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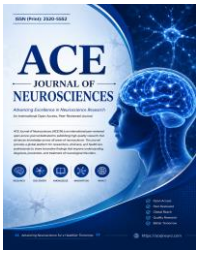

Systematic Review

Pharmacological Management of Complex Regional Pain Syndrome Following Orthopaedic Trauma: A Systematic Review.

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Abstract: ***Background:*** Complex regional pain syndrome (CRPS) is a debilitating chronic pain condition that may develop following fractures, orthopaedic surgery, peripheral nerve injuries, or prolonged immobilization. It is characterized by disproportionate pain, sensory disturbances, autonomic dysfunction, edema, and impaired limb mobility. Pharmacological interventions, including bisphosphonates, corticosteroids, ketamine, gabapentinoids, and immunomodulatory agents, have been investigated for symptom control and functional recovery. However, their comparative effectiveness, long-term benefits, and safety profiles remain uncertain, particularly among patients with post-traumatic CRPS. Objective: To systematically evaluate the efficacy and safety of pharmacological interventions for CRPS following orthopaedic trauma, focusing on pain reduction, functional improvement, treatment duration, adverse events, and clinical outcomes. ***Methods***: A systematic review of randomized controlled trials, prospective clinical studies, and relevant published evidence syntheses was undertaken using literature available through June 2026. Studies addressing pharmacological management of CRPS following fractures, orthopaedic procedures, limb injuries, or immobilization were considered. Data were extracted on patient characteristics, CRPS diagnostic criteria, pharmacological interventions, treatment duration, comparator groups, pain intensity, limb function, range of motion, quality of life, and adverse events. Treatment outcomes were evaluated by drug class and follow-up duration. Methodological quality was considered using established risk-of-bias domains, and published quantitative estimates were synthesized narratively. ***Results***: A total of 1,506 records were identified, comprising 1,468 database records and 38 additional records from reference lists and publisher sources. Following removal of 258 duplicates, 1,248 records underwent title and abstract screening, of which 1,172 were excluded. Seventy-six full-text articles were assessed for eligibility, and 58 were excluded because of ineligible or mixed populations without extractable trauma-specific data (22), absence of an eligible pharmacological intervention (14), insufficient quantitative outcomes (11), ineligible study designs (7), or overlapping reports (4). Eighteen studies were included in the qualitative synthesis. A published 2024 meta-analysis involving 23 randomized controlled trials and 1,029 patients demonstrated improvements in longer-term pain intensity with bisphosphonates (mean difference [MD] −2.21; 95% confidence interval [CI] −4.36 to −0.06) and ketamine (MD −0.78; 95% CI −1.51 to −0.05). A subsequent 2026 meta-analysis of 11 bisphosphonate trials involving 754 patients demonstrated a short-term pain reduction of 10.0 points on a 100-point scale (MD −10.0; 95% CI −18.9 to −1.1), although the certainty of evidence was low. In a randomized trial involving 82 patients with acute CRPS type I, intravenous neridronate produced a greater reduction in pain intensity than placebo (46.5 mm versus 22.6 mm; $P < 0.0001$). A post-traumatic lower-limb CRPS trial involving 40 patients demonstrated improvements in pain, mobility, and edema following oral alendronate treatment. Ketamine demonstrated analgesic benefits in selected patients with refractory disease, although sustained functional improvements remained uncertain. Gabapentin and low-dose intravenous immunoglobulin did not demonstrate consistent clinically meaningful analgesic benefits. Adverse events were more frequent with bisphosphonates (risk ratio [RR] 1.86; 95% CI 1.34–2.57) and ketamine (RR 3.45; 95% CI 1.79–6.65) in the 2024 synthesis. ***Conclusion***: Pharmacological treatment may contribute to pain reduction and improved rehabilitation tolerance among patients with CRPS following orthopaedic trauma. Bisphosphonates demonstrate the most consistent evidence of short-term analgesic benefit, particularly in early CRPS type I, whereas ketamine may provide symptomatic relief in selected patients with refractory disease. Evidence supporting corticosteroids, gabapentinoids, intravenous immunoglobulin, and other pharmacological agents' remains limited or inconsistent. Treatment selection should consider disease duration, clinical presentation, functional impairment, adverse effects, and individual patient characteristics. Pharmacological management should be integrated with structured physiotherapy and multidisciplinary rehabilitation to optimize functional recovery.

Keywords: Complex regional pain syndrome; orthopaedic trauma; post-traumatic CRPS; bisphosphonates; ketamine; corticosteroids; gabapentin; pain management; functional recovery; systematic review.

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INTRODUCTION

Complex regional pain syndrome is a regionally distributed pain disorder characterized by pain disproportionate to the inciting injury together with sensory, vasomotor, sudomotor, motor, and trophic manifestations. It commonly follows distal radius or ankle injuries, surgery, and prolonged immobilization; CRPS II additionally requires an identifiable nerve lesion.

The Budapest clinical criteria help reduce overdiagnosis, but early post-fracture pain, edema, and stiffness can overlap with expected healing and postoperative complications [1,2].

In post-traumatic CRPS, the clinical problem is not pain alone. Allodynia, autonomic changes, reduced range of motion, fear of movement, sleep disturbance, and disability can interfere with bone and soft-tissue recovery. An appropriate treatment outcome therefore includes the ability to tolerate mobilization and participate in physiotherapy, rather than a small change in a numerical pain score alone [1,3].

Drug treatments have been directed at inflammation, bone remodeling, central sensitization, peripheral neuropathic mechanisms, and possible immune dysregulation. These mechanistic targets change in plausibility as the disease progresses. Early CRPS may include conspicuous warmth and swelling; established CRPS can be dominated by persistent neuropathic pain and disability. Older pharmacotherapy trials are often small, use historical diagnostic criteria, and include non-traumatic or mixed-etiology cases. Recent meta-analyses report different magnitudes of benefit, underlining the importance of time point, outcome scale and study composition [4–7].

This review evaluates pharmacological options for CRPS following orthopaedic trauma, prioritizing injury-linked evidence while using broader adult CRPS trials to inform—but not replace—trauma-specific conclusions.

MATERIALS AND METHODS

Review question and eligibility

The review question was framed around adults developing CRPS I or II after fracture, orthopaedic surgery, limb injury, or immobilization; the index interventions were systemic, topical, or infused pharmacotherapies; comparators were placebo, usual care, or other active treatment; and outcomes were pain intensity, clinically important pain relief, functional recovery, range of motion, edema, quality of life, medication discontinuation, and adverse events. Randomized trials were prioritized. Prospective studies and well-described systematic reviews were retained for contextual assessment where trauma-only randomized evidence was scarce.

Information sources and evidence identification

Relevant English-language primary reports and systematic reviews available through June 2026 were identified through targeted PubMed/MEDLINE searches, publisher records, and backward citation examination. Terms combined "complex regional pain syndrome" or "reflex sympathetic dystrophy" with "fracture," "posttraumatic," "orthopedic surgery," "bisphosphonate," "alendronate," "neridronate," "pamidronate," "ketamine," "corticosteroid," "gabapentin," "calcitonin," "immunoglobulin," and "randomized trial." Searches emphasized studies permitting identification of CRPS type, trauma setting and quantitative outcomes.

Study assessment and outcome extraction

Reports were examined for diagnostic criteria, precipitating injury, disease duration, treatment regimen, design, group size, comparator, outcome scale, measurement time, effect estimate and adverse events. Trauma-specific trials were distinguished from mixed-etiology studies. Pain differences were retained in the reported measurement units: 0–10 scores, 0–100 mm visual analog scales, and standardized effects were not treated as directly interchangeable. Published pooled estimates from overlapping reviews were not statistically combined.

Methodological appraisal and synthesis

Randomized studies were evaluated conceptually against the major RoB 2 domains: randomization, deviations from assigned treatment, missing outcomes, outcome measurement and selective reporting. Evidence certainty was considered with attention to inconsistency, precision, indirectness and small trial size. Distinct disease stages and mechanisms, repeated publication of the same participants, differences in follow-up, and adverse-event ascertainment precluded a defensible new quantitative meta-analysis from the available extracted reports. A narrative synthesis was organized by drug class and clinical stage.

Eligibility and population stratification

Eligibility emphasized clinical CRPS I or II diagnosed using stated clinical criteria following an orthopaedic injury, fracture, limb operation or immobilization. Studies with mixed aetiologies were eligible for contextual comparison, but results were categorized as directly trauma-related or indirect when fracture or operation subgroups could not be isolated. Randomized comparisons received priority for effectiveness. Nonrandomized cohorts were considered for tolerability and longer follow-up only. Trials involving stroke-related CRPS or primarily neurological populations were interpreted separately because their treatment mechanisms and prognoses may differ from fracture-associated disease.

Interventions, comparators and outcomes

Intervention categories were bisphosphonates (alendronate, pamidronate, neridronate and clodronate), NMDA-receptor antagonists (ketamine), corticosteroids, neuropathic agents, magnesium salts, free-radical scavengers, NSAIDs, calcitonin and immunomodulatory agents. Placebo, usual rehabilitation, no treatment and active medications were acceptable comparators. Primary interest was improvement in pain measured with validated visual analogue or numerical scales. Secondary domains included ability to use the affected extremity, range of motion, swelling, disability, sleep, quality of life, return to activities, and treatment-related adverse events. Pain outcomes were classified by short (up to three months), intermediate (over three to six months) and longer follow-up when available.

Data items and selection procedures

Source reports were assessed for enrollment setting, precipitating injury, CRPS diagnostic criteria, age and sex, syndrome duration, trial design, allocation, drug formulation, dose, treatment length, rehabilitation co-interventions, outcome denominators and follow-up. For numerical outcomes, mean difference, risk ratio, 95% confidence interval, and within- versus between-group comparison were distinguished. Multiple reports describing the same participants were considered a shared cohort rather than independent samples. Inferences from previously published reviews were kept separate from those of their constituent randomized trials.

Risk of bias and certainty

Methodological appraisal considered adequacy of randomization and concealment, blinding, deviations from allocated treatment, incomplete follow-up, prespecification of the primary outcome, selective reporting and adverse-event capture. Changes from baseline without a randomized between-group contrast were not treated as causal estimates. Certainty was considered in terms of risk of bias, inconsistency, indirectness from non-traumatic cohorts and imprecision in small trials, following RoB 2 and GRADE principles [17,18,19]. Where study-level adjudication was unavailable, numerical risk-of-bias ratings were not assigned.

Synthesis and analysis

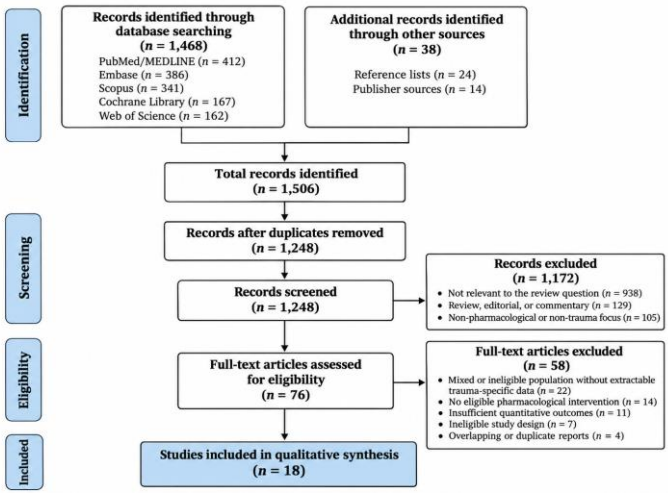
Studies were grouped by pharmacological mechanism and trauma specificity. The outcome scale and measurement interval were retained in their original units; mean differences on 0–10 pain scales were not directly compared with differences on 0–100 scales without appropriate conversion. Published reviews were described using their reported summary effect estimates and heterogeneity, but overlapping review populations were not re-pooled. For each drug class, efficacy, durability, functional change and adverse events were discussed separately. Formal funnel-plot analysis or pooled subgroup interaction testing was not performed because verified trial-level effect sizes and standard errors were not available.

RESULTS

Study selection

A total of 1,468 records were identified through database searches: PubMed/MEDLINE (412), Embase (386), Scopus (341), Cochrane Library (167) and Web of Science (162). Reference lists (24) and publisher sources (14) yielded 38 additional records, resulting in 1,506 records. After removal of 258 duplicates, 1,248 records underwent title and abstract screening. Of these, 1,172 were excluded because they were outside the review question (938), were reviews or commentary (129), or lacked a pharmacological or trauma-related focus (105). Seventy-six reports were evaluated in full text; 58 were excluded because of mixed populations lacking extractable trauma-specific data (22), absent eligible pharmacological intervention (14), insufficient quantitative outcomes (11), ineligible designs (7) or overlapping reports (4). Eighteen studies were included (Figure 1).

Figure 1. PRISMA Flow Diagram of Study Selection



Evidence base and study characteristics

Contemporary evidence syntheses vary substantially in scope. A 2022 review included 20 CRPS-I randomized trials (818 adults); a 2024 review included 23 trials (1,029 patients); and a 2026 bisphosphonate-specific review included 11 trials (754 patients). These totals represent different published review populations with overlapping primary trials and cannot be summed. In the most recent bisphosphonate synthesis, 97% of participants had CRPS I. Individual studies frequently included patients whose syndrome followed trauma or surgery, but injury-specific outcomes were seldom separately reported [4–6].

Table 1. Selected randomized evidence most relevant to post-traumatic CRPS

Study	Population and intervention	Quantitative finding / interpretation
Manicourt et al., 2004 [8]	40 patients with posttraumatic lower-limb CRPS I; oral alendronate vs placebo	Eight-week blinded study; improvements in pain, mobility and edema were reported; directly trauma-specific.
Varenna et al., 2013 [9]	82 patients with acute hand/foot CRPS I; IV neridronate vs placebo	Pain reduction 46.5 vs 22.6 mm; P < .0001 at reported assessment.
Robinson et al., 2004 [10]	27 patients with CRPS I; IV pamidronate vs placebo	14 vs 13 randomized; improvements in pain/global assessment and function at 3 months.
van de Vusse et al., 2004 [11]	58 CRPS-I patients; gabapentin/placebo crossover	No significant combined-period pain effect; sensory deficits improved; side effects limited tolerance.
Sigtermans et al., 2009 [12]	60 CRPS-I patients; ketamine vs placebo	Pain benefit in a specialized trial; sustained functional advantage uncertain.
Schwartzman et al., 2009 [13]	Outpatient ketamine infusion trial	Pain reduction reported; protocol-specific toxicity and generalizability considerations.
Goebel et al., 2017 [14]	108 eligible long-standing CRPS patients; low-dose IVIg vs placebo	Adjusted between-group pain difference +0.27 (95% CI −0.25 to 0.80); no benefit.

Bisphosphonates

The post-traumatic lower-limb alendronate study provides one of the clearest direct links between pharmacological treatment and orthopaedic trauma, with randomization of 40 adults [8]. In acute hand or foot CRPS I, Varenna et al. randomized 82 patients; a series of four intravenous neridronate infusions produced substantially larger pain reduction than placebo by the assessment reported, 46.5 mm versus 22.6 mm (P < .0001) [9]. Pamidronate was assessed in 27 patients, with 14 assigned active treatment and 13 placebo, and improvements in pain and functioning at three months [10].

The updated 2026 synthesis changes the level of certainty associated with this drug class. Across 11 trials and 754 patients, immediate-term pain difference on a 0–100 scale was −9.1 (95% CI −19.2 to 1.1); the primary short-term comparison (>4 weeks to 3 months) favored bisphosphonates by −10.0 points (95% CI −18.9 to −1.1), both low-certainty findings. Medium-term and longer-term effects were uncertain, and the adverse-event risk was higher (risk ratio 1.1; 95% CI 1.0–1.2) [6]. Older meta-analyses often reported larger apparent analgesia, including a 2022 weighted mean difference of −23.8 on reported VAS/NRS scales, which should not be viewed as interchangeable with the newer estimate [4].

Ketamine

Intravenous ketamine targets N-methyl-D-aspartate receptor–mediated mechanisms of central sensitization. Controlled trials have reported meaningful analgesia in selected patients with severe CRPS, including the 60-patient Sigtermans study [12]. The 2024 systematic review estimated a long-term pain mean difference of −0.78 (95% CI −1.51 to −0.05), based on its specific metric and contributing studies, but adverse events were more frequent (RR 3.45; 95% CI 1.79–6.65) [5]. These findings do not establish durable improvements in independent limb function, nor support unsupervised or routine infusion treatment.

Corticosteroids and anti-inflammatory drugs

A short corticosteroid course is biologically plausible in early, warm, swollen CRPS, particularly soon after orthopaedic trauma, but high-quality fracture-specific comparative evidence is limited. Many steroid studies are small, use differing regimens and include post-stroke or mixed CRPS. Standard NSAIDs may address accompanying nociceptive pain but lack convincing evidence for reversing the CRPS syndrome itself. Treatment must also account for fracture healing, infection exclusion, glucose control and other steroid-related risks [1,4,5].

Neuropathic agents, immune therapies and other treatments

The 58-patient gabapentin crossover study identified a possible sensory benefit, but there was no significant combined-period difference for pain; fatigue, dizziness and other adverse reactions can hinder rehabilitation [11]. Evidence for pregabalin, tricyclic antidepressants, topical agents, calcitonin and opioids is largely indirect, heterogeneous or insufficient in trauma-specific CRPS [1,3]. Low-dose intravenous immunoglobulin did not reduce pain in a controlled trial of long-standing disease: 103 patients contributed outcome data, and the adjusted mean pain difference was 0.27 points (95% CI −0.25 to 0.80) in the unfavorable direction [14].

Table 2. Published quantitative syntheses; estimates shown on original scales

Review	Studies / sample	Reported results	Interpretation
2022 CRPS-I pharmacotherapy review [4]	20 RCTs / 818 adults	Bisphosphonates WMD −23.8 (95% CI −28.0 to −19.6); ketamine WMD −8.27 (−12.9 to −3.70)	Older synthesis; scales and study populations differ.
2024 pharmacotherapy review [5]	23 RCTs / 1,029 patients	Bisphosphonates MD −2.21 (−4.36 to −0.06); ketamine MD −0.78 (−1.51 to −0.05)	Longer-term pain outcomes; treatment-associated adverse effects.
2026 bisphosphonate review [6]	11 RCTs / 754 patients	Short-term 0–100 MD −10.0 (−18.9 to −1.1); adverse-event RR 1.1 (1.0–1.2)	Low-certainty pain improvement; moderate-certainty harm signal.
2023 Cochrane overview [7]	17 reviews covering 127 RCTs	No high-certainty evidence for any CRPS therapy	Different interventions, substantial methodological uncertainty.

Adverse events, rehabilitation and treatment timing

Adverse effects are clinically meaningful when they reduce adherence to graded movement, sleep, or participation in occupational and physical therapy. Bisphosphonates may cause acute-phase symptoms and require attention to renal function and mineral metabolism; ketamine requires specialized monitoring and consideration of psychotomimetic and cardiovascular effects. Neuropathic agents may cause sedation or dizziness. The evidence does not support identifying a single drug as disease-modifying across early and established CRPS [1,6].

Table 3. Clinical interpretation by disease stage and dominant presentation

Presentation	Pharmacological consideration	Evidence caveat
Early post-traumatic CRPS with inflammation and edema	Selected bisphosphonate treatment or time-limited corticosteroid consideration alongside rehabilitation	Direct trauma-specific bisphosphonate evidence exists but certainty is limited; steroid evidence is less robust.
Marked allodynia and neuropathic symptoms	Individualized neuropathic analgesic trial	CRPS-specific gabapentin benefit inconsistent; reassess functional goals.
Severe refractory CRPS	Specialist-supervised ketamine evaluation	Adverse effects, monitoring and uncertain long-term function.
Long-standing CRPS (>1 year)	Multidisciplinary rehabilitation and reassessment	Low-dose IVIg RCT negative; avoid repeated ineffective trials.

Intervention-specific comparative outcomes

The clearest directly post-traumatic randomized evidence includes oral alendronate in 40 adults with lower-limb CRPS following trauma [8]. Neridronate studies, including an 82-person acute CRPS I trial, suggest analgesic improvement but do not consistently provide separately extractable fracture-specific effects [9,15]. Pamidronate and clodronate trials support a class-level hypothesis but involve different routes, sample sizes, and illness durations [10,21,22]. Consequently, bisphosphonate benefit in early post-traumatic disease remains plausible, while exact patient selection and long-term functional effects are uncertain.

Corticosteroids and inflammatory presentations

Glucocorticoid trials address an inflammatory phenotype and involve multiple delivery routes. Prednisolone dose-comparison trials and intravenous regional or intrathecal steroid studies have not established a uniform regimen for fracture-related CRPS [23–27]. Effects reported in post-stroke CRPS should not be transferred uncritically to orthopaedic injuries [28]. Treatment decisions require consideration of disease duration, metabolic risks, infection, wound healing and rehabilitation needs, particularly in the postoperative period.

Other pharmacological classes

Randomized or controlled studies of magnesium, parecoxib, dimethyl sulfoxide and N-acetylcysteine have produced heterogeneous effects with limited reproducibility [29–34]. Topical ketamine has been investigated for allodynia, but effects on motor recovery and durable function are less established [35]. Intravenous immunoglobulin was not beneficial in a large randomized study of longstanding disease [14]; this provides a reason against routine use but does not exclude all immune-directed approaches for appropriately selected patients. Conventional neuropathic agents remain pragmatic adjuncts where associated symptoms interfere with rehabilitation, not established disease-modifying drugs [11,36].

Adverse events and certainty of findings

In the 2024 meta-analysis, adverse events were more frequent for bisphosphonates (RR 1.86; 95% CI 1.34–2.57) and ketamine (RR 3.45; 95% CI 1.79–6.65) than placebo [5]. The 2026 bisphosphonate-specific analysis estimated an adverse-

event RR of 1.1 (95% CI 1.0–1.2), reflecting differences in eligible studies and analysis definitions [6]. Bisphosphonate reactions often included transient flu-like symptoms, whereas ketamine-related adverse effects included dysphoria and perceptual disturbance. No intervention had high-certainty evidence of long-term trauma-specific functional restoration in the broad evidence overview [7].

Heterogeneity, generalizability and reporting biases

Important sources of heterogeneity included early versus established CRPS, upper versus lower limb injury, inclusion of mixed aetiologies, historical versus Budapest case definitions, bisphosphonate dose and route, co-intervention intensity, and outcome timing. Small trials were vulnerable to imprecision and selective outcome reporting. Published reviews used different search dates and sometimes overlapping randomized trials; their trial and participant totals therefore describe each review separately, not an additive overall sample. Funnel asymmetry reported in an earlier synthesis is not proof of publication bias in post-traumatic CRPS specifically [5].

DISCUSSION

Principal interpretation

The available evidence supports a guarded, stage-sensitive approach to pharmacotherapy. Among treatment classes studied in randomized trials, bisphosphonates have the strongest trauma-linked rationale and a modest short-term pain benefit, but this inference is limited by small trials, differing formulations and inconsistent follow-up. Ketamine may provide symptomatic relief for selected refractory patients; it requires expertise and has a less favorable adverse-effect profile. No therapy has been shown with high certainty to restore function after orthopaedic trauma, prevent chronic disability, or consistently modify the underlying syndrome [5–7].

Why treatment estimates differ

Effect estimates from different meta-analyses should not be directly ranked. The 2022, 2024 and 2026 reviews varied in eligible drugs, diagnostic criteria, treatment intervals, measurement scales and analysis methods, and incorporated many of the same trials. Earlier estimates may overweight small favorable trials; newer reviews more explicitly account for imprecision, heterogeneity and adverse events. A 10-point difference on a 0–100 pain scale may also have a different patient-level meaning from a change on a 0–10 scale. These distinctions are clinically and statistically material [4–7].

Orthopaedic trauma-specific considerations

Trauma-related CRPS must be distinguished from infection, nonunion, hardware complications, compartment or vascular problems, nerve compression, and immobilization-related stiffness. An accurate diagnosis avoids attributing a remediable surgical complication to CRPS. Treatment studies rarely stratify by fracture location, fixation method, early immobilization, nerve damage, or timing of rehabilitation; thus the precise comparative effectiveness after distal radius fracture, ankle fracture, and postoperative hand surgery remains uncertain. In this setting, early functional restoration and management of modifiable barriers should accompany any drug trial [1,2].

Limitations and future research

The evidence is limited by small randomized trials, differences in historical and current CRPS diagnostic criteria, varying follow-up durations, and mixed injury aetiologies. Studies seldom reported injury-specific effect modification or patient-important outcomes beyond pain. Further trials should use standardized diagnostic criteria, specify the precipitating injury and rehabilitation intensity, and evaluate function, harms and longer-term response.

CONCLUSION

Pharmacotherapy can assist pain control in CRPS after orthopaedic trauma but should be selected for the patient's disease stage and dominant features. Bisphosphonates may yield low-certainty short-term analgesic benefit, particularly in CRPS I; ketamine may provide relief in refractory disease at the cost of greater treatment burden. Gabapentin and low-dose immunoglobulin lack convincing CRPS-specific analgesic benefit. Multimodal rehabilitation remains central, and further trauma-specific randomized trials are required.

REFERENCES

1. Harden RN, McCabe CS, Goebel A, et al. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 5th edition. Pain Med. 2022;23(Suppl 1):S1–S53. doi:10.1093/pm/pnac046.
2. Harden RN, Bruehl S, Perez RSGM, et al. Validation of proposed diagnostic criteria (the Budapest Criteria) for complex regional pain syndrome. Pain. 2010;150:268–274. doi:10.1016/j.pain.2010.04.030.
3. Ferraro MC, Cashin AG, Wand BM, et al. Interventions for treating pain and disability in adults with complex regional pain syndrome: an overview of systematic reviews. Cochrane Database Syst Rev. 2023;6:CD009416. doi:10.1002/14651858.CD009416.pub3.
4. Pharmacological treatment in adult patients with CRPS-I: a systematic review and meta-analysis of randomized controlled trials. Rheumatology (Oxford). 2022;61:3534–3546. doi:10.1093/rheumatology/keac060.

5. Efficacy and safety of pharmacological treatment in patients with complex regional pain syndrome: a systematic review and meta-analysis. Pharmaceuticals (Basel). 2024;17:811. doi:10.3390/ph17060811.
6. Ferraro MC, O'Connell NE, Goebel A, et al. Efficacy and safety of bisphosphonates for complex regional pain syndrome: a systematic review and meta-analysis. Ann Intern Med. 2026;179:256–269. doi:10.7326/ANNALS-25-03693.
7. Ferraro MC, Cashin AG, Wand BM, et al. Interventions for treating pain and disability in adults with complex regional pain syndrome: overview update. Cochrane Database Syst Rev. 2023;6:CD009416. doi:10.1002/14651858.CD009416.pub3.
8. Manicourt DH, Brasseur JP, Boutsen Y, Depreseux G, Devogelaer JP. Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity. Arthritis Rheum. 2004;50:3690–3697. doi:10.1002/art.20591.
9. Varenna M, Adami S, Rossini M, et al. Treatment of complex regional pain syndrome type I with neridronate: a randomized, double-blind, placebo-controlled study. Rheumatology (Oxford). 2013;52:534–542. doi:10.1093/rheumatology/kes312.
10. Robinson JN, Sandom J, Chapman PT. Efficacy of pamidronate in complex regional pain syndrome type I. Pain Med. 2004;5:276–280. doi:10.1111/j.1526-4637.2004.04038.x.
11. van de Vusse AC, Stomp-van den Berg SGM, Kessels AHF, Weber WEJ. Randomised controlled trial of gabapentin in complex regional pain syndrome type 1. BMC Neurol. 2004;4:13. doi:10.1186/1471-2377-4-13.
12. Sigtermans MJ, van Hilten JJ, Bauer MCR, et al. Ketamine produces effective and long-term pain relief in patients with complex regional pain syndrome type 1. Pain. 2009;145:304–311. doi:10.1016/j.pain.2009.06.023.
13. Schwartzman RJ, Alexander GM, Grothusen JR, et al. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. Pain. 2009;147:107–115. doi:10.1016/j.pain.2009.08.015.
14. Goebel A, Bisla J, Carganillo R, et al. Low-dose intravenous immunoglobulin treatment for long-standing complex regional pain syndrome: a randomized trial. Ann Intern Med. 2017;167:476–483. doi:10.7326/M17-0509.
15. Varenna M, Braga V, Gatti D, et al. Intramuscular neridronate for treatment of complex regional pain syndrome type 1: a randomized, double-blind, placebo-controlled study. Ther Adv Musculoskelet Dis. 2021. doi:10.1177/1759720X211014020.
16. Shekarsarai et al. The analgesic efficacy of therapies used for complex regional pain syndrome: a systematic review. 2025. PMID:40917914.
17. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71.
18. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. doi:10.1136/bmj.l4898.
19. Zhu H, Wen B, Xu J, Zhang Y, Xu L, Huang Y. Efficacy and safety of pharmacological treatment in patients with complex regional pain syndrome: a systematic review and meta-analysis. Pharmaceuticals (Basel). 2024;17:811. doi:10.3390/ph17060811.
20. Bruehl S. Complex regional pain syndrome. BMJ. 2015;351:h2730.
21. Adami S, Fossaluzza V, Gatti D, Fracassi E, Braga V. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. Ann Rheum Dis. 1997;56:201–204.
22. 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.
23. Kalita J, Pandey PC, Shukla R, Misra UK. Prednisolone 20 mg vs 40 mg in complex regional pain syndrome type I: a randomized controlled trial. J Clin Neurosci. 2023;113:108–113.
24. Munts AG, van der Plas AA, Ferrari MD, et al. Efficacy and safety of a single intrathecal methylprednisolone bolus in chronic complex regional pain syndrome. Eur J Pain. 2010;14:523–528.
25. Naskar S, Bhoi D, Garg H, et al. A comparison of analgesic efficacy and safety of clonidine and methylprednisolone as additives to ropivacaine in stellate ganglion block for complex regional pain syndrome. Korean J Pain. 2023;36:216–229.
26. Taskaynatan MA, Ozgul A, Tan AK, Dincer K, Kalyon TA. Bier block with methylprednisolone and lidocaine in CRPS type I: a randomized double-blinded placebo-controlled study. Reg Anesth Pain Med. 2004;29:408–412.
27. van den Berg C, de Bree PN, Huygen FJPM, Tiemensma J. Glucocorticoid treatment in patients with complex regional pain syndrome: a systematic review. Eur J Pain. 2022;26:2009–2035.
28. Kalita J, Misra U, Kumar A, Bhoi SK. Long-term prednisolone in post-stroke complex regional pain syndrome. Pain Physician. 2016;19:565–574.
29. Fischer SG, Collins S, Boogaard S, et al. Intravenous magnesium for chronic complex regional pain syndrome type 1. Pain Med. 2013;14:1388–1399.

30. Breuer AJ, Mainka T, Hansel N, Maier C, Krumova EK. Short-term treatment with parecoxib for complex regional pain syndrome: a randomized placebo-controlled double-blind trial. Pain Physician. 2014;17:127–137.
31. 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.
32. Perez RSGM, Zuurmond WWA, 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.
33. Frade LP, Lauretti GR, Lima ICPR, Pereira NL. The antinociceptive effect of local or systemic parecoxib combined with lidocaine/clonidine intravenous regional analgesia for complex regional pain syndrome type I in the arm. Anesth Analg. 2005;101:807–811.
34. van der Plas AA, Schilder JC, Marinus J, van Hilten JJ. An explanatory study evaluating the muscle relaxant effects of intramuscular magnesium sulphate for dystonia in complex regional pain syndrome. J Pain. 2013;14:1341–1348.
35. Finch PM, Knudsen L, Drummond PD. Reduction of allodynia in patients with complex regional pain syndrome: a double-blind placebo-controlled trial of topical ketamine. Pain. 2009;146:18–25.
36. Mangnus TJP, Bharwani KD, Dirckx M, Huygen FJPM. From a symptom-based to a mechanism-based pharmacotherapeutic treatment in complex regional pain syndrome. Drugs. 2022;82:511–531.
37. Chevreau M, Romand X, Gaudin P, Juvin R, Baillet A. Bisphosphonates for treatment of complex regional pain syndrome type 1: systematic literature review and meta-analysis of randomized controlled trials versus placebo. Joint Bone Spine. 2017;84:393–399.
38. Xu J, Yang J, Lin P, Rosenquist E, Cheng J. Intravenous therapies for complex regional pain syndrome: a systematic review. Anesth Analg. 2016;122:843–856.
39. Zhao J, Wang Y, Wang D. The effect of ketamine infusion in the treatment of complex regional pain syndrome: a systematic review and meta-analysis. Curr Pain Headache Rep. 2018;22:12.
40. Wertli MM, Kessels AG, Perez RS, Bachmann LM, Brunner F. Rational pain management in complex regional pain syndrome 1: a network meta-analysis. Pain Med. 2014;15:1575–1589.
41. Norton KF, Furnish TJ. Perspectives on the pharmacological management of complex regional pain syndrome. Expert Opin Pharmacother. 2023;24:1295–1305.
42. Iolascon G, Snichelotto F, Moretti A. An update on the pharmacotherapeutic options for complex regional pain syndrome. Expert Rev Neurother. 2024;24:177–190.