

APPLIED EVIDENCE

New research findings that are changing clinical practice

Complex regional pain syndrome: Which treatments show promise?

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

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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 preventive² 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 bene-

fit 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

FAST TRACK

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

drugs, antidepressants, opiates, or anti-seizure 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 (Bonafos) without adverse effects resulted in significant overall improvements for the duration of the 2 trials, 4 weeks¹⁴ 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 calcitonin⁷ 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

FAST TRACK

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 (bretylum, 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 bretylum 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 days¹⁴ or intravenous clodronate 300 mg once daily for 10 days.¹⁵

Calcitonin: intranasal 400 IU once daily²⁶ or 100 IU 3 times daily²⁷ 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.

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