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Pharmacologic Therapies for Complex Regional Pain Syndrome

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Abstract

Complex regional pain syndrome (CRPS) remains a challenging condition to diagnose and treat. There are few large-scale, randomized trials of pharmacologic agents, and most published studies are small, uncontrolled, or presented only in abstract form at meetings. The most commonly used agents, such as anticonvulsants, anti-depressants, and opiates, have been found to be useful for other neuropathic pain conditions in large-scale trials but have not been adequately studied in CRPS. Systemic steroids delivered by multiple routes continue to be used, with some good evidence for short-term administration. N-methyl-D-aspartate antagonists have recently gained in popularity, without evidence from well-controlled trials. Bisphosphonates have been well studied and offer promise. In addition, there has been interest in thalidomide; however, we are still awaiting well-controlled trials. This article presents an overview of the available data regarding pharmacologic therapies for CRPS. These agents should be used in conjunction with a comprehensive interdisciplinary approach aimed at functional restoration and improved quality of life.

Introduction

Complex regional pain syndromes (CRPS) type I and II, formally known as reflex sympathetic dystrophy and causalgia, respectively, are two of the most puzzling and complicated chronic neuropathic pain syndromes involving sensory, motor, and autonomic changes. There are few diagnoses that cause more patient disability and dysfunction, as well as treating physician frustration, than CRPS.

The common objectives for the CRPS patient are less pain, increased function, and return to gainful employment and every day life activities. Although piecemeal treatment approaches can be effective, these objectives are best reached through careful use of selected medications, psychological and behavioral techniques, and physical rehabilitation approaches together with limited invasive procedures. This should all be done in the context of a comprehensive and coordinated interdisciplinary functional restoration approach. The primary focus of CRPS management is to restore use of the affected limb [1•,2].

There are few randomized controlled trials of pharmacologic agents performed in CRPS patients. The reasons are many. CRPS patients tend to have a presentation that is both medically and psychologically more heterogeneous than patients with painful diabetic neuropathy or postherpetic neuralgia—the two most common conditions studied. Furthermore, ongoing litigation or disability payments, situations commonly seen in CRPS patients, are often exclusion criteria for pharmacologic studies. Consequently, most published CRPS pharmacologic studies are small in scale, noncontrolled, or have only been reported in poster form at meetings. Despite these obstacles, there is a plethora of medications that are used to treat CRPS. This article reviews the evidence for oral,

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intravenous, and topical pharmacologic therapies for CRPS. Intrathecal and epidural delivery, as well as regional anesthesia infusions and nerve blocks, are not reviewed in this article.

Antiepileptic Drugs

Gabapentin is one of the most commonly prescribed pain medications for neuropathic pain in general, and in CRPS specifically. One of earliest reported uses of the drug was in a case report for the treatment of CRPS [3]. Gabapentin is thought to work by modulating calcium channels at a specific alpha2delta subunit [4]. The drug has been studied extensively in painful diabetic neuropathy [5] and postherpetic neuralgia [6], with demonstrated efficacy. In one randomized, blinded trial in 58 patients with CRPS, gabapentin had a mild effect on pain [7•]. In the largest placebo-controlled trial of gabapentin that included CRPS patients (85 of the 305 studied), gabapentin was shown to cause a significant reduction in pain, compared to placebo [8]. Of note, although there was a 1.5-point improvement in pain with the gabapentin group, there was only a 0.5-point difference (0–10 point pain scale) between the placebo and gabapentin groups. This is less a reflection of lack of efficacy with gabapentin (or many other antineuropathic pain medicines), but more a testament to the power of placebo. In a placebo crossover study of gabapentin, van de Vusse et al. [7•] noted a mild benefit with gabapentin as well as a reduction in mechanical sensory deficits. More formal quantitative sensory testing studies need to be done to replicate this 3nding and assess its mechanistic implications.

Most analgesic trials use a monotherapy design to investigate efficacy. Recently, a novel study by Gilron et al. [9••] investigated gabapentin, morphine, or their combination for neuropathic pain. The authors found that better analgesia was obtained with lower doses of each drug used in combination than with either drug used alone. More pharmacologic combination studies are needed.

Pregabalin, a new antiepileptic drug (AED) that has a similar mechanism of action as gabapentin, has not been studied in CRPS. It has been extensively studied in postherpetic neuralgia [10] and diabetic neuropathy [11], with good efficacy. Its primary advantage over gabapentin is thought to be its more linear pharmacokinetic profile and twice-daily dosing. Its side effect profile is similar to that of gabapentin, and it is generally well tolerated.

Sodium channel–blocking AEDs may have some utility in CRPS patients; however, there are few studies directly demonstrating efficacy. Carbamazepine is an older AED indicated for trigeminal neuralgia that has been studied in CRPS in a randomized, controlled trial (seven of the 38 neuropathic pain patients studied had CRPS). Administration of 600 mg/day of carbamazepine over 8 days resulted in significant pain reductions, compared with placebo [12]. Typically, in our clinical practice, we use oxcarbazepine instead of carbamazepine because of oxcarbazepine's similar mechanism of action and efficacy, as well as reduced side effects and drug-drug interactions [13,14]. Oxcarbazepine has not been studied in CRPS patients.

Antidepressants

There is ample scientific evidence to support the use of tricyclic antidepressants (TCAs) in neuropathic pain [15,16]. Although the literature for use of TCAs in CRPS is lacking, the drugs are commonly used for CRPS management. The antihyperalgesic effects of TCAs are probably related to enhancement of noradrenergic and serotonergic descending inhibitory pathways and partial sodium-channel blockade [17], mechanisms that are independent of their antidepressant effects. TCAs are not benign drugs and, in an intentional overdose, can be toxic as compared with serotonin-selective antidepressants. Although there is literature

supporting the use of TCAs in a variety of neuropathic pain conditions, there is only anecdotal evidence supporting their use in CRPS.

The clinician should be aware of several different TCA drugs, as they have varied side effects that may sometimes be used to the patients' advantage. For the overweight patient with lethargy, the clinician may choose a TCA with more noradrenergic selectivity (eg, desipramine), which may be activating and can cause some appetite suppression. For patients with poor sleep hygiene, the sedating properties of certain TCAs, such as amitriptyline, are recommended [18].

Selective serotonin reuptake inhibitors have been disappointing for neuropathic pain in general and CRPS in particular. Most studies of the serotonin-selective type (nontricyclic) antidepressants have shown little or no analgesia [18]. Newer antidepressant agents such as duloxetine, venlafaxine, and mirtazapine show some promise and have the advantage of a different, more benign side effect and toxicity profile.

Duloxetine and venlafaxine—both serotonin and norepinephrine reuptake inhibitors—have demonstrated benefit in neuropathic pain. One trial shows that the efficacy of venlafaxine approached that of imipramine [19]. In patients with diabetic peripheral neuropathic pain, duloxetine has been shown effective in large-scale randomized controlled trials [20] and in several open-label studies [21]. Recent evidence also suggests that these agents have direct analgesic effects beyond their antide-pressant benefits [22].

Opioids

Considerable controversy exists regarding the use of opioids for treatment of chronic pain of noncancer origin, and this is particularly true for CRPS. It is generally thought that opioids are less effective in chronic neuropathic pain conditions as opposed to their use in acute and subacute nociceptive pain states [23]. However, there are good data demonstrating that opioids can reduce pain [24] and improve quality of life in patients with neuropathic pain [25]. However, there are no well-controlled studies demonstrating long-term improvements in neuropathic pain treated with opiates.

Side effects with opioids are common and can be problematic. Common opioid side effects, particularly with higher doses, include nausea, vomiting, constipation, cognitive impairment, and somnolence. More serious side effects can include respiratory depression and, in a small subset of patients, addiction. The dilemma with long-term opioid use in CRPS is that prolonged use of opioids may result in problems including tolerance, hyperalgesia [26], hormonal effects (decreased testosterone levels, decreased libido and sex drive, irregular menses) [27], and suppression of the immune system. Consequently, although opioid treatment may be prescribed to reduce pain and improve function, the treatment may lead to more pain and dysfunction in some patients.

Anti-inflammatory Drugs

NSAIDs are commonly used to treat the inflammatory symptoms and the pain complaints of CRPS. NSAIDs act by inhibiting cyclooxygenase and preventing the synthesis of prostaglandins, which mediate inflammation and hyperalgesia. There have not been consistent studies to confirm the effectiveness of NSAIDs in neuropathic pain or CRPS. With the recent recognition of the role of spinal cyclooxygenase and its effect on hyperalgesia [28], there is renewed interest in studying this older class of medications as well as the more Cox-2 selective agents. Preliminary animal studies are promising [29].

Systemic corticosteroids have been shown to be useful in the treatment of CRPS in several open-label studies [30]. One small prospective, randomized, controlled trial [31] using oral prednisone (30 mg/day) reported significant improvements compared with placebo in patients with early CRPS. Recently, prednisolone was compared with piroxicam in a randomized trial in patients with CRPS after stroke. The prednisolone group demonstrated significant improvement over the piroxicam group [32]. In a review of the literature, Kingery [33] concluded that a short trial of corticosteroids had good support from the studies. However, longer courses of corticosteroids have a questionable risk–benefit ratio, and there are numerous contraindications.

One possible mechanism of CRPS is that it is induced by an exaggerated inflammatory response to tissue injury that is mediated by excess production of oxygen radicals [34]. Free-radical scavengers (alpha lipoic acid, dimethyl sulfoxide [DMSO], N-acetylcysteine [NAC], and vitamin C) have been studied with some success [35,36]. Topical DMSO 50% and oral NAC were recently compared in a randomized, controlled trial and noted to have similar efficacy. Although no significant differences were found in the primary outcome measure, the DMSO group generally did better. Subgroup analysis revealed that the warm CRPS patients tended to do better with DMSO, whereas cold CRPS patients did better with NAC. Although the magnitude of the results was large, the lack of a placebo group lessens the strength of this study.

Bisphosphonates

Bisphosphonates (eg, pamidronate, clodronate, alendronate) inhibit bone resorption and have demonstrated efficacy in the treatment of CRPS in small, open [37,38], and placebo-controlled studies [39–42]. In two placebo-controlled trials of bisphosphonates for the treatment of CRPS, either alendronate (7.5 mg intravenously daily for 3 days) [40] or clodronate (300 mg intravenously daily for 10 days) [42] demonstrated improvement in pain, compared with placebo. More recently, alendronate (40 mg daily for 8 weeks) was studied in a randomized, placebo-controlled trial. All of the alendronate-treated patients had a marked improvement in levels of spontaneous pain, pressure tolerance, and joint mobility. Although the primary mechanism of these agents has been thought to be the prevention of osteoporosis associated with CRPS, other peripheral and central mechanisms may be responsible and deserve investigation.

Sodium Channel Blockers

Intravenous lidocaine has strong sodium channel–blocking properties and has demonstrated efficacy in several uncontrolled studies of neuropathic pain [43] (see the article by Carroll in this issue) and CRPS. For example, Wallace et al. [44] found that intravenous lidocaine reduced spontaneous pain and specific characteristics of evoked pain. We have used intravenous lidocaine extensively in our center, both as a diagnostic tool to assess responsiveness to a subsequent oral sodium channel blocker (eg, mexiletine, oxcarbazepine, and carbamazepine) as well as a therapeutic tool when delivered in an inpatient setting. We will occasionally admit patients with CRPS and administer intravenous lidocaine infusions in combination with an aggressive functional restoration and cognitive-behavioral program.

N-methyl-D-aspartate Antagonists

In animal studies of neuropathic pain, an increase in expression of N-methyl-D-aspartate (NMDA) receptors has been demonstrated to play a role in clinical chronic neuropathic pain, including CRPS. Therefore, it would be reasonable to hypothesize that NMDA receptor antagonism would be beneficial for CRPS. The utility of these agents has been limited by

their significant side effect pro-3le. Agents that have clinically relevant NMDA-blocking properties include ketamine, amantadine, memantine, dextromethorphan, and methadone.

Ketamine is a strong NMDA antagonist that has been used intravenously for the treatment of CRPS and other neuropathic pain conditions. Recently, Correll et al. [45] used relatively low intravenous doses (10–30 mg/hour) of ketamine in CRPS patients for several days to 2 weeks in an inpatient setting. In their retrospective study, they noted significant long-term benefit from an open-label infusion protocol. Intravenous ketamine also has been used in CRPS patients at much higher doses (5–7 mg/kg/hour) for 5 to 7 days' duration in an intensive care unit, although these results have only been presented in abstract form. More formal study is needed to assess both efficacy and safety of ketamine for neuropathic pain.

Dextromethorphan, memantine, and amantadine are weaker NMDA receptor blockers, and consequently, are also thought to have fewer central nervous system side effects. Dextromethorphan is effective in painful diabetic neuropathy but not in postherpetic neuralgia [46]. The drug has also been thought to reduce the development of tolerance when given with opiates. However, a recent multicenter study with MorphiDex (morphine sulfate/dextromethorphan hydrobromide combination [Endo Pharmaceuticals, Chadds Ford, PA]) failed to demonstrate any enhancement of opioid analgesia or reduction in tolerance [47]. Amantadine (an anti-influenza medication) was beneficial for chronic pain in a small-scale study, with reductions in experimental sensitization [48]. Memantine (an Alzheimer's disease drug) has been anecdotally useful for neuropathic pain, but a recent placebo-controlled trial in phantom limb patients failed to demonstrate efficacy [49]. There are no published studies on amantadine, dextromethorphan, or memantine in CRPS patients. The concept of NMDA antagonism as a therapeutic target in neuropathic pain remains sound. There is a strong need for more studies and perhaps development of newer agents with fewer central nervous system side effects.

Adrenergic Drugs

Alpha-adrenergic antagonists (eg, phentolamine, phenoxybenzamine, clonidine, and reserpine) have been used clinically for the treatment of CRPS without good evidence from prospective randomized trials. The rationale for their use is the recognized role of the sympathetic nervous system in CRPS and the theory that blockade will provide pain relief. Phenoxybenzamine has been reviewed [50] and studied in small-case series [51]. Phentolamine in intravenous form has been used to assess sympathetically maintained pain [52]. Oral clonidine has not demonstrated significant efficacy in neuropathic pain and is challenging to use because of its side effect profile. It is more widely used as an intrathecal agent.

Topical Agents

Topical agents have gained popularity for use in certain neuropathic pain conditions, such as diabetic neuropathy, postherpetic neuralgia, or neuroma pain, but they are also prescribed for CRPS. Topical agents for CRPS deliver medication directly to the affected skin. They are different from topical transdermal drug delivery systems (eg, transdermal clonidine and the fentanyl patch). Topical agents for CRPS include a lidocaine patch 5%, eutectic mixture of local anesthetics cream, and capsaicin, none of which has been directly studied in CRPS with controlled trials. Additionally, other compounded mixtures (eg, ketamine, TCAs) are prescribed and then 3lled by pharmacies, although benefit with use of such unique compounded creams is anecdotal.

The lidocaine patch is approved by the US Food and Drug Administration for the treatment of postherpetic neuralgia and is being used increasingly for CRPS [53–55]. Topical

lidocaine is thought to produce pain relief through decreased ectopic discharges within peripheral sensory afferents, as the pain relief occurs in the absence of local anesthesia. Side effects of topical local anesthetics are minimal and include localized skin irritation and swelling that generally disappears within 2 to 3 hours after the local anesthetic(s) is removed from the skin. Blood concentrations of topical local anesthetics are well below toxic levels. In fact, they are also well below therapeutic levels used in lidocaine infusions.

Capsaicin is the active ingredient in chili peppers. It is a vanilloid compound that causes activation and subsequent dying back of nociceptive nerve endings. However, at the site of application, it often induces a painful burning sensation that many patients have trouble tolerating, thus resulting in poor compliance [56,57]. Robbins et al. [58] demonstrated significant efficacy with CRPS patients in an open-label study with high-dose topical capsaicin. These patients required a regional anesthetic block to tolerate the high-dose capsaicin. A high-dose capsaicin patch is currently in clinical trials.

Thalidomide

Recently, there has been significant interest in the use of thalidomide as a treatment for CRPS. This is based on the rationale that inflammatory cytokines may play a role in CRPS, and thalidomide is an inhibitor of tumor necrosis factor alpha. There are no published clinical trials on thalidomide use in CRPS, only case reports demonstrating efficacy [59,60]. The drug is currently being studied in clinical trials, but because of its history of causing birth defects, women of childbearing age have been excluded, and extensive monitoring is required.

Conclusions

Optimal treatment of CRPS involves a comprehensive interdisciplinary approach focused on functional restoration. The pharmacotherapies listed here have not been demonstrated to significantly change the overall course of the syndrome and have been used primarily to help patients progress with their rehabilitative program. Most pharmacotherapy for CRPS remains empirical, with few well-designed, prospective, controlled trials. The only agents studied in multiple controlled trials are the bisphonates. The remainder of the studies of agents demonstrating analgesic efficacy were not in CRPS but, more commonly, diabetic neuropathy and postherpetic neuralgia. However, it would appear that based on overlapping pathophysiologic mechanisms of neuropathic pain, treatment with TCAs, serotonin-norepinephrine reuptake inhibitors, opiates, and certain anticonvulsants is justified. There are few conditions that take as devastating a toll on a patient’s life as CRPS. Large-scale trials of these and newer agents are strongly needed. In particular, newer study designs combining multiple agents and integrating active physical therapy will provide practicing clinicians with the best information to base their treatment decisions.

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