Plain Language Summary

Efficacy and Safety of Bisphosphonates for Complex Regional Pain Syndrome: A Systematic Review and Meta-analysis.

What is Complex regional pain syndrome (CRPS)?

Complex regional pain syndrome (CRPS) is a painful condition that usually affects an arm or leg after an injury or surgery. It leads to severe pain, swelling, changes in temperature or skin colour, and difficulties with movement. Effective treatment options for CRPS are limited.

What are bisphosphonates?

Bisphosphonates are a group of medicines used to treat bone diseases such as osteoporosis. Some doctors and scientists think that bisphosphonates can help CRPS by reducing inflammation or changes to the bone that may happen with the condition.

What did we want to find out?

We wanted to find out if bisphosphonates reduce pain or improve function for adults with CRPS, and whether they cause unwanted effects. We also wanted to find out whether they improve physical function and quality of life.

What did we do?

We searched for randomised controlled trials that compared any bisphosphonate with a placebo ("dummy" medicine). We compared and summarised the trial results and rated our confidence in the evidence, based on factors such as trial methods and sizes.

What did we find?

We found 11 trials with 754 adults with CRPS. Most patients had CRPS for less than 18 months. The trials looked at 5 bisphosphonate types (alendronate, clodronate, neridronate, pamidronate, zoledronate) that were given through a vein, taken by mouth, or injected into muscles. Most trials were conducted in high-income countries (e.g., the United States and Germany).

Main results

<u>Pain</u>

- In the short term (4 weeks to 3 months after starting treatment), bisphosphonates may reduce pain. The results varied widely across trials, with some showing a benefit and others showing none.
- In the immediate term (up to 4 weeks), medium term (3 to 6 months), and long term (more than 6 months), it is unclear whether bisphosphonates reduce pain.

- It is unclear if any one bisphosphonate type (e.g. neridronate) or way of taking bisphosphonate (e.g. through a vein) is best.

Unwanted effects

- Treatment with bisphosphonates probably leads to unwanted effects such as muscle aches and joint pain.
- Treatment with bisphosphonates probably does not increase the risk of unwanted side effects or stopping treatment due to unwanted effects.

Physical function and quality of life

- It is unclear whether bisphosphonates improve physical function and quality of life

What are the limitations of the evidence?

We have little confidence in the evidence supporting the effects on pain for a few reasons. Not all trials provided data about everything we were interested in. The results of the individual trials varied widely.

What does this mean?

This review is the biggest and most complete study of bisphosphonates for CRPS. We found that bisphosphonates may provide slight short-term pain relief for CRPS, but the magnitude of the benefit and its duration are unclear. We didn't find any clear evidence that any one bisphosphonate type, or way of giving them, is better than others. Although we didn't find clear evidence about the types of people who might benefit most from bisphosphonate treatment, the trials that showed a benefit mostly included people with very recent CRPS (less than 6 months of symptoms) and altered bone activity. Bisphosphonates probably cause unwanted effects like muscle and joint pain, but they are likely brief and insignificant.

How up-to-date is this evidence?

The evidence is current as of September 2025.

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Annals of Internal Medicine

REVIEW

Efficacy and Safety of Bisphosphonates for Complex Regional Pain Syndrome

A Systematic Review and Meta-analysis

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Background: Clinical guidelines recommend bisphosphonates for complex regional pain syndrome (CRPS) despite limited evidence of efficacy.

Purpose: To determine the efficacy and safety of bisphosphonates compared with placebo for CRPS.

Data Sources: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and 3 trial registries from inception to 16 September 2025.

Study Selection: Randomized controlled trials enrolling adults with CRPS (type I or II) to bisphosphonate treatment or placebo.

Data Extraction: Primary outcomes were pain intensity and adverse events. Data were synthesized with random-effects meta-analyses. Risk of bias and certainty of evidence were assessed using the Cochrane Risk of Bias 2 Tool and GRADE (Grading of Recommendations Assessment, Development and Evaluation).

Data Synthesis: Eleven trials (754 participants; CRPS type I, 97%), evaluating alendronate ($n = 2$), clodronate ($n = 1$), neridronate ($n = 5$), pamidronate ($n = 1$), and zoledronate ($n = 2$), were included. Bisphosphonates may result in little to no difference in pain intensity in the immediate term (≤4 weeks; 0-to-100 scale; mean difference [MD], −9.1 [95% CI, −19.2 to 1.1]; low certainty). In the short term (>4 weeks to 3 months; primary time point), bisphosphonates may reduce pain intensity (MD, −10.0 [CI, −18.9 to −1.1]; low certainty), and in the medium term (>3 to 6 months), they may result in little to no difference in pain intensity (MD, 8.0 [CI, −15.4 to 31.4]; low certainty). The evidence is very uncertain about the effects of bisphosphonates on pain intensity in the long term (>6 months; MD, −2.5 [CI, −19.6 to 14.6]). Bisphosphonates probably increase risk for adverse events (risk ratio, 1.1 [CI, 1.0 to 1.2]; moderate certainty).

Limitations: High heterogeneity and uncertain medium- and long-term effects. Evidence mostly applies to CRPS type I and includes non–U.S.-approved formulations (neridronate, clodronate).

Conclusion: Bisphosphonates may reduce CRPS pain intensity in the short term, but treatment is accompanied by adverse events. Future research should resolve uncertainty around which patients with CRPS are most likely to benefit from bisphosphonates.

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Complex regional pain syndrome (CRPS) (previously reflex sympathetic dystrophy or causalgia) is a chronic primary pain disorder that usually occurs distally, in a single limb, after fracture, sprain, or surgery (1, 2). It is characterized by severe pain and autonomic, motor, trophic, and metabolic bone abnormalities (1, 3). Population-based studies estimate CRPS incidence at 5.5 to 26.2 cases per 100 000 person-years, which meets criteria from the U.S. Food and Drug Administration and European Medicines Agency for rare ("orphan") diseases (4–6). The personal, societal, and economic burdens of CRPS are considerable –two thirds of patients develop long-term work incapacity, and treatment costs are 13 times greater than for non-CRPS injuries (7).

Complex regional pain syndrome is resistant to most treatments, and management is often suboptimal, with no interventions supported by high- or moderate-certainty evidence of effectiveness (8). Bisphosphonates, a class of antiresorptive medicines (9), have been promoted as a first-line agent for CRPS (10). These medicines are hypothesized to exert their therapeutic effects through antiosteoclastic, anti-inflammatory, antiangiogenic, and analgesic pathways (11, 12). Bisphosphonates are often administered in the acute phase of CRPS, when inflammatory and metabolic bone mechanisms are considered likely (13–15). The promise of a disease-modifying therapy with the potential to alter the course of CRPS has attracted substantial research interest and industry investment (16, 17).

See also:

Web-Only
Supplemental material

Bisphosphonates are licensed for the treatment of CRPS in Italy and endorsed in U.S., U.K., Dutch, and German clinical guidelines (18–21). However, recommendations for their use are supported by limited evidence. Our 2023 Cochrane overview of systematic reviews (8) found that bisphosphonates may be efficacious for CRPS type I, although this was based on low-certainty evidence from a review with critically low quality (22). Furthermore, results of recent published and unpublished randomized trials, including multinational, industry-sponsored studies of orphan formulations, are now available. We conducted a systematic review to provide patients, clinicians, and guideline developers with an up-to-date and comprehensive summary of the efficacy and safety of bisphosphonates for CRPS.

METHODS

This systematic review and meta-analysis was prospectively registered on PROSPERO (CRD42024559783) and Open Science Framework (https://osf.io/tsdxn). Deviations from the protocol are listed in Part 1 of the **Supplement** (available at Annals.org). Our review is reported in accordance with PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 (23). A CRPS patient partner contributed to the interpretation of findings and future research recommendations and drafted a plain-language summary for dissemination to patient organizations.

Data Sources and Searches

We searched MEDLINE (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, the European Union Clinical Trials Register, and the World Health Organization's International Clinical Trial Registry Platform from inception to 16 September 2025 with no language limits (Part 2 of the **Supplement**). We searched the reference lists from retrieved full-text articles and previous systematic reviews, and we contacted authors and sponsors of studies included in the review to identify unpublished and ongoing trials. We ensured that no included articles were retracted by managing included references in Zotero software with retracted item notifications enabled (24, 25).

Study Selection

We included randomized trials that enrolled adult participants (aged ≥18 years) with CRPS (or alternate diagnostic terms), without (type I) or with (type II) nerve injury, and with average baseline pain intensity of at least 4 of 10. We included studies evaluating any bisphosphonate formulation, via any route of administration, compared with placebo. Included studies were published as full texts, abstracts, or trial registry records. Data from trial registry reports were included because the exclusion of such data may lead to overestimation of the efficacy of an intervention (26). We applied no restrictions on language or publication date.

Two review authors (M.C.F. and N.E.O. or A.G.C.) independently screened titles and abstracts of identified records and full texts of all potentially eligible studies in duplicate. We resolved disagreements through discussion or recourse to a third review author (J.H.M.). We screened records with Covidence, enabling automated removal of nonrandomized trials using the Cochrane RCT Classifier (27). We collated multiple reports of the same study, so that each study was the unit of interest in the review.

Data Extraction and Quality Assessment

Outcome selection was informed by the Core Outcome Measurement set for complex regional PAin syndrome Clinical sTudies (COMPACT) and the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines (28, 29). The primary outcomes were participant-reported pain intensity, and adverse events. Secondary outcomes were disability or physical function, CRPS severity score (30), health-related quality of life, serious adverse events, tolerability (treatment discontinuation due to adverse events), and specific adverse events (nausea, vomiting, dizziness, headache, fatigue, fever, influenza-like illness, arthralgia, myalgia, bone pain, hypocalcemia, renal dysfunction, osteonecrosis, and iritis).

Pairs of review authors (M.C.F. and N.E.O. or A.G.C.) independently extracted summary data in duplicate, using a standardized, piloted form. Disagreements were resolved by discussion or recourse to a third review author (J.H.M.). We used WebPlotDigitizer (Automeris) (31), in duplicate, to extract data from figures for studies that did not report numerical results. We contacted study authors for additional or missing data.

For continuous outcomes, we extracted mean values, SDs, and the number of participants in each group. Where SDs were not available, we calculated them from SEs or 95% CIs using formulas outlined in chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (32). We derived means and SDs from studies that reported median and IQR using methods from Cai and colleagues (33). Where measures of variance were missing or considered implausible, we imputed them using the mean SD in the meta-analysis (34). We extracted the number of events and number of participants in each group for dichotomous outcomes. Our outcome extraction hierarchy is reported in Part 3 of the **Supplement**, and details of extracted data, conversions, and imputation procedures are provided in **Supplement Table 1** (available at Annals.org).

For outcomes assessing benefit (pain intensity, disability or function, CRPS severity, and health-related quality of life), we classified follow-up times into the immediate term (≤4 weeks after randomization), short term (>4 weeks to 3 months after randomization), medium term (>3 to 6 months after randomization), and

long term (>6 months after randomization), taking the latest time point when data for multiple time points were available. Short-term follow-up was chosen as the primary time point because bisphosphonates are believed to achieve their maximal therapeutic effect for CRPS within this period (that is, via antiresorptive mechanisms) (35). For outcomes assessing harms (adverse events, serious adverse events, specific adverse events, and tolerability), we took data measured until the end of the treatment period.

Two review authors (M.C.F. and N.E.O. or A.G.C.) independently assessed risk of bias, in duplicate, using the Cochrane Risk of Bias 2 Tool (36). We resolved disagreements by discussion or recourse to a third review author (J.H.M.). We assessed the risk of bias for the effect of assignment to the interventions (the "intention-to-treat" effect) for all outcomes (applying adverse events judgments to specific adverse events) and time points. We assigned an overall risk of bias judgment (low risk, some concerns, or high risk) based on the least favorable judgment across domains (36).

Two review authors (M.C.F. and A.G.C.) independently assessed the certainty of evidence for each result using the 5 GRADE (Grading of Recommendations Assessment, Development and Evaluation) (37) considerations: study limitations, inconsistency, indirectness, imprecision, and publication bias. Evidence certainty was initially considered high and could be downgraded to moderate, low, or very low. We communicated the certainty of our findings in line with GRADE guidance (38). The GRADE assessment criteria are provided in Part 4 of the **Supplement**, and the judgments that informed the GRADE certainty-of-evidence ratings are detailed in **Supplement Table 2** (available at Annals.org).

Data Synthesis and Analysis

We synthesized outcome data for all bisphosphonates and routes of administration, for each outcome and time point of interest. To avoid unit-of-analysis errors, we combined the intervention groups of studies that contributed multiple eligible groups to an analysis. Aggregate outcome data for pain intensity were converted to a visual analogue scale of 0 (no pain) to 100 (worst imaginable pain) to aid interpretation of our results (29).

Random-effects meta-analysis models were fitted using inverse variance and restricted maximum likelihood estimation using the meta package (using metacont, metabin, and metagen functions) in RStudio, version 2024.04 (Posit PBC). We analyzed continuous data as mean differences (MDs) and 95% CIs. Where studies used different scales to measure the same outcome domain, we used standardized mean differences (SMDs) with 95% CIs. We calculated dichotomous measures using risk ratios (RRs) and 95% CIs, or if event rates were low, Peto odds ratios and 95% CIs. For pain intensity, we also presented outcomes in a dichotomized format (responder analysis), considering a 50% or greater reduction in pain intensity to represent a substantially important benefit, and calculated the number needed to treat for an additional beneficial outcome (29).

Heterogeneity was evaluated using χ^2, τ^2, and I^2 statistics. We used these measures, together with visual inspection of forest plots, to form judgments about heterogeneity. For meta-analyses that included 10 studies or more, we calculated 95% prediction intervals (39), and we investigated small-study effects with funnel plots and the Egger regression test.

We conducted planned subgroup analyses to investigate bisphosphonate formulation, route of administration (for pain intensity at short-term follow-up and adverse events), and CRPS diagnostic criteria (for pain intensity at short-term follow-up) as important sources of heterogeneity. Data were unavailable for planned subgroup analyses to assess the effect of CRPS subtype (I vs. II) and symptom duration (≤6 months vs. >6 months). Because bisphosphonates may be more effective in the presence of metabolic bone changes (which are most prevalent in acute CRPS [40]), we did a post hoc subgroup analysis to investigate trials that required changes to bone metabolism (via bone scintigraphy) as an entry criterion.

We conducted sensitivity analyses to assess the robustness of treatment effects to trials with results at high overall risk of bias, trials where measures of variance were imputed, and trials that included participants with more than 6 months' symptom duration. We did a post hoc sensitivity analysis to assess the effect of the choice of estimator by repeating the primary analyses using the Hartung–Knapp estimator with ad hoc correction.

Role of the Funding Source

This study received no funding.

RESULTS

The search identified 953 records. After screening 729 titles and abstracts, we appraised the full texts of 18 records. Of these, 1 record was excluded because it was not a randomized controlled trial (41). Eleven trials, comprising 17 records, were included in the systematic review: 6 were available as published reports (34, 42–46) and 5 as unpublished reports (47–51). We identified no ongoing trials. Unpublished data from CREATE-1 and NCT01788176 were provided by the sponsor and chief investigator, respectively, in response to requests. The results of the search are shown in **Appendix Figure 1** (available at Annals.org).

Study Characteristics

Table 1 provides a detailed summary of study and participant characteristics. All 11 trials used a parallel design. Eight trials were industry-sponsored, and 3 trials (42, 43, 44) did not report a funding source. Four were multinational (47, 49–51). Most (n = 9) were

Table 1. Characteristics of Included Studies

Study, Year (Reference); Publication Status	Study Characteristics	Demographic Characteristics	Clinical Characteristics	Intervention and Dose (Participants Allocated); Control (Participants Allocated); Regimen	Outcomes of Interest Assessed (Measure)
Adami et al, 1997 (42); published	Design: parallel RCT Country: Italy Setting: NR Centers: NR Follow-up: 2 wk Funding: NR	Age range: Int, 39–79 y; Ctrl, 48–80 y Female: Int, 70%; Ctrl, 50% Race: NR Ethnicity: NR	Diagnostic criteria: Kozin 1981 (RSD) Subtype: CRPS I Inciting event: Int = 1 trauma, 6 fracture, 1 neurologic, 2 unknown; Ctrl = 2 trauma, 7 fracture, 1 unknown Time since inciting event: NR Mean time since onset: Int, 16 wk (SD, 17); Ctrl, 19 wk (SD, 19) Time since diagnosis: NR Baseline pain intensity: range, 3–8 of 10 Bone changes required for inclusion: diffuse/patchy osteopenia confirmed by densitometry	Int: IV alendronate, 7.5 mg/d (n = 10) Ctrl: placebo (n = 10) Regimen: 3 infusions over 3 consecutive days	Pain intensity (0-to-10 VAS) AEs
CREATE-1, 2018 (51); unpublished	Design: parallel RCT Countries: Australia, United Kingdom, United States Setting: NR Centers: 44 Follow-up: 12 wk Funding: Axsome Therapeutics	Mean age: Int, 45.3 y (SD, 14.3); Ctrl, 49.4 y (SD, 12.4) Female: Int, 72.5%; Ctrl, 85.4% Race: Int = 2 AI/AN, 37 White, 1 other; Ctrl = 4 Black or African American, 36 White (36), 1 other Hispanic or Latino ethnicity: Int, 5; Ctrl, 3	Diagnostic criteria: Budapest clinical criteria Subtype: CRPS I Inciting event: Int = 14 fracture, 2 sprain, 2 crushing injury, 13 orthopedic injury, 9 other; Ctrl = 18 fracture, 3 sprain, 3 crushing injury, 14 orthopedic injury, 3 other Mean time since inciting event: Int, 7.8 mo (SD, 6.2); Ctrl, 7.2 mo (SD, 3.1) Time since onset: NR Mean time since diagnosis: Int, 1.5 mo (SD, 1.8); Ctrl, 2.1 mo (SD, 1.9) Mean baseline pain intensity: Int, 6.6 (SD, 1.0) of 10; Ctrl, 6.8 (SD, 1.0) of 10 Bone changes required for inclusion: none	Int: oral disodium zoledronate tetrahydrate, 50 mg (n = 40) Ctrl: placebo (n = 41) Regimen: taken once weekly for 6 wk	Pain intensity (0-to-10 scale) HRQoL (EQ-5D) AEs SAEs Tolerability
EUCTR2014-001915-37-GB, 2017 (47); unpublished	Design: parallel RCT Country: Germany, United Kingdom, United States Setting: NR Centers: NR Follow-up: 12 mo Funding: Grünenthal	Mean age: Int 1, 45.2 y (SD, 11.8); Int 2, 46.1 y (SD, 13.1); Ctrl, 43.9 y (SD, 12.8) Female: Int 1, 70.1%; Int 2, 75.3%; Ctrl, 84.2% Race: Int 1 = 1 AI/AN, 4 Black or African American, 69 White, 3 other; Int 2 = 3 Black or African American, 74 White; Ctrl = 1 AI/AN, 2 Black or African American, 70 White, 2 more than one race, 1 other Hispanic or Latino ethnicity: Int 1, 4; Int 2, 1; Ctrl, 5	Diagnostic criteria: Budapest clinical criteria Diagnostic subgroup: CRPS I Inciting event: NR Time since inciting event: NR Time since onset: NR* Time since diagnosis: NR Baseline pain intensity: NR Bone changes required for inclusion: none	Int 1: IV neridronic acid, 62.5 mg (n = 77) Int 2: IV neridronic acid, 62.5 mg (n = 77) Ctrl: placebo (n = 76) Regimen: 4 infusions over 10 d (Int 1, active days 1 and 4; placebo, days 7 and 10)	Pain intensity (0-to-10 NRS) Physical function (Pain Disability Index) HRQoL (EQ-5D-5L) CRPS severity score† AEs SAEs Tolerability

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Table 1–Continued

Study, Year (Reference); Publication Status	Study Characteristics	Demographic Characteristics	Clinical Characteristics	Intervention and Dose (Participants Allocated); Control (Participants Allocated); Regimen	Outcomes of Interest Assessed (Measure)
Manicourt et al, 2004 (34); published	Design: parallel RCT Country: France Setting: NR Centers: NR Follow-up: 8 wk Funding: Merck Sharp & Dohme	Mean age: Int, 44.6 y (SD, 12.3); Ctrl, 45.2 y (SD, 12.5) Female: Int, 45%; Ctrl, 60% Race: NR Ethnicity: NR	Diagnostic criteria: IASP 1999 research criteria Subtype: CRPS I Inciting event: Int = 10 sprain/strain, 4 surgery, 3 fracture, 3 contusion; Ctrl = 11 sprain/strain, 3 surgery, 4 fracture, 2 contusion Time since inciting event: NR Mean time since onset: Int, 7 mo (SD, 2); Ctrl, 8 mo (SD, 3) Time since diagnosis: NR Median baseline pain intensity: Int, 49.9 (Q1–Q3, 47.9–54.5) of 100; Ctrl, 50.6 (Q1–Q3, 46.7–52.3) of 100 Bone changes required for inclusion: positive 3-phase bone scintigraphy	Int: oral alendronate, 40 mg/d (n = 20) Ctrl: placebo (n = 20) Regimen: taken daily for 8 wk	Pain intensity (100-mm VAS) AEs Tolerability
NCT01788176, 2018 (48); unpublished	Design: parallel RCT Country: Brazil Setting: rehabilitation medicine clinic Centers: 1 Follow-up: 12 mo Funding: Novartis	Mean age: Int, 43.1 y (SD, 7.7); Ctrl, 48.7 y (SD, 6.5) Female: Int, 50.0%; Ctrl, 25.0% Race: NR Ethnicity: NR	Diagnostic criteria: Budapest clinical criteria Subtype: CRPS I Inciting event: NR Time since inciting event: NR Time since onset: NR‡ Time since diagnosis: NR Mean baseline pain intensity: Int, 6.5 (SD, 3.1) of 10; Ctrl, 6.6 (SD, 1.1) of 10 Bone changes required for inclusion: none	Int: IV zoledronic acid, 5 mg (n = 4) Ctrl: placebo (n = 4) Regimen: single infusion	Pain intensity (0-to-10 VAS) Disability (SF-36 physical functioning) HRQoL (SF-36 general health) Adverse events
NCT03530345, 2019 (50); unpublished	Design: parallel RCT Country: Australia, Germany, New Zealand, South Korea, Spain, United States Setting: NR Centers: 67 Follow-up: 26 wk Funding: Grünenthal	Mean age: Int, 46.1 y (SD, 11.0); Ctrl, 49.4 y (SD, 12.1) Female: Int, 78.6%; Ctrl, 75.9% Race: Int = 2 Asian, 2 Black or African American, 24 White; Ctrl = 1 Black or African American, 28 White Ethnicity: NR	Diagnostic criteria: Budapest clinical criteria Subtype: Int = 25 CRPS I, 3 CRPS II; Ctrl = 21 CRPS I, 8 CRPS II Inciting event: NR Time since inciting event: NR Median time since onset: Int, 17.7 mo (Q1–Q3, 7.6–22.0 mo); Ctrl, 13.5 mo (Q1–Q3, 8.2–18.9 mo) Median time since diagnosis: Int, 9.2 mo (Q1–Q3, 4.8–16.1 mo); Ctrl, 11.4 mo (Q1–Q3, 3.3–17.9 mo) Baseline pain intensity: NR Bone changes required for inclusion: none	Int: IV neridronic acid, 100 mg (n = 28) Ctrl: placebo (n = 29) Regimen: 4 infusions over 10 d	Pain intensity (0-to-10 NRS) Physical function (PROMIS-29 physical function subscale) HRQoL (EQ-5D-5L) CRPS severity score† AEs SAEs Tolerability
NCT03560986, 2019 (49); unpublished	Design: parallel RCT Country: Canada, Czechia, Slovakia, United Kingdom, United States Setting: NR Centers: 71 Follow-up: 26 wk Funding: Grünenthal	Mean age: Int, 49.5 y (SD, 12.7); Ctrl, 50.4 y (SD, 12.6) Female: Int, 73.0%; Ctrl, 70.1% Race: Int = 2 AI/AN, 3 Black or African American, 42 White, 1 more than one race; Ctrl = 1 AI/AN, 6 Black or African American, 44 White Ethnicity: NR	Diagnostic criteria: Budapest clinical criteria Subtype: Int = 38 CRPS I, 5 CRPS II, 5 unknown; Ctrl = 33 CRPS I, 9 CRPS II, 9 unknown Inciting event: NR Time since inciting event: NR Median time since onset: Int, 12.9 mo (Q1–Q3, 7.3–18.9 mo); Ctrl, 11.8 mo (Q1–Q3, 6.0–18.6 mo) Median time since diagnosis: Int, 5.9 mo (Q1–Q3, 0.9–11.0 mo); Ctrl, 5.8 mo (Q1–Q3, 0.0–15.0 mo) Baseline pain intensity: NR Bone changes required for inclusion: none	Int: IV neridronic acid, 100 mg (n = 48) Ctrl: placebo (n = 51) Regimen: 4 infusions over 10 d	Pain intensity (0-to-10 NRS) Physical function (PROMIS-29 physical function subscale) CRPS severity score† HRQoL (EQ-5D-5L) AEs SAEs Tolerability

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Table 1–Continued

Study, Year (Reference); Publication Status	Study Characteristics	Demographic Characteristics	Clinical Characteristics	Intervention and Dose (Participants Allocated); Control (Participants Allocated); Regimen	Outcomes of Interest Assessed (Measure)
Robinson et al, 2004 (43); published	Design: parallel RCT Country: New Zealand Setting: regional multidisciplinary pain center Centers: 1 Follow-up: 3 mo Funding: NR	Mean age: 45 y (SD NR) Female: 66.7% Race: NR Ethnicity: NR	Diagnostic criteria: IASP 1994 criteria Subtype: CRPS I Inciting event: NR Time since inciting event: NR Mean time since onset: 21.6 mo Time since diagnosis: NR Median baseline pain intensity: Int, 8.2 (Q1–Q3, 7.5–8.7) of 10; Ctrl, 7.2 (Q1–Q3, 5.2–7.8) of 10 Bone changes required for inclusion: none	Int: IV pamidronate, 60 mg (n = 14) Ctrl: placebo (n = 13) Regimen: single infusion	Pain intensity (0-to-10 VAS) Disability (SF-36)
Varenna et al, 2000 (44); published	Design: parallel RCT Country: Italy Setting: rheumatology day hospital Centers: 1 Follow-up: 40 d Funding: NR	Mean age: Int, 58.1 y (SD, 7.7); Ctrl, 53.4 y (SD, 9.0) Female: Int, 60.0%; Ctrl, 58.8% Race: NR Ethnicity: NR	Diagnostic criteria: Kozin 1981 (RSD) Subtype: CRPS I Inciting event: Int = 4 fracture, 3 sprain, 1 postsurgery, 1 postarthroscopy, 1 arthritis, 5 unknown; Ctrl = 4 fracture, 3 sprain, 3 trauma, 1 postsurgery, 1 postarthroscopy, 1 diabetes, 4 unknown Time since inciting event: NR Mean time since onset: Int, 3.7 mo (SD, 1.9); Ctrl, 4.2 mo (SD, 2.6) Time since diagnosis: NR Mean baseline pain intensity: Int, 58.4 (SD, 23.1) of 100; Ctrl, 62.5 (SD, 29.0) of 100 Bone changes required for inclusion: positive bone scintigraphy	Int: IV clodronate, 300 mg/d (n = 15) Ctrl: placebo (n = 17) Regimen: 10 infusions over 10 consecutive days	Pain intensity (100-mm VAS)
Varenna et al, 2013 (45); published	Design: parallel RCT Country: Italy Setting: rheumatology units Centers: 6 Follow-up: 40 d Funding: Abiogen Pharma	Mean age: Int, 58.2 y (SD, 12.7); Ctrl, 57.0 y (SD, 10.3) Female: Int, 61.0%; Ctrl, 68.3% Race: NR Ethnicity: NR	Diagnostic criteria: Budapest research criteria Subtype: CRPS I Inciting event: Int = 11 fracture, 10 trauma, 5 surgery, 15 unknown; Ctrl = 17 fracture, 7 trauma, 4 surgery, 13 unknown Time since inciting event: NR Mean time since onset: Int, 4.7 wk (SD, 4.1); Ctrl, 5.0 wk (SD, 4.6) Time since diagnosis: NR Mean baseline pain intensity: Int, 71.6 (SD, 11.8) of 100; Ctrl, 70.4 (SD, 8.3) of 100 Bone changes required for inclusion: positive 3-phase bone scintigraphy	Int: IV neridronate, 100 mg/d (n = 41) Ctrl: placebo (n = 41) Regimen: 4 infusions over 10 d	Pain intensity (100-mm VAS) Disability (SF-36 physical functioning) HRQoL (SF-36 general health) AEs SAEs Tolerability
Varenna et al, 2021 (46); published	Design: parallel RCT Country: Italy Setting: rheumatology units Centers: 10 Follow-up: 30 d Funding: Abiogen Pharma	Mean age: Int, 59.3 y (SD, 10.2); Ctrl, 59.7 y (SD, 10.5) Female: Int, 61.0%; Ctrl, 73.0% Race: NR Ethnicity: NR	Diagnostic criteria: Budapest research criteria Subtype: CRPS I Inciting event: Int = 22 trauma, 10 fracture, 4 surgery, 5 other/unknown; Ctrl = 15 trauma, 10 fracture, 8 surgery, 4 other/unknown Time since inciting event: NR Time since onset: NR§	Int: IM neridronate, 25 mg/d (n = 41) Ctrl: placebo (n = 37) Regimen: 16 injections over 16 consecutive days	Pain intensity (100-mm VAS) Disability (SF-36 physical functioning) HRQoL (SF-36 general health) AEs SAEs Tolerability

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Table 1–Continued

Study, Year (Reference); Publication Status	Study Characteristics	Demographic Characteristics	Clinical Characteristics	Intervention and Dose (Participants Allocated); Control (Participants Allocated); Regimen	Outcomes of Interest Assessed (Measure)
			Mean time since diagnosis: Int, 4.8 wk (SD, 4.9); Ctrl, 4.3 wk (SD, 5.5) Mean baseline pain intensity: Int, 73.4 (SD, 12.5) of 100; Ctrl, 74.6 (SD, 11.2) of 100 Bone changes required for inclusion: positive bone scintigraphy		

AE = adverse event; AI/AN = American Indian or Alaska Native; CRPS = complex regional pain syndrome; Ctrl = control; EQ-5D-5L = 5-level EuroQol 5-dimensional questionnaire; HRQoL = health-related quality of life; IASP = International Association for the Study of Pain; Int = intervention; IM = intramuscular; IV = intravenous; NR = not reported; PROMIS-29 = 29-item Patient-Reported Outcomes Measurement Information System; Q = quartile; RCT = randomized controlled trial; RSD = reflex sympathetic dystrophy; SAE = serious AE; SF-36 = Short Form-36 Health Survey; VAS = visual analogue scale.

* No upper limit on symptom duration reported in eligibility criteria.

† Outcome measured but data not reported.

‡ Inclusion criterion, 6- to 24-mo symptom duration.

§ Inclusion criterion, <4-mo symptom duration.

conducted exclusively in high-income countries. Five trials were terminated early, 4 because they demonstrated futility at planned interim analyses (results from NCT03530345 and NCT03560986 were pooled for interim analysis) (47, 49–51) and 1 because the sponsor withdrew funding (48).

Included trials enrolled 754 participants. The median sample size was 57 participants (IQR, 52). The percentage of women ranged from 38% (48) to 79% (51). In 4 trials that reported data on race or ethnicity, the percentage of White participants ranged from 87% (49) to 93% (47). Participants were diagnosed according to International Association for the Study of Pain (IASP) Budapest criteria (52, 53) in 7 trials, IASP 1999 criteria (54) in 1 trial, IASP 1994 criteria (55) in 1 trial, and Kozin criteria (56) (for reflex sympathetic dystrophy) in 2 trials. Inclusion was restricted to CRPS type I in all but 2 trials (49, 50) and represented 97% of all trial participants.

The bisphosphonates evaluated were intravenous ($n = 1$) (42) and oral ($n = 1$) (34) alendronate; intravenous clodronate ($n = 1$) (44); intravenous ($n = 4$) (45, 47, 49, 50) and intramuscular ($n = 1$) (46) neridronate; intravenous pamidronate ($n = 1$) (43); and intravenous ($n = 1$) (48) and oral ($n = 1$) (51) zoledronate. The duration of treatment ranged from a single administration (48) to an 8-week course (34).

Risk of Bias

We judged the overall risk of bias as low for 17% of all results ($n = 9$), high for 13% ($n = 7$), and some concerns for 69% ($n = 36$). Bias due to missing outcome data was the only domain to receive high risk judgments, affecting 13% of results ($n = 7$). We judged 69% of results ($n = 36$) as having some concerns about risk of bias in selection of the reported result because there was no clear evidence that results were analyzed in accordance with a prespecified plan. Risk of bias traffic lights are shown on the forest plots. Full consensus responses are provided in **Supplement Table 3** (available at Annals.org).

Effects of Interventions

Pain Intensity

Five trials assessed pain intensity at immediate-term follow-up (≤4 weeks) (34, 42, 45, 46, 51). Outcome data from Adami and colleagues (42) were not available for inclusion in the meta-analysis, but a statistically significant change in pain intensity was reported for alendronate compared with placebo. Our meta-analysis showed that bisphosphonates may result in little to no difference in pain intensity compared with placebo (0-to-100 scale; MD, −9.1 [95% CI, −19.2 to 1.1]; $I^2 = 78.4\%$; 4 trials, 280 participants; low certainty) (**Table 2**; **Appendix Figure 2**, available at Annals.org).

Ten trials assessed pain intensity at short-term follow-up (>4 weeks to 3 months), our main time point of interest (34, 43–51). We found low-certainty evidence that bisphosphonates may reduce pain intensity compared with placebo, although the CI was wide (MD, −10.0 [CI, −18.9 to −1.1]; 10 trials, 733 participants) (**Figure 1** and **Table 2**). There was evidence of heterogeneity ($I^2 = 86.2\%$), with 95% prediction intervals compatible with effects ranging from −41.1 to 21.1 out of 100. We found no clear evidence of small-study effects (Egger test $P = 0.178$) or funnel plot asymmetry (**Supplement Figure 1**, available at Annals.org). The number of participants with at least a 50% reduction in pain intensity was 75 of 236 in the bisphosphonate group and 33 of 153 in the placebo group (RR, 1.8 [CI, 1.2 to 2.9]; number needed to treat for an additional beneficial outcome, 5.8 [CI, 2.4 to 23.2]; 3 trials; low certainty) (**Supplement Figure 2**, available at Annals.org).

Table 2. GRADE Summary of Findings and Certainty of Evidence for Bisphosphonates Compared With Placebo for Primary Outcomes of Pain Intensity and Adverse Events

Follow-up	Anticipated Absolute Effects		RR (95% CI)	Participants (Studies), *n*	GRADE Certainty of the Evidence†	Conclusions
	Risk With Placebo*	Risk With Bisphosphonates (95% CI)				
Pain intensity (continuous; 0 to 100)						
Immediate-term (≤4 wk)	50 of 100	MD, 9.1 lower (19.2 lower to 1.1 higher)	–	280 (4)	⊕⊕⊖⊖ Low‡§	Bisphosphonates may result in little to no difference in pain intensity in the immediate term.
Short-term (>4 wk to 3 mo; primary time point)	53 of 100	MD, 10.0 lower (18.9 lower to 1.1 lower)	–	733 (10)	⊕⊕⊖⊖ Low‡‖	Bisphosphonates may reduce pain intensity in the short term.
Medium-term (>3 to 6 mo)	54 of 100	MD, 8.0 higher (15.4 lower to 31.4 higher)	–	8 (1)	⊕⊕⊖⊖ Low¶	Bisphosphonates may result in little to no difference in pain intensity in the medium term.
Long-term (>6 mo)	64 of 100	MD, 2.5 lower (19.6 lower to 14.6 higher)	–	8 (1)	⊕⊖⊖⊖ Very low¶**	The evidence is very uncertain about the effect of bisphosphonates on pain intensity in the long term.
Adverse events (*n* participants with ≥1 event)						
End of treatment	532 per 1000	585 per 1000 (532 to 638 per 1000)	1.1 (1.0 to 1.2)	614 (8)	⊕⊕⊕⊖ Moderate††	Treatment with bisphosphonates probably increases risk for adverse events.

GRADE = Grading of Recommendations Assessment, Development and Evaluation; MD = mean difference; RR = risk ratio.
* Baseline risk is based on mean control group scores for pain intensity (where reported) and total control group event rates for adverse events.
† GRADE Working Group grades of evidence. *High certainty:* We are very confident that the true effect lies close to the estimate of the effect. *Moderate certainty:* We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. *Low certainty:* Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. *Very low certainty:* We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
‡ Downgraded 1 level for inconsistency: evidence of statistical heterogeneity.
§ Downgraded 1 level for imprecision: CI consistent with large effect and no effect.
‖ Downgraded 1 level for imprecision: effect estimate not robust to choice of estimator; sensitivity analysis using the Hartung–Knapp estimator with ad hoc correction pushed the lower bound of the CI over the line of no effect.
¶ Downgraded 2 levels for imprecision: 8 participants included in analysis, CI consistent with large effect and no effect.
** Downgraded 2 levels for risk of bias: all participants from a single study with high risk of bias due to missing outcome data. The amount of missing outcome data would have had an important impact on the effect estimate.
†† Downgraded 1 level for imprecision: CI consistent with no difference in risk and increased risk.

Planned subgroup analyses showed subgroup effects for bisphosphonate formulation (**Figure 1**; **Supplement Table 4**, available at Annals.org) (test for subgroup differences $P < 0.001$) and CRPS diagnostic criteria ($P = 0.024$) but not route of administration ($P = 0.40$) (**Supplement Table 4** and **Supplement Figure 3**, available at Annals.org). A post hoc subgroup analysis showed subgroup effects for trials that required changes to bone metabolism as an entry criterion ($P < 0.001$) (**Supplement Table 4** and **Supplement Figure 3**).

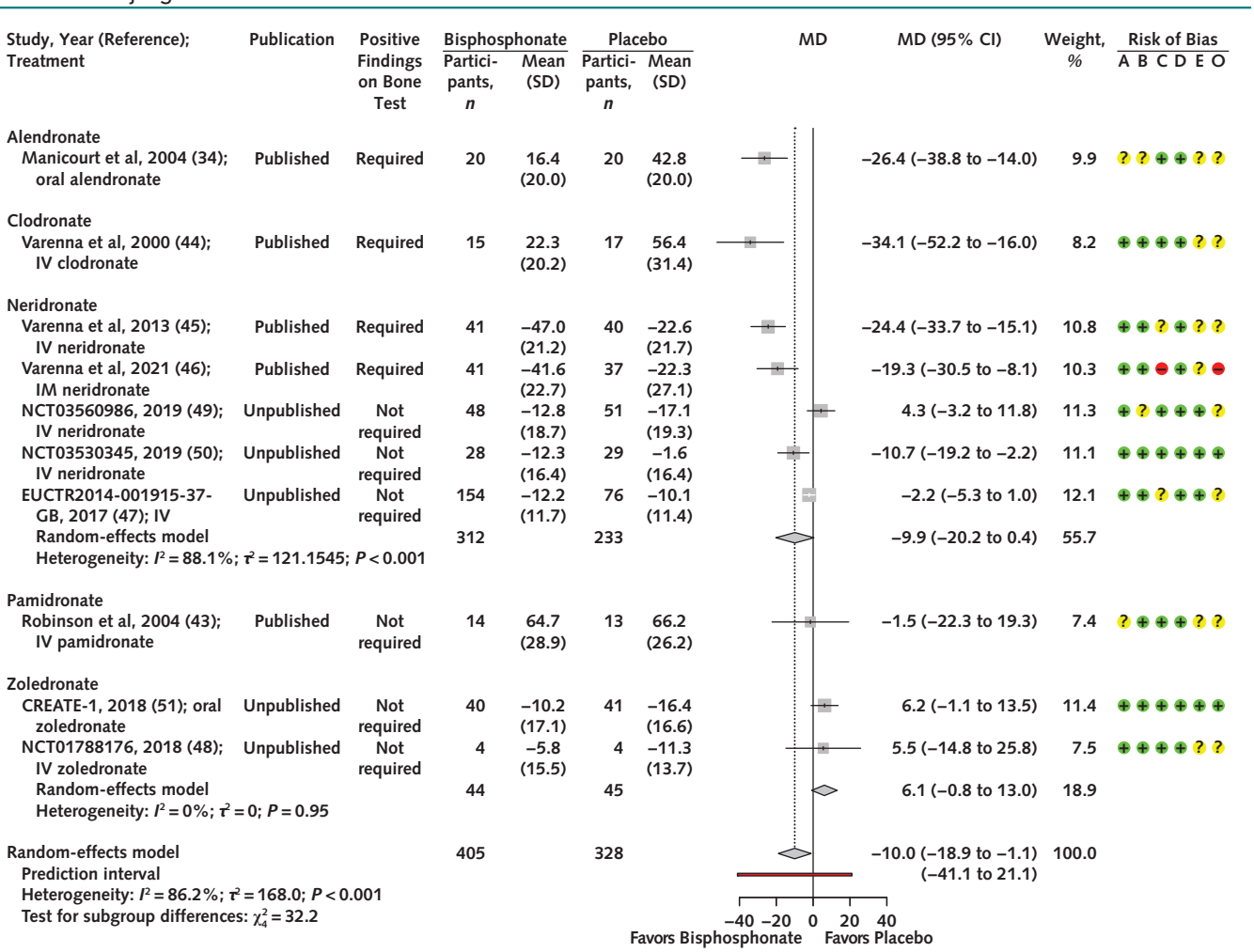
Effect estimates for pain intensity at short-term follow-up were affected by all 3 planned sensitivity analyses. When results at high overall risk of bias were removed (46), the lower bound of the CI crossed the line of no effect (MD, −9.0 [CI, −18.7 to 0.8]; $I^2 = 86.2\%$; 9 studies, 655 participants). When studies that included participants with greater than 6-month symptom duration were excluded (34, 43, 47–51), the size and precision of the effect estimate increased (MD, −23.9 [CI, −30.6 to −17.2]; $I^2 = 0\%$; 3 studies, 191 participants). Removal of a single study for which an SD was imputed (34) reduced the effect size and pushed the lower bound of the CI over the line of no effect (MD, −8.2 [CI, −17.2 to 0.9]; $I^2 = 84.9\%$; 9 studies, 693 participants). A post hoc sensitivity analysis using the Hartung–Knapp estimator with ad hoc correction pushed the lower bound of the CI over the line of no effect (MD, −10.0 [CI, −20.4 to 0.4]; $I^2 = 86.2\%$).

In the medium term (>3 to 6 months), bisphosphonates may result in little to no difference in pain intensity (MD, 8.0 [CI, −15.4 to 31.4]; 1 trial, 8 participants; low certainty). At long-term follow-up (>6 months), the evidence is very uncertain about the effect of bisphosphonates on pain intensity (MD, −2.5 [CI, −19.6 to 14.6]; 1 study, 8 participants; very low certainty) (**Table 2**; **Appendix Figure 2**).

Adverse Events

Eight trials reported the number of participants who had at least 1 adverse event (34, 42, 45–50). We found moderate-certainty evidence that bisphosphonates probably increase risk for adverse events (RR, 1.1 [CI, 1.0 to 1.2]; 8 studies, 614 participants) (**Figure 2** and **Table 2**). Heterogeneity was not observed ($I^2 = 0\%$), and

Figure 1. MDs (95% CIs) for pain intensity at short-term follow-up (>4 wk to 3 mo), with subgroup effects for bisphosphonate formulation, and risk-of-bias judgments.



Pain intensity is expressed on a 0-to-100 scale. A = bias arising from the randomization process; B = bias due to deviations from the intended intervention; C = bias due to missing outcome data; D = bias in measurement of the outcome; E = bias in selection of the reported result; IM = intramuscular; IV = intravenous; MD = mean difference; O = overall risk of bias.

planned subgroup analyses did not show evidence of subgroup effects for bisphosphonate formulation (P = 0.58) or route of administration (P = 0.51) (**Supplement Figure 3**). No study results were at high risk of bias, precluding our planned sensitivity analysis. A post hoc sensitivity analysis using the Hartung–Knapp estimator with ad hoc correction widened the 95% CI slightly (RR, 1.1 [CI, 0.9 to 1.2]).

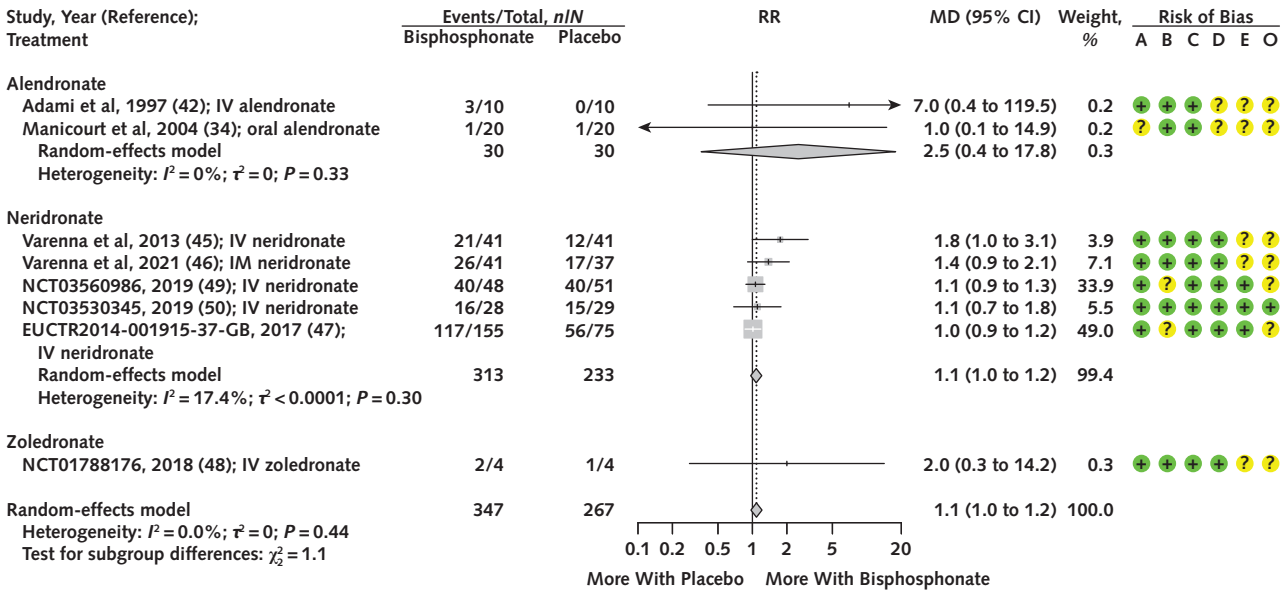
Treatment with bisphosphonates may result in little to no difference in serious adverse events (Peto odds ratio, 1.1 [CI, 0.3 to 4.0]; I^2 = 53.1%; 6 trials, 554 participants; low certainty), and probably results in little to no difference in treatment discontinuation due to adverse events (Peto odds ratio, 2.2 [CI, 0.5 to 9.9]; I^2 = 1.4%; 8 trials, 675 participants; moderate certainty) (**Supplement Figure 3**).

There was moderate-certainty evidence that bisphosphonates probably increase risk for arthralgia (RR, 1.7 [CI, 1.0 to 2.9]; I^2 = 0.0%; 5 studies, 546 participants) and high-certainty evidence that they increase risk for myalgia (RR, 3.9 [CI, 1.5 to 9.8]; I^2 = 0.0%; 4 studies, 464 participants) and decrease risk for nausea (RR, 0.4 [CI, 0.3 to 0.7]; I^2 = 0.0%; 5 studies, 434 participants) (**Supplement Figure 2**). Treatment with bisphosphonates probably results in little to no difference in fatigue or influenza-like symptoms (moderate certainty) and may result in little to no difference in vomiting, dizziness, headache, fever, bone pain, hypocalcemia, or renal dysfunction (low certainty) (**Supplement Figure 2**).

Disability or Function

The evidence is very uncertain about the effects of bisphosphonates on disability at short- and long-term follow-up (very low certainty), and they may result in little to no difference in disability at medium-term follow-up (low certainty) (**Supplement Figure 2**).

Figure 2. RRs (95% CIs) for adverse events, with subgroup effects for bisphosphonate formulation, and risk-of-bias judgments.



A = bias arising from the randomization process; B = bias due to deviations from the intended intervention; C = bias due to missing outcome data; D = bias in measurement of the outcome; E = bias in selection of the reported result; IM = intramuscular; IV = intravenous; RR = risk ratio; O = overall risk of bias.

Health-Related Quality of Life

The evidence is very uncertain about the effects of bisphosphonates on health-related quality of life at short- and long-term follow-up (very low certainty), and they may result in little to no difference in health-related quality of life at medium-term follow-up (low certainty) (Supplement Figure 2).

Discussion

Our systematic review evaluated the benefits and harms of bisphosphonates for CRPS. We included 11 trials in the systematic review and up to 10 trials in the meta-analyses. We found low-certainty evidence that bisphosphonates may reduce pain intensity at short-term follow-up. There was moderate-certainty evidence that bisphosphonates probably increase risk for at least 1 adverse event and arthralgia; high-certainty evidence that they increase risk for myalgia and decrease risk for nausea; and moderate-certainty evidence of little to no difference in fatigue, influenza-like symptoms, or treatment discontinuations due to adverse events. Effects on pain intensity in the immediate, medium, and long term; disability; and health-related quality of life remain unclear, owing to limited data and low to very low certainty of evidence.

The main strength of this review was the attainment of data from all known trials of bisphosphonates for CRPS, reducing risk of bias due to missing evidence (57). We analyzed the data of 754 participants, including 475 participants from 4 unpublished trials, representing the largest and most complete (to our knowledge) pairwise meta-analysis for CRPS to date. This review also has some limitations. Due to incomplete reporting in primary studies, data were obtained using graphical extraction software for several studies (34, 43, 45, 46). We extracted these data in duplicate but cannot exclude the possibility of error. We approximated means and SDs from medians and IQRs using validated methods (33) but recognize that this may have introduced inaccuracies. We assessed a single validated measure of disease severity (30), which was established after the conduct of several trials. Disease-modifying effects may have been incompletely evaluated as a result. Finally, our subgroup analyses are at risk of aggregation bias because they were informed by trial-level information (58).

A 2022 systematic review of pharmacologic treatments concluded that, on the basis of 7 studies, bisphosphonates are safe and effective (MD, −23.8 [CI, −28.0 to −19.6]) for treatment of CRPS type I (10). However, that review combined active and placebo comparator groups, did not include unpublished data, and did not consider the certainty of evidence. Although our analysis also found evidence of efficacy at the primary end point, the addition of data from unpublished trials attenuated the effect size. Moreover, the 2022 review did not synthesize safety data, whereas we found that bisphosphonates are associated with increased risk for adverse events.

Our results suggest that treatment with bisphosphonates may reduce pain intensity in the short term, but this finding should be interpreted with caution. We identified important heterogeneity in the treatment

effect, with prediction intervals spanning −41.1 to 21.1 out of 100. This suggests that, in a future setting, bisphosphonates may be very beneficial or have no benefit at all (39). Between-study heterogeneity was reduced by subgrouping 4 trials with positive findings that restricted participation to patients with metabolic bone changes (34, 44–46). Although bisphosphonates may be more effective in the presence of such changes (through antiosteoclastic and anti-inflammatory effects that reduce sensitization of bone nociceptors [11, 59]), the credibility of this subgroup analysis is low: It was based on across-trial information, and the prevalence of bone changes in trials without this entry criterion is unknown. In addition, sensitivity analyses affected the precision of the primary estimate. Removing a result with high overall risk of bias, excluding a trial with imputed SDs, and applying the Hartung–Knapp estimator each widened the CI to include the possibility of no effect. Therefore, we downgraded the certainty of evidence (for imprecision) from moderate to low.

Efforts to replicate trials with positive results have failed in recent multinational, industry-sponsored initiatives. The inclusion of patients with longstanding CRPS has been hypothesized to dilute the treatment effect because bone and inflammatory profiles change as the condition persists (40, 60, 61). Data were insufficient to explore the moderating effect of symptom duration, with 4 of 10 trials not reporting mean or median values (46–48, 51). Although it remains unclear whether patient- or trial-level factors explain the divergence in observed results, participant characteristics in 3 of 4 trials with positive findings warrant attention. Across Varenna and colleagues' studies from 2000 (44), 2013 (45), and 2021 (46), 24% of patients had no documented inciting event, typically a "red flag" for CRPS misdiagnosis (62). Furthermore, the mean disease duration in Varenna and colleagues' 2013 report was around 1 month, indicating that some participants were identified in specialist rheumatology centers at the point of symptom onset—a deviation from usual CRPS management pathways. Accordingly, the generalizability of these trials to broader CRPS populations may be limited.

Moderate-certainty evidence showed that bisphosphonates may be associated with increased risk for an adverse event. Risk did not vary by bisphosphonate formulation or route of administration, but this finding is based on very few data. We found moderate- and high-certainty evidence, respectively, that participants receiving bisphosphonates had higher rates of arthralgia and myalgia, consistent with the known transient cytokine-mediated reaction that occurs with intravenous administration (9). There was no clear evidence that bisphosphonates increase odds of a serious adverse event or treatment discontinuation due to adverse events, although our analyses were limited by low event rates. Risk for nausea, an established adverse effect (9) was shown to decrease with bisphosphonates, which likely represents a chance finding due to unusually high event rates in placebo groups. No studies assessed the occurrence of rare complications, such as osteonecrosis of the jaw, but these events are unlikely to occur during the brief treatment and follow-up periods of studies in this review (9, 63).

Although our review highlights the potential of bisphosphonates as an effective therapy for CRPS, several factors are important to consider when applying results to clinical practice and policy. First, although the included evidence mostly applies to CRPS type I, the characteristics of patients likely to benefit from bisphosphonate therapy remain uncertain. Acute symptoms, "warm" subtypes, and fracture as a predisposing event are hypothesized predictors of treatment response but require validation (64). Second, we could not determine the optimal formulation, route of administration, or dose. Dose-dependent effects are possible, but preferencing a particular formulation may not be justified (64). Bisphosphonates are not approved for CRPS treatment in most countries, and formulation availability varies internationally (for example, neridronate and clodronate are not marketed in the United States). Cost and accessibility are therefore important considerations for clinicians, guideline developers, and policymakers. Of note, because of licensing in Italy, a medical tourism market has emerged for neridronate infusions (clinical costs estimated at $19 000) despite no clear evidence of superiority over other formulations (65–67). Third, limited medium- and long-term follow-up data precluded investigation of whether bisphosphonates merely provide a short-term analgesic effect or alter the trajectory of the condition. The duration of treatment effect and requirements for repeated administration are unknown. Fourth, there are no patient-informed thresholds against which to benchmark the clinical importance of the benefits and harms of bisphosphonates identified in this review. Discussion around the uncertainty of the evidence, possible magnitude of benefits, and risk and nature of adverse events is critical to allow patients to make informed treatment decisions.

The evidence that bisphosphonates reduce short-term pain intensity is of low certainty, meaning that the true effect may be substantially different from the estimate of the effect (37). There remains a need for research to address the key uncertainty identified in this review; that is, whether bisphosphonates are most, or only, effective for patients with early CRPS and metabolic bone changes. Future trials should include participants with and without these characteristics to enable valid assessment of treatment effect modification. The low incidence of CRPS remains a barrier to conducting large-scale randomized trials. As such, individual participant data, which could not be obtained for this review, may be synthesized in future meta-analyses to increase statistical power. Finally, stopping trials for futility, as was done for several in this review, is critical to decrease cost, resources, and participant burden (68).

However, this approach may be less suited to scenarios where strong evidence of no effect is important to inform use of implemented treatments. We therefore recommend that future trials be continued until the predefined number of participants have been recruited.

In conclusion, this review found that bisphosphonates may reduce CRPS pain intensity in the short term, although treatment is likely accompanied by adverse events. While this review represents the best evidence to date on treatment of CRPS, unexplained heterogeneity and limited medium- or long-term data restrict clinical application. Large, randomized trials and individual participant data meta-analyses are needed to resolve uncertainty around which patients with CRPS are most likely to benefit from bisphosphonates.

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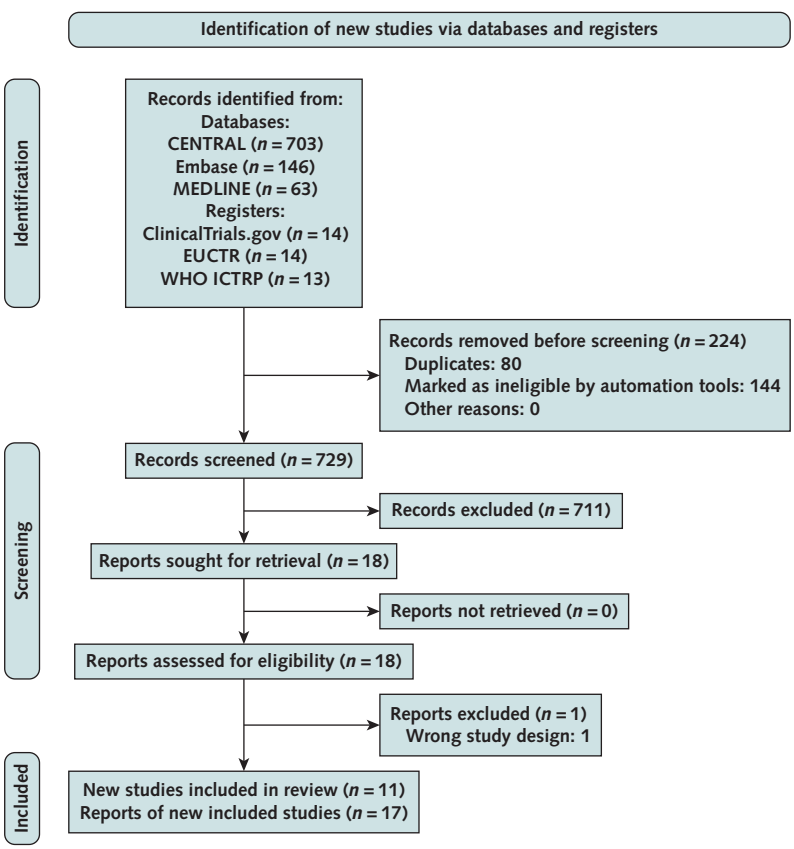
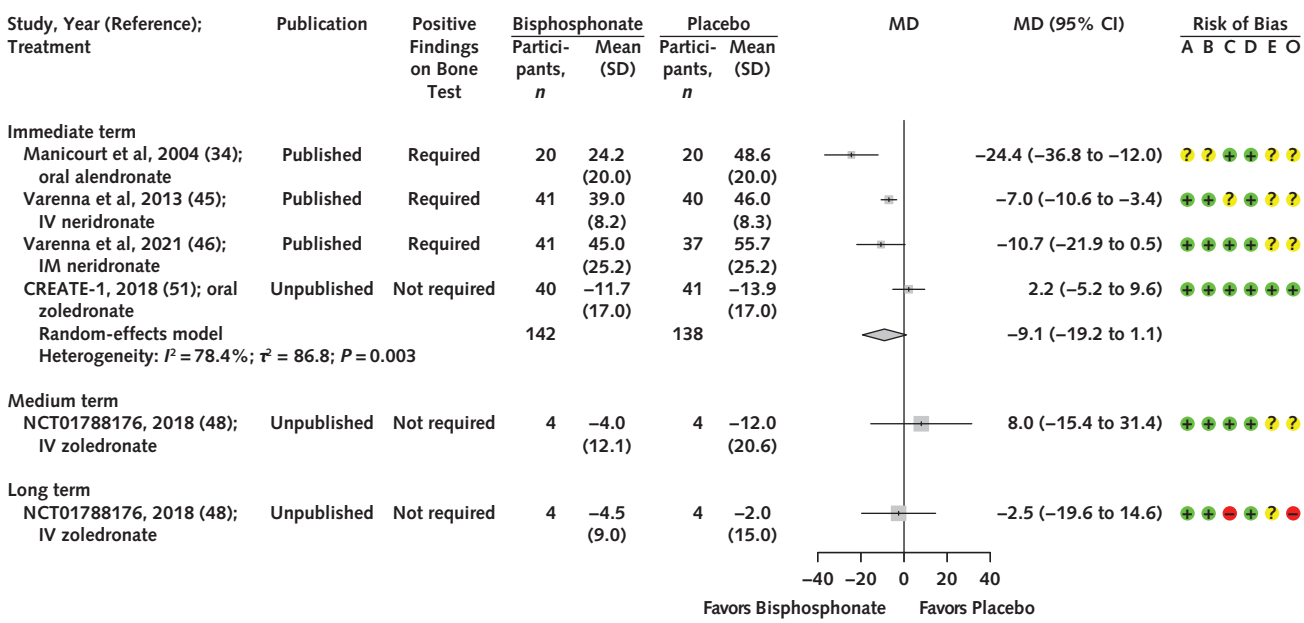
Appendix Figure 1. Evidence search and selection.



CENTRAL = Cochrane Central Register of Controlled Trials; EUCTR = European Union Clinical Trials Register; ICTRP = International Clinical Trials Registry Platform; WHO = World Health Organization.

Appendix Figure 2. MDs (95% CIs) and risk-of-bias judgments for pain intensity at immediate-term (≤4 wk postrandomization), medium-term (>3 to 6 mo postrandomization), and long-term (>6 mo postrandomization) follow-up.



Pain intensity is expressed on a 0-to-100 scale. Studies are ordered by bisphosphonate formulation. A = bias arising from the randomization process; B = bias due to deviations from the intended intervention; C = bias due to missing outcome data; D = bias in measurement of the outcome; E = bias in selection of the reported result; IM = intramuscular; IV = intravenous; MD = mean difference; O = overall risk of bias.