

Pharmacologic Management of Complex Regional Pain Syndrome

Michael C. Rowbotham, MD

Abstract: Few randomized controlled trials of oral pharmacotherapy have been performed in patients with complex regional pain syndrome (CRPS). The prevalence of CRPS is uncertain. Severe and advanced cases of CRPS are easily recognized but difficult to treat and constitute a minority compared with those who meet minimum criteria for the diagnosis. Unsettled disability or liability claims limit pharmaceutical industry interest in the disorder. Many studies are small or anecdotal, or are reported on only via posters at meetings. Targeting the process of bone resorption with bisphosphonate-type compounds such as calcitonin, clodronate, and alendronate has shown efficacy in three published randomized controlled trials. Intravenous phentolamine has been studied both alone and in comparison to intravenous regional blockade or stellate ganglion block. Steroids continue to be administered by multiple routes without large-scale placebo-controlled trials. Topical medications have received little attention. There has been considerable interest in the use of thalidomide and TNF-alpha blockers for CRPS, but no published controlled trials as of yet. Numerous other oral drugs, including muscle relaxants, benzodiazepines, antidepressants, anticonvulsants, and opioids, have been reported on anecdotally. Some therapies have been the subject of early controlled studies, without subsequent follow-up (eg, ketanserin) or without an analogous well-tolerated and equally effective oral treatment (eg, intravenous ketamine). Gabapentin, tricyclic antidepressants, and opioids have been proven effective for chronic pain in disorders other than CRPS. Each has shown a broad enough spectrum of analgesic activity to be cautiously recommended for treatment of CRPS until adequate randomized controlled trials settle the issue. The relative benefit of oral medications compared with the widely used treatments of intensive physical therapy, nerve blocks, sympathectomy, intraspinally administered drugs, and neuromodulatory therapies (eg, spinal cord stimulation) remains uncertain. In summary, treatment of CRPS has received insufficient study and remains largely empirical.

Key Words: pharmacology, complex regional pain syndrome

(*Clin J Pain* 2006;22:425-429)

Complex regional pain syndrome (CRPS), type I and type II (previously known as reflex sympathetic dystrophy [RSD] and causalgia), remains endlessly fascinating to all persons interested in pain management. No other chronic pain syndrome is as shrouded in confusion and controversy—to the detriment of efforts to rigorously define an evidence-based treatment strategy. Depending on how broadly the definition of the syndrome is applied, the incidence of CRPS varies from common to almost nonexistent. Severe and advanced cases are easy enough to recognize: distal extremity pain, diffuse swelling, smooth shiny skin with abnormal color and temperature, allodynia, joint pain and tenderness, juxta-articular osteoporosis, and sometimes even joint contractures. Such “classic” cases are not only highly refractory to therapy but also constitute a minority compared with the number of patients with pain who meet minimum criteria for the diagnosis. In many patients the diagnosis of CRPS is disputed, such as in patients with regional pain of unknown origin without a clear initiating event, or those with multi-limb or total body symptoms. Overall, the present situation is most unfortunate, considering the very high burden of suffering, lost productivity, and a cost of treatment that may exceed \$100,000.

Few randomized controlled trials of oral pharmacotherapy have been performed in CRPS patients. The presence of unsettled disability or liability claims, a common issue in CRPS patients, is usually an exclusion for entry into pharmaceutical industry-sponsored studies, and an added reason why few industry-sponsored trials have been performed in this group. However, a few recent controlled trials of oral therapies for neuropathic pain have included subjects with CRPS. A trial of the experimental sodium channel blocking drug 4030W92 and a trial of GV196771, a selective antagonist of the glycine binding site of the NMDA complex, both failed to show efficacy, and only a few CRPS patients were in the trials.^{1,2} Likewise, only a few patients with CRPS have been included in the large randomized controlled trials of gabapentin, but subgroup analyses are not available.³

Received for publication July 25, 2005; accepted July 25, 2005.
From the UCSF Pain Clinical Research Center, Departments of Neurology and Anesthesia, University of California, San Francisco, School of Medicine, San Francisco, CA.
Reprints: Michael C. Rowbotham, MD, 1701 Divisadero Street, Suite 480, San Francisco, CA 94115 (e-mail: Fax mcrwind@itsa.ucsf.edu).
Copyright © 2006 by Lippincott Williams & Wilkins

In distinct contrast, numerous randomized controlled pharmacotherapy trials have been performed in the past decade in patients with diabetic neuropathy and post-herpetic neuralgia, and these studies have resulted in specific labeling indications in the United States for two therapies, gabapentin and the lidocaine patch. However, it is difficult to extrapolate clinical trial results in diabetic neuropathy and post-herpetic neuralgia patients to the treatment of CRPS. This is underscored by the mechanistic uncertainty about CRPS and the belief that the mechanisms underlying this disorder are unique.⁴⁻⁶ Clinical mechanism-oriented studies directly comparing patients with CRPS and patients with other types of neuropathic pain in a controlled trial format are lacking. Based on animal studies, a role for adrenergic receptors is not unique, as Chabal et al⁷ injected epinephrine near neuromas and Choi and Rowbotham⁸ performed a placebo-controlled study in which they injected epinephrine into the skin of patients with post-herpetic neuralgia and found pain increases not too dissimilar from what has been reported in CRPS patients by Torebjörk et al⁹ and others.^{7,8} Uncontrolled studies of intravenous lidocaine dating back to the 1950s and before have included groups of patients with post-herpetic neuralgia, diabetic neuropathy, and RSD,¹⁰ and Wallace et al¹¹ focused specifically on CRPS.

Recent systematic reviews of CRPS treatment trials by Forouzanfar et al¹² and Kingery¹³ are the most complete, and reviews by Ribbers et al¹⁴ and Rho et al¹⁵ are also useful. Drawing on multiple databases and using a rigorous quantitative rating system, Forouzanfar et al found fewer than a dozen controlled trials of oral or systemic intravenous therapies meeting minimum quality criteria. This brief review will concentrate on oral, intravenous, transdermal, and topical therapies subjected to randomized controlled trials (RCTs). Drugs given by the intrathecal route, such as clonidine, baclofen, and conotoxin-derived compounds, will not be discussed in this article, although more reports are beginning to appear.¹⁶ Nerve blocks and regional intravenous infusions will also not be reviewed in this article.

BISPHOSPHONATE COMPOUNDS

The most thoroughly studied therapy has been the bisphosphonate-type compounds, which target the process of bone resorption. Subsequent to uncontrolled studies that reported very high response rates, placebo-controlled studies have been conducted with intranasal calcitonin,¹⁷ intravenous clodronate,¹⁸ and intravenous alendronate.¹⁹ Outcome measures common to all three studies were active movement and motor function. A total of 118 patients were studied, and all three studies showed a statistically significant improvement with active therapy. However, Bickerstaff and Kanis²⁰ treated 40 patients with intranasal calcitonin and reported no significant improvement compared with placebo after 3 months of therapy. Clodronate may be the most potent as

it acts on several inflammatory mediators, including IL-1, IL-6, PGE₂, lactic acid, and TNF- α , but there are no studies comparing the different compounds in this category.

ADRENERGIC ACTIVE DRUGS

Intravenous phentolamine has been studied both alone and in comparison to intravenous regional blockade (with guanethidine or bretylium) or stellate ganglion block.²¹⁻²³ Verdugo et al^{24,25} reported two placebo-controlled studies (total of 77 patients) of intravenous phentolamine in both RSD patients and peripheral neuropathy patients, with one of the two studies including intravenous phenylephrine administration to see if would be pain-provoking. The studies reported no significant pain relief with phentolamine and no significant worsening with phenylephrine. Patients who experienced a significant reduction in pain during the placebo run-in phase were deemed placebo responders. However, as both studies included a single-blind placebo infusion preceding the active treatment, there was opportunity for investigator bias to influence the results. In contrast, many investigators have reported increased pain with local injection of an adrenergic agonist in patients with longstanding CRPS.⁹ In clinical practice, many physicians use sympatholytic agents in the belief that CRPS symptoms will be relieved, despite the lack of prospective controlled trials. These agents include clonidine (oral and transdermal), reserpine, phenoxybenzamine, and others.

SYSTEMIC STEROIDS

Steroids have been and continue to be administered by multiple routes for CRPS therapy. After early reports of success with systemic steroids,²⁶ Christensen et al²⁷ studied 23 patients and reported that 30 mg/d of oral prednisone was significantly better than placebo.

TOPICAL MEDICATIONS

Topical medications have received little attention in controlled studies. Zuurmond et al²⁸ studied DMSO and found benefit, but no difference compared with active therapy with regional blockade. More recently, Perez et al²⁹ compared topical DMSO and an oral free radical scavenger and reported them to have similar efficacy. Topical lidocaine has been tried on an uncontrolled basis with reported success.³⁰

OTHER THERAPIES

There has been considerable recent interest in the use of thalidomide for CRPS, but no controlled trials have been conducted as yet. The mechanism of action of thalidomide is of importance because of hypotheses that cytokines might play a major role in the development of the CRPS syndrome. There is a single supplier of this compound, with a mandatory registration and follow-up program to monitor its use. Women of childbearing potential have largely been excluded from receiving this

treatment because of its well-known teratogenic effects. Drugs that work through TNF-alpha blockade and follow-up compounds to thalidomide are under active development, with controlled trials in progress.

Numerous other oral drugs have been tried on an anecdotal basis in the treatment of CRPS, but their efficacy cannot be fairly commented upon because there are no RCTs for that treatment category in CRPS patients. These agents include various muscle relaxants, benzodiazepines, antidepressants, anticonvulsants, and opioids. Some therapies have been the subject of early controlled studies, without subsequent follow-up or without a well-tolerated and widely available analogous oral treatment; for example, ketanserin was the subject of two controlled studies in the 1980s, and intravenous ketamine therapy reports have also appeared.^{31,32}

TRANSFERRING TREATMENT RECOMMENDATIONS FROM RCT DATA IN OTHER DISORDERS

Gabapentin, tricyclic antidepressants, and opioids are mainstays of neuropathic pain treatment. Each has been proven effective in RCTs for conditions other than CRPS, and they have shown a broad enough spectrum of analgesic activity that they can be recommended for treatment of CRPS. Therapy with these compounds is advocated in reviews of CRPS treatment, and all three are widely used in clinical management of CRPS. The evidence in favor of their use for CRPS treatment, however, is anecdotal. It would be speculative to rank-order their utility for CRPS therapy, and clinical trials in other types of chronic pain have rarely directly compared these categories. A notable exception is the recent placebo-controlled crossover trial by Raja et al³³ comparing amitriptyline and opioids in patients with post-herpetic neuralgia, in which opioids produced the greatest reduction in pain. The lowest number needed to treat (NNT) scores have been associated with tricyclic antidepressants. The NNT value is calculated from placebo-controlled trials to describe the efficacy of the active treatment after taking into account the success rate with placebo treatment, but for clinical practice NNT translates into a measure of how many patients need to receive a given treatment in order for one patient to obtain clear benefit.³⁴ In pain therapy, an NNT of 3 means that for every three patients treated, one will achieve "moderate" or better pain relief or experience a 50% reduction in pain intensity. In general, pain therapy RCTs with an NNT of approximately 5.5 or lower show statistically significant pain reduction for active treatment compared with placebo. Many other compounds, including essentially all anticonvulsants, are used for neuropathic pain but remain almost entirely unstudied for CRPS.^{6,13,35}

Many trials of tricyclic antidepressant have calculated NNT values of 3 or lower, but the design and analysis of some may have produced artificially low NNT

values. Anecdotally, tricyclic antidepressants may be very useful for CRPS management, although these drugs are quite lethal in an intentional overdose compared with serotonin-selective antidepressants. Furthermore, the tricyclic antidepressants are potent sodium channel blockers, with the potential for additive toxicity when high local anesthetic blood levels are achieved during nerve block therapy for CRPS. Most studies of non-tricyclic antidepressants of the serotonin-selective type have shown little or no analgesia. Venlafaxine and other antidepressants that block reuptake of both serotonin and norepinephrine may be more effective, with one recent trial showing that the efficacy of venlafaxine approached that of imipramine.³⁶

One of the first literature reports to describe the efficacy of gabapentin was a case series of CRPS patients.³⁷ The drug has safety advantages over tricyclic antidepressants and has shown evidence of analgesic efficacy in human experimental pain models and for postoperative pain.^{38,39} There are no data to suggest that gabapentin doses should be different for CRPS compared with chronic neuropathic pain. Other anticonvulsants have received less study for CRPS, although essentially all of them have been used in individual patients with CRPS. Anticonvulsants with sodium channel blocking activity, such as carbamazepine, might be especially useful for CRPS type II because peripheral nerve injury alters the distribution and expression of subtypes of sodium channels on axonal membranes.

Using opioids to treat CRPS is much more controversial than using gabapentin or antidepressants. Opioids remain the gold standard for treatment of acute pain. Prospective controlled studies demonstrating efficacy for chronic neuropathic pain have steadily accumulated in recent years and now include post-herpetic neuralgia, peripheral neuropathy, and other types of neuropathic pain.⁴⁰⁻⁴² Higher dosage strengths have been shown to be more potent at reducing pain intensity than lower strengths, but at a cost of increased side effects. Some patients, especially those with central nervous system injury, may experience no pain relief from opioids. Although tolerance has not proven to be a significant issue during the relatively short treatment periods used in clinical trials (4-8 weeks), the risk of rapid dose escalation and loss of analgesic efficacy is believed by some clinicians to be high in CRPS. Tramadol, a drug with a dual action on serotonin/norepinephrine reuptake and weak agonist effects on mu-opioid receptors, has been proven effective in two RCTs for peripheral neuropathy and may also be useful for some patients with CRPS.^{35,43}

CONCLUSIONS

Treatment of CRPS is largely empirical. The only systemic therapy evaluated in multiple controlled trials has been drugs affecting bone resorption, such as the bisphosphonates. Oral, topical, and intravenous medications targeting alpha-adrenergic receptors and the sympathetic nervous system have not been proven effective by

RCTs. Conventional therapies for neuropathic pain have not been specifically studied in CRPS patients. It appears logical, though not specifically justified by the literature, to try non-opioid medications such as tricyclic antidepressants and the anticonvulsant gabapentin. Opioids may have a therapeutic role, although their use in CRPS appears even more controversial than in other chronic pain disorders. In addition, there are essentially no data addressing the extremely important question of the relative benefit of oral medications compared with the widely used treatments of intensive physical therapy, nerve block therapy, intraspinally administered drugs, and neuromodulatory therapies such as spinal cord stimulation. Obviously, the more expensive therapies have large upfront costs, but no comparative data are available on long-term benefit. Most controlled studies of new treatments have been conducted in disorders such as post-herpetic neuralgia and diabetic neuropathy, in which the diagnosis can be made unequivocally and in which litigation is rare. Unfortunately, for as long as controversy exists about diagnostic criteria (extending to the legitimacy of the diagnosis of CRPS), and for as long as many cases are embroiled in litigation, CRPS is not likely to be the subject of large-scale multicenter trials of new therapies.

REFERENCES

- Wallace MS, Rowbotham M, Bennett GJ, et al. A multicenter, double-blind, randomized, placebo-controlled crossover evaluation of a short course of 4030W92 in patients with chronic neuropathic pain. *J Pain*. 2002;3:227–233.
- Wallace MS, Rowbotham M, Katz N, et al. A double-blind, placebo-controlled trial of a glycine antagonist in neuropathic pain. *Neurology*. 2002;59:1694–1700.
- Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. *Clin Ther*. 2003;25:81–104.
- Baron R, Levine JD, Fields HL. Causalgia and reflex sympathetic dystrophy: does the sympathetic nervous system contribute to the generation of pain? *Muscle Nerve*. 1999;22:678–695.
- Bennett GJ. Are the complex regional pain syndromes due to neurogenic inflammation? *Neurology*. 2001;57:2161–2162.
- Jensen TS, Baron R. Translation of symptoms and signs into mechanisms of neuropathic pain. *Pain*. 2003;102:1–8.
- Chabal C, Jacobson L, Russell LC, et al. Pain response to perineuronal injection of normal saline, epinephrine, and lidocaine in humans. *Pain*. 1992;49:9–12.
- Choi B, Rowbotham MC. Effect of adrenergic receptor activation on post-herpetic neuralgia pain and sensory disturbances. *Pain*. 1997;69:55–63.
- Torebjörk E, Wahren L, Wallin G, et al. Noradrenaline-evoked pain in neuralgia. *Pain*. 1995;63:11–20.
- Galer BS, Miller KV, Rowbotham MC. Response to intravenous lidocaine infusion differs based on clinical diagnosis and site of nervous system injury. *Neurology*. 1993;43:1233–1235.
- Wallace MS, Ridgeway BM, Leung AY, et al. Concentration-effect relationship of intravenous lidocaine on the allodynia of complex regional pain syndrome types I and II. *Anesthesiology*. 2000;92:75–83.
- Forouzanfar T, Koke AJ, van Kleef M, et al. Treatment of complex regional pain syndrome type I. *Eur J Pain*. 2002;6:105–122.
- Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain*. 1997;73:123–139.
- Ribbers GM, Geurts AC, Stam HJ, et al. Pharmacologic treatment of complex regional pain syndrome I: a conceptual framework. *Arch Phys Med Rehabil*. 2003;84:141–146.
- Rho RH, Brewer RP, Lamer TJ, et al. Complex regional pain syndrome. *Mayo Clin Proc*. 2002;77:174–180.
- van Hilten BJ, van de Beek W-JT, Hoff JI, et al. Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. *N Engl J Med*. 2000;343:625–630.
- Gobelet C, Waldburger M, Meier JL. The effect of adding calcitonin to physical treatment on reflex sympathetic dystrophy. *Pain*. 1992;48:171–175.
- Varena 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.
- Adami S, Fossaluzza V, Gatti D, et al. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. *Ann Rheum Dis*. 1997;56:201–204.
- Bickerstaff DR, Kanis JA. The use of nasal calcitonin in the treatment of post-traumatic algodystrophy. *Br J Rheumatol*. 1991;30:291–294.
- Arnér S. Intravenous phentolamine test: diagnostic and prognostic use in reflex sympathetic dystrophy. *Pain*. 1991;46:17–22.
- Raja SN, Treede RD, Davis KD, et al. Systemic alpha-adrenergic blockade with phentolamine: a diagnostic test for sympathetically maintained pain. *Anesthesiology*. 1991;74:691–698.
- Dellemijn PL, Fields HL, Allen RR, et al. The interpretation of pain relief and sensory changes following sympathetic blockade. *Brain*. 1994;117:1475–1487.
- 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.
- Verdugo RJ, Ochoa JL. "Sympathetically maintained pain." I. Phentolamine block questions the concept. *Neurology*. 1994;44:1003–1010.
- Kozin F, McCarty DJ, Sims J, et al. The reflex sympathetic dystrophy syndrome. I. Clinical and histologic studies: evidence for bilaterality, response to corticosteroids and articular involvement. *Am J Med*. 1976;60:321–331.
- Christensen K, Jensen EM, Noer I. The reflex dystrophy syndrome response to treatment with systemic corticosteroids. *Acta Chir Scand*. 1982;148:653–655.
- Zuurmond WW, Langendijk PN, Bezemer PD, et al. Treatment of acute reflex sympathetic dystrophy with DMSO 50% in a fatty cream. *Acta Anaesthesiol Scand*. 1996;40:364–367.
- Perez RS, Zuurmond WW, Bezemer PD, et al. The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study. *Pain*. 2003;102:297–307.
- Devers A, Galer BS. Topical lidocaine patch relieves a variety of neuropathic pain conditions: an open-label study. *Clin J Pain*. 2000;16:205–208.
- Bounameaux HM, Hellemans H, Verhaeghe R. Ketanserin in chronic sympathetic dystrophy. An acute controlled trial. *Clin Rheumatol*. 1984;3:556–557.
- Hanna MH, Peat SJ. Ketanserin in reflex sympathetic dystrophy. A double-blind placebo controlled cross-over trial. *Pain*. 1989;38:145–150.
- Raja SN, Haythornthwaite JA, Pappagallo M, et al. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology*. 2002;59:1015–1021.
- Moore RA. New developments in evidence-based decision-making: relevance to pain treatment and research. In: Max M, ed. *Pain 1999: An Updated Review*. Seattle: IASP Press; 1999:423–430.
- Sindrup SH, Andersen G, Madsen C, et al. Tramadol relieves pain and allodynia in polyneuropathy: a randomised, double-blind, controlled trial. *Pain*. 1999;83:85–90.

36. Sindrup SH, Bach FW, Madsen C, et al. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. *Neurology*. 2003;60:1284–1289.
37. Mellick GA, Mellick LB. Reflex sympathetic dystrophy treated with gabapentin. *Arch Phys Med Rehabil*. 1997;78:98–105.
38. Dirks J, Fredensborg BB, Christensen D, et al. A randomized study of the effects of single-dose gabapentin versus placebo on post-operative pain and morphine consumption after mastectomy. *Anesthesiology*. 2002;97:560–564.
39. Dirks J, Petersen KL, Rowbotham MC, et al. Gabapentin suppresses cutaneous hyperalgesia following heat-capsaicin sensitization. *Anesthesiology*. 2002;97:102–107.
40. Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology*. 1998;50:1837–1841.
41. Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology*. 2003;60:927–934.
42. Rowbotham MC, Twilling L, Davies PS, et al. Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med*. 2003;348:1223–1232.
43. Harati Y, Gooch C, Swenson M, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology*. 1998;50:1842–1846.