention that results of early treatment will be better than those when the pain is treated late."[2] Yet, the great majority of these patients may have improved just as readily without

CORRESPONDING AUTHOR
Anna Quisel, MD, c/o Cheryl Mongillo, Family Medicine Center, 1401 Foulk Road, Wilmington, DE 19803.
E-mail: DrQuisel@comcast.net

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Many treatments for managing pain are minimally if at all effective, including such common therapies as NSAIDs, opiates, and antidepressants

treatment. For the few cases of undiagnosed CRPS type 1 that will persist to become chronic and treatment resistant, it is unknown whether early treatment would have been preventive[2] or how clinicians could distinguish these cases early enough to target them for treatment.

Intriguing but limited data exist for using preventive therapies in all at-risk patients. One prospective cohort study documented a lower rate of CRPS type 1 in stroke patients who underwent early inpatient rehabilitation, compared with patients in earlier studies who rarely received early rehabilitation. This finding indirectly suggests a possible preventive effect of physical/occupational therapy (LOE: **3**, cross-study comparison).[3] Luckily, early inpatient rehabilitation in stroke patients has become the standard of care, which may prevent many cases of CRPS type 1 as a side effect.

It also appears that injury to a newly hemiplegic arm may contribute to the shoulder-hand syndrome; a study that alerted patients and care-takers to the risk of injury reduced the rate of shoulder hand syndrome from 27 to 8% (LOE: **2**, lower-quality RCT).[4] Among post-traumatic patients with wrist fracture, a double-blind randomized placebo controlled trial (n=115) of vitamin C 500 mg tabs initiated upon diagnosis of fracture and continued for 50 days resulted in a marked decrease of CRPS type 1 from 22% in the placebo group to 7% in the vitamin C group (relative risk=0.17) (LOE: **1**, high-quality RCT).[5] These results have not been tested in subsequent trials, however.

Guideline recommendations: Physical and psychological therapy, pain management

Many treatments for CRPS have been tried and are summarized without a systematic or evidence-based approach to the literature in a consensus statement released in 2002 by an interdisciplinary expert panel (LOE: **3**, consensus guideline).[1] These guidelines suggest rapid initiation of multidisciplinary treatment with advancement to higher levels of intervention if no benefit from initial therapy occurs in 2 weeks. Simultaneous physical rehabilitation, psychological therapy, and pain management are recommended.

Rehabilitation through physical therapy and occupational therapy starts with desensitization and stress loading, progresses to increasing flexibility with gentle active range of motion and stretching, and eventually to normalization of use.

Psychological therapy starts with teaching patients that 1) pain sensations in CRPS type 1 do not indicate tissue damage, and 2) reactivation of the affected limb is important. With persistent symptoms, clinical psychological assessment is recommended, eventually followed by cognitive behavioral therapy.

Pain management starts with oral or topical medications typically used for other neuropathic pain conditions (eg, amitriptyline (Elavil), gabapentin (Neurontin), opioids, and nonsteroidal antidepressants). The guideline also recommends steroids, calcitonin, and alpha-1 adrenoceptor antagonists (terazosin [Hytrin] or phenoxybenzamine [Dibenzylene]). With persistent symptoms, intravenous regional sympathetic blocks (IRSBs) and somatic nerve blocks are recommended. According to the guideline, treatment for resistant cases may progress to epidural catheters for sympathetic blockade, spinal cord stimulation, intrathecal baclofen (Lioresal), or sympathectomy.[1]

Reviews of medication trials show minimal effectiveness

Meta-analyses and systematic reviews of the literature reveal that many of the treatments recommended in the guidelines are minimally if at all effective, or have been inadequately researched.[6–12] This is particularly so concerning invasive therapies such as sympathetic ganglion block,[13] sympathectomy,[12] and spinal cord stimulation[9,10] that introduce the possibility of adverse effects. Yet, evidence is equally sparse for common pain therapies in CRPS type 1, such as nonsteroidal anti-inflammatory

drugs, antidepressants, opiates, or antiseizure medications.

Systematic review and meta-analysis of medication trials for CRPS only partially agree.[6–8,11] A 1999 systematic review concluded that oral corticosteroids demonstrated a consistent and long-term analgesic effect in CRPS.[6] This review identified only limited data to suggest an analgesic effect from topical dimethylsulfoxide (DMSO), epidural clonidine and IRSB with ketanserin (not available in the US), and bretylium. The review concluded there was contradictory evidence of an analgesic effect from calcitonin or intravenous phentolamine and most likely no effect, and evidence against the effectiveness of guanethidine and reserpine IRSBs, and droperidol and atropine IRSBs.[6]

A 1995 systematic review of IRSBs concluded as well that overall there was no effect on pain, but a single RCT of each bretylium and ketanserin showed an analgesic effect.[8] In a systematic review focused on upper extremity post-stroke CRPS (also known as shoulder-hand syndrome), 1 RCT was identified, and indicated that corticosteroids had an analgesic effect.[11] High-quality evidence for the use of intramuscular calcitonin was lacking.[11]

Calcitonin may be one exception. A systematic review of medical treatment for CRPS type 1 identified 21 randomized trials, enough to undertake a statistical analysis of the analgesic effect of 4 types of treatment: sympathetic suppressors, guanethidine, intravenous regional blocks, and calcitonin.[7] Of the 4, only calcitonin appeared to have a significant beneficial effect on pain.[7]

IV bisphosphonates show promise. More recently, intravenous bisphosphonates have demonstrated clinical and analgesic benefits in 2 small but high-quality RCTs.[14,15] Strikingly, short-term therapy of 3 to 10 days of IV alendronate (Fosamax) or clodronate (Bonefos) without adverse effects resulted in significant overall improvements for the duration of the 2 trials, 4 weeks[14] and 180 days.[15]

Nonpharmacologic treatments

Nonmedical treatments that have been studied include spinal cord stimulation, physical therapy, occupational therapy, and acupuncture. Spinal cord stimulation demonstrated a modest long-term (2-year) reduction in pain and improvement in health related quality of life in 1 RCT,[16] but with no improvement in patient functioning and a 34% rate of adverse occurrences.[9] Similarly, physical therapy and occupational therapy have been studied only in 1 large RCT (n=135).

Treatment with physical therapy did decrease pain compared with occupational therapy and control therapy,[17] but revealed no improvement in active range of motion with physical or occupational therapy compared with control therapy.[17] Furthermore, physical therapy led only to uncertain diminishment of impairment when data were analyzed in 2 different ways, 1 of which showed a benefit of physical and occupational therapy over control treatment,[18] 1 of which did not.[19]

Acupuncture demonstrated no improvement over sham treatment.[20]

Applying the evidence: Medical treatment

Choose any of the therapies least likely to do harm and supported by evidence of efficacy: topical 50% DMSO cream (SOR: B), intravenous bisphosphonates (SOR: A), or limited courses of oral corticosteroids (SOR: B). Despite some contradictory findings in the literature,[6,17,18] other studies demonstrate that physical therapy[18,19] and calcitonin[7] reduce pain, and neither is likely to cause harm (SOR: B).

Epidural clonidine injection,[6] IRSB with bretylium,[6–8] and spinal cord stimulation[9,16] have demonstrated some efficacy, but due to the invasiveness of the treatments and the modest benefits, patients should be counseled carefully before initiating these therapies (SOR: B) (**TABLE 1**).

Therapies to avoid. Therapies to avoid due to lack of evidence, lack of efficacy, or

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Despite some contradictory findings, studies demonstrate that physical therapy and calcitonin reduce pain and are unlikely to cause harm

TABLE 1

Effectiveness of treatments for CRPS type 1

TREATMENT	STUDY TYPE	STUDY QUALITY	EFFECT*
DMSO	SR[6]	2 – small RCT (n=32)[21]	(+): Analgesia during therapy
Bisphosphonates	RCTs[14,15]	1 – multiple RCTs (n=32)[15] and (n=20)[14]	(+): Long-term (4 weeks[14] to 180 days[15]) overall clinical improvement with significant analgesia
Corticosteroids	2 SRs[6,11]	2 – 2 small RCTs, 1 in post-traumatic CRPS type 1 (n=23)[22] and 1 (poor-quality) in shoulder-hand syndrome (n=36)[3]	(+): 75% clinical improvement to 12 wk in CRPS type 1;[22] and resolution of symptoms in shoulder-hand syndrome[3]
Clonidine	SR[6]	2 – small RCT (n=26)[23]	(+): Temporary analgesia
Spinal cord stimulation	SR[9–11]	2 – multiple SRs based on 1 RCT (n=36)[16]	(+): Modest long-term (2-y)[16] analgesic effect, improved health-related quality of life, no improvement in patient functioning and 34% rate of adverse occurrences[9]
Physical therapy and occupational therapy	RCT[17–19]	1 – RCT (n=135)	(+/–): Contradictory analyses using different methods of measuring impairment, 1 showing no advantage of PT or OT over control,[17] the other showing improvement with both.[18] Significant improvement in pain at 1 y with PT over OT and control, no significant improvement in active ROM.[19]
Calcitonin	SR[6,7]	1 – multiple RCTs[24–26]	(+/–): Contradictory results – 1 SR indicating a significant analgesic effect[7] the other suggesting no analgesic effect[6]
IRSBs (bretylium, ketanserin, guanethidine, reserpine, droperidol, or atropine)	SR[6–8]	1 and 2 – Good-quality RCTs of guanethidine, otherwise small or poor quality RCTs	(+/–): When collectively analyzed, no overall positive effect.[7,8] When evaluated by particular medication, limited evidence for analgesia with bretylium and ketanserin (not available in the US),[6,8] and no analgesia with guanethidine, reserpine, droperidol and atropine[6]
Sympathetic ganglion blocks (lidocaine/ bupivacaine)	RCT[13]	2 – small RCT (n=7)	(+/–): Short-term analgesia with longer duration of pain control in treatment group (3.5 days) vs placebo (1 day)
Sympathectomy (chemical or surgical)	SR[12]	2 – SR based on poor-quality evidence, no placebo-controlled RCTs	(+/–): No evidence of effectiveness, high rates (>10%) of adverse effects including worse pain, new neuropathic pain and pathological body sweating
Acupuncture (30 min 5x/wk for 3 wk	RCT[20]	2 – small RCT (n=14)	(–): Immediate and long-term (6-mo) clinical improvement and analgesia in sham/acupuncture treatment groups
Sympathetic inhibition	SR[6]	1 & 2 – variable-quality RCTs[27–29]	(+/–): Contradictory results, with the best-designed study showing only a 9% short-term relief of pain[28]

DOSAGES: DMSO: 50% cream applied 5x/d for at least 2 mo.[21]
Bisphosphonates: IV alendronate 7.5 mg once daily for 3 days[14] or intravenous clodronate 300 mg once daily for 10 days.[15]
Calcitonin: intranasal 400 IU once daily[26] or 100 IU 3 times daily[27] or intramuscular 100 IU once daily for 3 weeks.[28]
Corticosteroids: prednisone 10 mg 3 times daily until remission, max. up to 12 weeks,[22] or prednisolone 32 mg daily for 2 wk with a 2-wk taper.[4]
Clonidine: 300 μg epidural injection.[23]
Sympathetic inhibition: IV phentolamine.[27–29]
*Effect: (+) = positive, (+/–) = contradictory results or poor quality evidence, (–) = no effect.
SR, systematic review; MA, meta-analysis; RCT, randomized controlled trial; DMSO, dimethylsulfoxide; PT, physical therapy; OT, occupational therapy; ROM, range of motion.

likelihood of adverse outcomes include IV regional blocks with everything but bretylium,[6–8] sympathetic ganglion blocks with local anesthetics (very short duration of analgesia),[13] systemic intravenous sympathetic inhibition,[6] acupuncture,[20] and sympathectomy (SOR: **B**).[12] ■

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

REFERENCES

1. Stanton-Hicks MD, Burton AW, Bruehl SP, et al. An updated interdisciplinary clinical pathway for CRPS: Report of an expert panel. *Pain Practice* 2002; 2:1–16.
2. Commentary on RSD focus article. *Bandolier* 2002. Available at: www.jr2.ox.ac.uk/bandolier/booth/painpag/wisdom/RSD.html.
3. Petchkrua W, Weiss DJ, Patel RR. Reassessment of the incidence of complex regional pain syndrome type 1 following stroke. *Neurorehabil Neural Repair* 2000; 14:59–63.
4. Braus DF, Krauss JK, Strobel J. The shoulder-hand syndrome after stroke: a prospective clinical trial. *Ann Neurol* 1994; 36:728–733.
5. Zollinger PE, Tuienebreijer WE, Kreis RW, Breederveld RS. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial. *Lancet* 1999; 354:2025–2028.
6. Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain* 1997; 73:123–139.
7. Perez RS, Kwakkel G, Zuurmond WW, de Lange JJ. Treatment of reflex sympathetic dystrophy (CRPS type 1). a research synthesis of 21 randomized clinical trials. *J Pain Symptom Manage* 2001; 21:511–526.
8. Jadad AR, Carroll D, Glynn CJ, McQuay HJ. Intravenous regional sympathetic blockade for pain relief in reflex sympathetic dystrophy: a systematic review and a randomized, double-blind crossover study. *J Pain Symptom Manage* 1995; 10:13–20.
9. Turner JA, Loeser JD, Deyo RA, Sanders SB. Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications. *Pain* 2004; 108:137–147.
10. Grabow TS, Tella PK, Raja SN. Spinal cord stimulation for complex regional pain syndrome: an evidence-based medicine review of the literature. *Clin J Pain* 2003; 19:371–383.
11. Geurts AC, Visschers BA, van Limbeek J, et al. Systematic review of aetiology and treatment of post-stroke hand oedma and shoulder-hand syndrome. *Scan J Rehabil Med* 2000; 32:4–10.
12. Mailis A, Furlan A. Sympathectomy for neuropathic pain. *Cochrane Database Syst Rev* 2003; 2.
13. Price DD, Long S, Wilsey B, Rafii A. Analysis of peak magnitude and duration of analgesia produced by local anesthetics injected into sympathetic ganglia of complex regional pain syndrome patients. *Clin J Pain* 1998; 14:216–226.
14. Adami S, Fossaluzza V, Gatti D, et al. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. *Ann Rheum Dis* 1997; 56:201–204.
15. Varenna M, Zucchi F, Ghiringhelli D, et al. Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. A randomized double blind, placebo controlled study. *J Rheumatol* 2000; 27:1477–1483.
16. Kemler MA, De Vet HC, Barendse GA, Van Den Wildenberg FA, Van Kleef M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. *Ann Neurol* 2004; 55:13–18.
17. Oerlemans HM, Goris JA, de Boo T, Oostendorp RA. Do physical therapy and occupational therapy reduce the impairment percentage in reflex sympathetic dystrophy? *Am J Phys Med Rehabil* 1999; 78:533–539.
18. Oerlemans HM, Oostendorp RA, de Boo T, van der Laan L, Severens JL, Goris JA. Adjuvant physical therapy versus occupational therapy in patients with reflex sympathetic dystrophy/complex regional pain syndrome type I. *Arch Phys Med Rehabil* 2000; 81:49–56.
19. Oerlemans HM, Oostendorp RA, de Boo T, Goris RJ. Pain and reduced mobility in complex regional pain syndrome I: outcome of a prospective randomised controlled clinical trial of adjuvant physical therapy versus occupational therapy. *Pain* 1999; 83:77–83.
20. Korpan MI, Dezu Y, Schneider B, Leitha T, Fialka-Moser V. Acupuncture in the treatment of posttraumatic pain syndrome. *Acta Orthop Belg* 1999; 65:197–201.
21. Zuurmond WW, Langendijk PN, Bezemer PD, Brink HE, de Lange JJ, van loenen AC. Treatment of acute reflex sympathetic dystrophy with DMSO 50% in a fatty cream. *Acta Anaesthesiol Scand* 1996; 40:364–367.
22. Christensen K, Jensen EM, Noer I. The reflex dystrophy syndrome response to treatment with systemic corticosteroids. *Acta Chirurgica Scandinavica* 1982; 148:653–655.
23. Rauck RL, Eisenach JC, Jackson K, Young LD, Southern J. Epidural clonidine treatment for refractory reflex sympathetic dystrophy. *Anesthesiology* 1993; 79:1163–1169.
24. Bickerstaff DR, Kanis JA. The use of nasal calcitonin in the treatment of post-traumatic algodystrophy. *Br J Rheumatol* 1991; 30:291–294.
25. Gobelet C, Waldburger M, Meier JL. The effect of adding calcitonin to physical treatment on reflex sympathetic dystrophy. *Pain* 1992; 48:171–175.
26. Gobelet C, Meier J, Schaffner W, et al. Calcitonin and reflex sympathetic dystrophy syndrome. *Clin Rheumatol* 1986; 5:382–388.
27. Raja AN, Treed RD, Davis KD, Campbell JN. Systematic alpha-adrenergic blockade with phentolamine: a diagnostic test for sympathetically maintained pain. *Anesthesiol* 1991; 74:691–698.
28. Verdugo RJ, Ochoa JL. Sympathetically maintained pain. I. Phentolamine block questions the concept. *Neurology* 1994; 44:1003–1010.
29. Verdugo RJ, Campero M, Ochoa JL. Phentolamine sympathetic block in painful polyneuropathies. II. Further questioning of the concept of "sympathetically maintained pain." *Neurology* 1994; 44:1010–1014.