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Review Article

Rational Pain Management in Complex Regional Pain Syndrome 1 (CRPS 1)—A Network Meta-Analysis

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Abstract

Objective. Guidelines for complex regional pain syndrome (CRPS) 1 advocate several substance classes to reduce pain and support physical rehabilitation, but guidance about which agent should be prioritized when designing a therapeutic regimen is not provided. Using a network meta-analytic approach, we examined the efficacy of all agent classes investigated in randomized clinical trials of CRPS 1 and provide a rank order of various substances stratified by length of illness duration.

Design. In this study a network meta-analysis was conducted.

Patients. The participants of this study were patients with CRPS 1.

Method. Searches in electronic, previous systematic reviews, conference abstracts, book chapters, and the reference lists of relevant articles were performed. Eligible studies were randomized controlled trials comparing at least one analgesic agent with placebo or with another analgesic and reporting efficacy in reducing pain. Summary efficacy stratified by symptom duration and length of follow-up was computed across all substance classes. Two authors independently extracted data.

Results. In total, 16 studies were included in the analysis. Bisphosphonates appear to be the treatment of choice in early stages of CRPS 1. The effects of calcitonin surpass that of bisphosphonates and other substances as a short-term medication in more chronic stages of the illness. While most medications showed some efficacy on short-term follow-up, only bisphosphonates, NMDA analogs, and vasodilators showed better long-term pain reduction than placebo.

Limitation. For some drug classes, only a few studies were available and many studies included a small group of patients. Insufficient data were available to analyze efficacy on disability.

Conclusion. This network meta-analysis indicates that a rational pharmacological treatment strategy of pain management should consider bisphosphonates in early CRPS 1 and a short-term course of calcitonin in later stages. While most medications showed some efficacy on short-term follow-up, only bisphosphonates, NMDA analogs and vasodilators showed better long-term pain reduction than placebo.

Key Words. Complex Regional Pain Syndrome; CRPS; Pain Management; Treatment Strategy; Network Meta-Analysis

Introduction

In complex regional pain syndrome (CRPS) type 1, sensory changes including pain, allodynia, and hyperalgesia represent cardinal symptoms that form a considerable health burden for the patient [1]. Several agents have been suggested to reduce the severity of these symptoms, but to date, there is no clear guidance about which agent should be prioritized when tailoring a personalized therapeutic regimen for individual patients. Guidelines propose several substance classes to reduce pain or pain sensitization and support physical rehabilitation. For example, the two latest guidelines remain unspecific with respect to treatment alternatives for different illness stages [2,3]. These guidelines only provide a summary of the available evidence without putting treatment options into clinically applicable context. Therefore, in clinical practice, the view that a patient should be treated early and aggressively in the hope to prevent chronic stages still prevails [4].

At present, treatment recommendations include conventional analgesics (paracetamol, nonsteroidal anti-inflammatory drugs [NSAID], and opioids), anesthetics, anticonvulsants, antidepressants, free radical scavengers, oral muscle relaxants, corticosteroids, calcitonin, bisphosphonates, and calcium channel blockers [5]. The magnitude of treatment options reflects the uncertainty and dilemma regarding the optimal choice. Uncertainty for both the patient and the clinician regarding the efficacy of a treatment prevails and could have a negative effect on the course of CRPS.

Recently, network meta-analysis, a new systematic review approach, has become available, which allows for complete assessment across different drugs used for a specific indication [6–10]. In particular, this method provides a rank order that can be used for benchmarking purposes and decision-analytic modeling. Using such a network meta-analytic approach, this study examines the efficacy of all agent classes investigated within randomized clinical trials and provides a rank order of various substances stratified by length of illness duration.

Methods

A search method was used according to the PRISMA statement (Figure 1) for conducting meta-analyses of randomized controlled trials (RCTs) [11,12].

Literature Search

We identified RCTs in patients with CRPS 1, published between 1990 and January 2013, by searching the following databases: MEDLINE (OvidSP), MEDLINE In-Process Citations (OvidSP), Embase (OvidSP), Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), and PsycINFO (OvidSP). The terms for the search strategies were identified through discussion between an information specialist and the review team, by scanning the background literature and by browsing the MEDLINE Thesaurus (MeSH). Two detailed search strategies are described in Appendix I. To ensure the completeness of the literature search, the reviewers, experienced researchers in the field of CRPS 1, screened bibliographies of all included studies and retrieved review articles and current treatment guidelines in an additional hand search, and all potentially eligible references were included in the full-text review (inclusion and exclusion criteria applied).

Eligibility Criteria

All RCTs were considered eligible for inclusion in this investigation, which were published between January 1990 und January 2013 and met the PICO reporting system (patient, intervention, control, outcome) the following way: CRPS 1 patients, effect of pharmaceutical treatments, placebo controlled, pain, and disability reduction. In order to reduce potential confounders caused by clinical, interventional, and pharmacological heterogeneity, we decided to limit our analysis to medications administered orally or intravenously. No limits for the study setting or language of the publication were applied. Excluded were nonrandomized studies or conference proceedings.

Study Selection

The bibliographic details of all retrieved articles were stored. Two reviewers (M.M.W. and F.B.) independently screened 1,915 references by title and abstract. The full text was reviewed by both reviewers (M.M.W. and F.B.) independently in all studies meeting the predefined eligibility criteria (N = 98). Disagreements were discussed and resolved by consensus or by third party arbitration (L.M.B.). Researchers with specific language proficiencies reviewed non-English language references. In the case of several publications for the same RCT without change in outcome or follow-up duration, the most recent publication was chosen and missing information from the previous publication added.

Outcome

Due to insufficient and heterogeneous reporting on other outcomes such as physical function or health-related quality of life, the analysis was limited to the outcome "pain." All studies reporting a valid and comparable pain measure on a visual analog scale or a numeric rating scale were included in the analysis.

Data Extraction and Synthesis

Summary estimates per group (means, changes in means) with measures of variability (standard deviation [SD], 95% confidence interval [CI]), as available, were extracted. We summarized different formulations and routes of administration. Medications were categorized into the following groups: 1) calcitonin; 2) bisphosphonates; 3) traditional analgesics (acetaminophen, NSAID, and opioids); 4) radical scavengers; 5) NMDA; 6) steroids; 7) NO-transmitted vasodilatation; and 8) anticonvulsants.

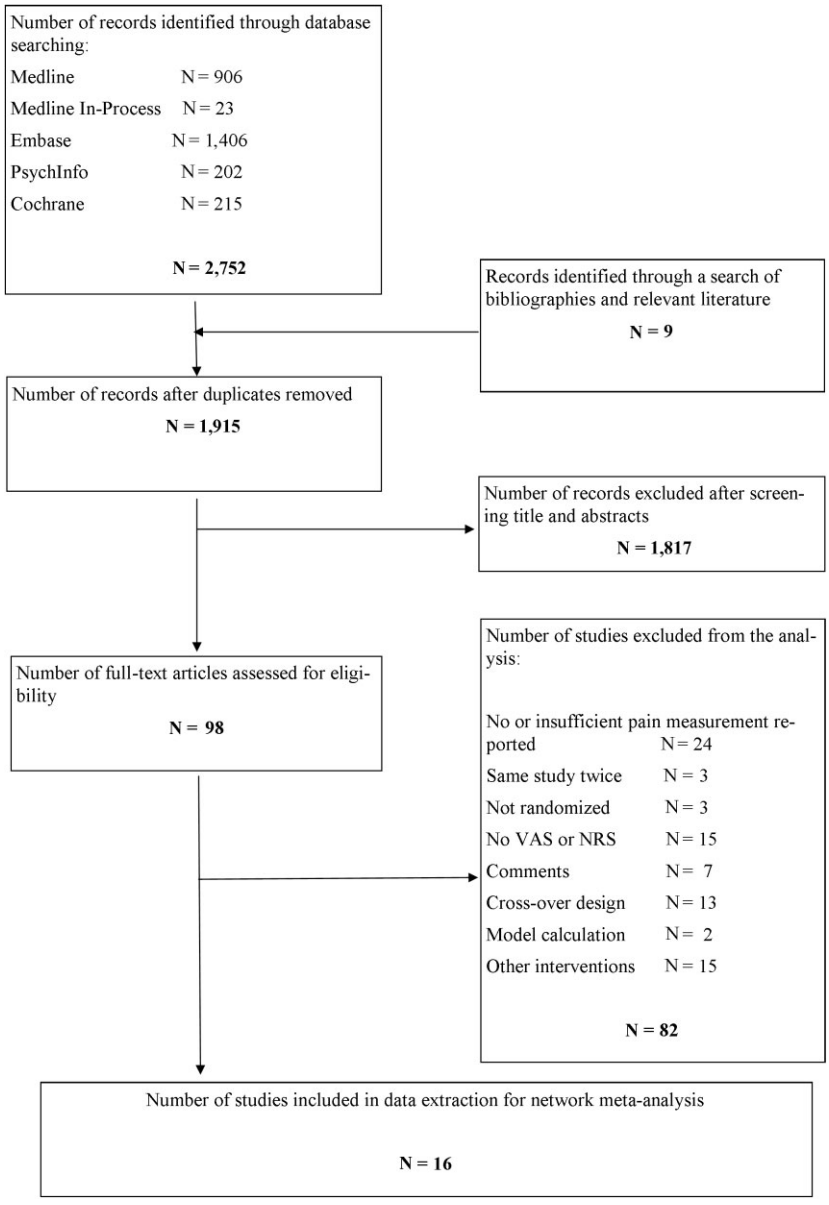

Figure 1 Study flow. NRS = numeric rating scale; VAS = visual analog scale.

Methodological Quality

Two reviewers (M.M.W. and F.B.) independently assessed the methodological quality of each study as recommended [11] by using the Jadad score [13]. The Jadad score is a simple, short, reliable, and valid three-item scale (randomization procedure, blinding, dropout) developed to assess the quality of clinical reports in pain relief. Methodology was considered high when the score was 3 and more. A score of less than 3 comprises an increased risk for bias. The authors agreed in 96%, consensus was reached in a total 4% of the ratings. We did not exclude studies based on their quality rating.

Statistical Analysis

The analysis was based on methodology described earlier by Kessels et al. using a network meta-analytic approach [10]. A linear regression is used to determine the parameters describing the difference in effect between a specific intervention and the reference intervention, and to check the assumptions needed to model the effect parameters. The method provides an easy and transparent way to estimate treatment effect parameters in meta-analyses involving studies with more than two arms [10].

Whenever available, we used results from the intention-to-treat analysis. If required, we imputed missing SDs of

mean changes for each treatment using the largest SD reported in the set of included studies for this outcome. This procedure was necessary in six cases. For each participant, we simulated the outcome by sampling from a normal distribution with the mean and SD of the outcome in a specific treatment arm as described in the study report. Because of chance, the mean and SD parameters could be different from the original values. Therefore, these differences were corrected by a simple linear transformation. For all the treatment classes, a data set was generated in such a manner that it led to the same likelihood function as that from the original data. To that new data set, a linear regression model was fitted. Drug classes, creating a unique code for each class, were entered as covariates. To preserve randomization within each trial, we included an indicator variate for each study. This variate adjusted for all differences in risk profiles and study setup among trials. From this regression model, we estimated an effect size and 95% CIs between placebo and all other treatment options.

Analyses were repeated for two a priori defined subgroups: 1) studies with baseline mean disease duration of less than 12 months vs studies with baseline mean disease duration of 12 months and more; and 2) follow-up duration of less than 2 months vs follow-up duration of 2 months and more.

All analyses were performed with Stata SE 11.2 (StataCorp LP, Station, TX, USA).

Ethical Review Board Approval

For this study, no ethical approval was required. No protocol was published or registered. All methods were determined a priori.

Results

Study Selection

The search and inclusion process is summarized in Figure 1. Out of 1,915 records, 98 were reviewed in full text. The full-text assessment utilizing the inclusion and exclusion criteria resulted in the exclusion of 82 studies. The main reasons for exclusion are summarized in Figure 1 and included other nonrandomized studies (N = 18), other interventions not meeting the inclusion criteria (N = 15), and insufficient or invalid outcome measures (N = 39). In total, 16 RCTs were included in the analysis.

Study Characteristics

A detailed description of the studies, the treatment under investigation, and additional treatments is summarized in Table 1. The diagnosis of CRPS 1 was either based on the International Association for the Study of Pain (IASP)-Orlando diagnostic criteria (N = 6), the Bruehl/Harden criteria (N = 3), the Kozin classification (N = 2), the Steinbrocker (N = 2), the Atkins (N = 1), or Budapest (N = 1) criteria. One study reported no diagnostic criteria [14]. An overview of the definitions is given in Appendix II.

Mean disease duration was less than 12 months in eight studies [14–20]. Mean disease duration of 12 months or more was reported in seven studies [21–27]. One study did not report disease duration and was classified as mean duration less than 12 months [28]. The number of patients included in each treatment arm ranged from 9 to 30 patients; the follow-up duration was between 14 and 127 days. Follow-up duration of two and more months was reported in eight studies [14,16,17,19,21,25–27]. Study quality was moderate to good in 11 studies (Jadad score 3 and higher, Appendix III). Five studies had a Jadad score of less than 3 points [14,18,23,26].

Randomized comparison against placebo or a control group was conducted for the groups as follows: 1) calcitonin in three studies (calcitonin 100 U i.m. [23], 200 [18] to 400 U i.n. [16]); 2) bisphosphonates in four studies (clodronate 300 mg [20], pamidronate 60 mg [26], alendronate 7.5 mg i.v. [15], and alendronate 40 mg p.o. [17]); 3) pain medications in two studies (paracetamol 1,500 mg [18], parecoxib 0.7 and 2.9 i.v. [28]); 4) radical scavengers in one study (mannitol 10% i.v. [25]); 5) NMDA in three studies (memantine 40 mg p.o. [22], ketamine 100 mg i.v. [19], and 7.2 μg/kg/min [27]); 6) corticosteroids in two studies (methylprednisolone 5.7 mg i.v. [29], prednisone 5 mg p.o. [14]); 7) NO-transmitted vasodilatation in one study (tadalafil 16 mg p.o. [21]); and 8) anticonvulsants in one study (gabapentin 1,800 mg [24]).

Treatment Efficacy Overall

Figure 2 summarizes the overall efficacy to reduce pain of all of the included pharmacological categories. Bisphosphonates and calcitonin were most effective followed by NMDA analogs, conventional analgetics, vasodilators, and steroids. The radical scavengers mannitol and the anticonvulsants gabapentin were similarly effective than placebo in decreasing pain.

Results for Symptom Duration of Less and More Than 12 Months

In patients with symptom duration of less than 12 months, bisphosphonates were most effective. Patients with symptom duration for more than 12 months responded best to calcitonin. For details, please see Figures 3 and 4.

Results for Follow-Up after Less and More Than 2 Months

In studies with a follow-up of less than 2 months, calcitonin was most effective. More effective than placebo were NMDA analogs, bisphosphonates, analgesics, and steroids (Figure 5). The effect of steroids was more effective than placebo but less effective than bisphosphonates and analgesics. In studies with follow-up of 2 months and more, bisphosphonates (N = 14) were most effective (Figure 6). NMDA analogs and the vasodilator tadalafil were also more effective than placebo. Steroids, the radical scavenger mannitol, and calcitonin were not more effective than placebo.

Table 1 Baseline characteristics

Author	Treatment	N (f/m)	A (SD) Years	Diagnostic Criteria	Disease Duration (SD) Days	Additional Treatment	Treatment Duration (Days)	Follow-Up (Days)	Jadad Score
Adami et al. [15]	Group 1: Placebo	10 (5/5)	60 (6.4)	Kozin	133 (133)	PT	3	14	3
	Group 2: Alendronate 7.5 mg i.v.	10 (7/3)	64 (8.0)		112 (119)	PT	3	14	
Bickerstaff and Kanis [16]	Group 1: Placebo	20 (15/5)	65.5 (8.0)	Atkins	41 (8.5)	None	28	84	5
	Group 2: Calcitonin 400 IU i.n.	20 (19/1)	60.8 (12.1)		38 (8)	None	28	84	
Frade et al. [28]	Group 1: Control	12 (6/6)	41 (8.0)	Budapest	n.r.	Loco regional 1 mg/kg lidocaine +30 mg clonidine, amitriptyline 25 mg, and PT	7	7	4
	Group 2: i.v. loco-regional 5 mg parecoxib 1×/week	10 (5/6)	41 (8.0)		n.r.	Same	7	7	
	Group 3: 20 mg parecoxib i.v. 1/week	12 (6/6)	44 (10)		n.r.	Same	7	7	
Groeneweg et al. [21]	Group 1: Placebo	12 (11/1)	36.5 (10.6)	Bruehl	1,671 (1,569)	Standardized graded EP (by Kempler), instruction 1×/week	84	84	5
	Group 2: Tadalafil 10 mg/4 weeks, 20 mg/8 weeks	12 (9/4)	39.8 (13.1)		1,113 (735)	Same	84	84	
Gustin et al. [22]	Group 1: Placebo	20 (12/8)	51 (12)	n.r.	492 (360)	Standardized PT: (manual, balneophysical, manual lymphatic drainage), OC therapy	49	56	
	Group 2: Memantine (NMDA receptor antagonist, 40 mg/day)				468 (269)	Same		56	
Hamamci et al. [23]	Group 1: Placebo	16 (10/6)	59.5 (5.9)	Steinbrocker	756 (1,008)	PT	28	28	
	Group 2: Calcitonin 100 U i.m./day	25 (11/14)	57.8 (10.2)		648 (504)	Same	28	28	
Lukovic et al. [14]	Group 1: Placebo	30 (21/9)	48.6 (13.8)	n.r.	Acute	Actively supported EP, PEMF + IC	127	127	
	Group 2: Prednisone 5 mg p.o.	30 (21/9)	46.3 (12)		Acute	Same	119	119	
Manicourt et al. [17]	Group 1: Placebo	20 (12/8)	45.2 (12.5)	IASP	240 (90)	None	56	84	
	Group 2: Alendronate 40 mg p.o./day	19 (9/10)	44.6 (12.3)		210 (60)	None	56	84	

Table 1 Continued

Author	Treatment	N (f/m)	A (SD) Years	Diagnostic Criteria	Disease Duration (SD) Days	Additional Treatment	Treatment Duration (Days)	Follow-Up (Days)	Jadad Score
Perez et al. [25]	Group 1: Placebo	19 (15/4)	43.9 (12.9)	Bruehl	525 (556)	PT, NSAID, antidepressants, anticonvulsants	5	63	
	Group 2: Mannitol 10% i.v.	22 (18/4)	46.5 (11.5)		495 (556)	Same	5	63	
Robinson et al. [26]	Group 1: Placebo	13 (4/9)	45 (6.0)	IASP	648 (414)	Paracetamol and morphine at stable dosage if needed	1	90	
	Group 2: Pamidronate 60 mg i.v. single infusion	14 (5/9)	45 (6.0)		648 (414)	Same	1	90	
Sahin et al. [18]	Group 1: Paracetamol 1,500 mg/day	17 (13/4)	60 (12.3)	Steinbrocker	42 (25)	PT, EP, TENS	60	60	0
	Group 2: Salmon calcitonin 200 U/day nasal + calcium 500 mg/day	18 (12/6)	60 (12.3)		38 (17.5)	Same	60	60	
Schwartzman et al. [19]	Group 1: Placebo	10 (9/1)	45.5 (10.5)	IASP	219 (673.6)	Clonidine + midazolam	10	84	
	Group 2: Ketamine max 100 mg i.v.	9 (9/0)	38 (7.6)		177 (369)	Same	10	84	
Sigtermans et al. [27]	Group 1: Placebo	30 (26/4)	47.5 (13.1)	n.r.	2,196 (1,836)	Preexisting medication: e.g., NSAID, SSRI	4.2	77	
	Group 2: Ketamine 7.2 μg/kg/min	30 (22/8)	43.7 (11.5)		3,384 (2,880)	Same	4.2	77	
Taskaynatan et al. [29]	Group 1: Placebo	10 (n.r.)	22.3 (1.6)	n.r.	93 (42)	ROM, stretching, strengthening, bath 1×/day	21	45	
	Group 2: Methylprednisolone 40 mg, lidocaine 10 mL 2% i.v.	12 (n.r.)	22.3 (1.6)		93 (42)	Same	21	45	
van de Vusse et al. [24]	Group 1: Placebo	24 (21/3)	42 (13)	IASP	1,290 (1,080)	None	21	21	5
	Group 2: Gabapentin (escalating dosage 600 mg to 3×/day from day 5–21)	22 (18/4)	47 (14)		1,320 (630)	None	21	21	
Varenna et al. [20]	Group 1: Placebo	17 (10/7)	53.4 (9)	Kozin	126 (78)	None	10	40	5
	Group 2: Clodronate 300 mg /day i.v.	15 (9/6)	58.1 (7.7)		111 (57)	None	10	40	

EP = exercise program; f/m = female/male; IASP = International Association for the Study of Pain; IC = frequency of interference currents; n.r. = not reported; NSAID = nonsteroidal anti-inflammatory drugs; OC = occupational therapy; PEMF = pulsed electromagnetic field; PT = physical therapy; ROM = range of motion; SD = standard deviation; SSRI = selective serotonin re-uptake inhibitors; TENS = transcutaneous electrical nerve stimulation.

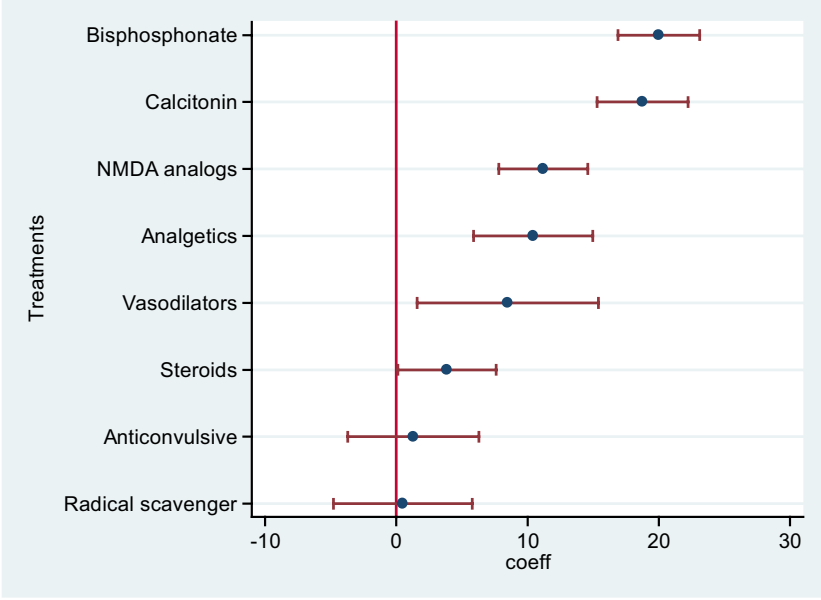

Figure 2 Summary of treatment efficacy overall.

Discussion

Main Findings

Whereas bisphosphonates appeared to be most beneficial in mean disease duration of CRPS of less than 12 months, the effects of calcitonin surpass those of bisphosphonates and other substances in more chronic stages of the illness. Calcitonin appears to be the treatment of choice as a short-term medication in advanced stages of CRPS. While most medications showed some efficacy on short-term follow-up, only bisphosphonates, NMDA analogs, and vasodilators showed better long-term pain reduction than placebo.

Results in Light with Existing Literature

Optimal treatment for CRPS 1 requires multidisciplinary functional rehabilitation. Recently published updated guidelines for the diagnosis and treatment of CRPS summarized the evidence on current treatment strategies in CRPS 1 [2,3]. Pharmacologic treatments are frequently used to alleviate pain in pain management. In a recent systematic review, bisphosphonates and oral tadalafil were identified to significantly reduce pain [30]. Although the existing literature is reviewed thoroughly, none of these publications provide a rank order of the available substances stratified by the length of illness duration. The current analysis expands our understanding of the efficacy

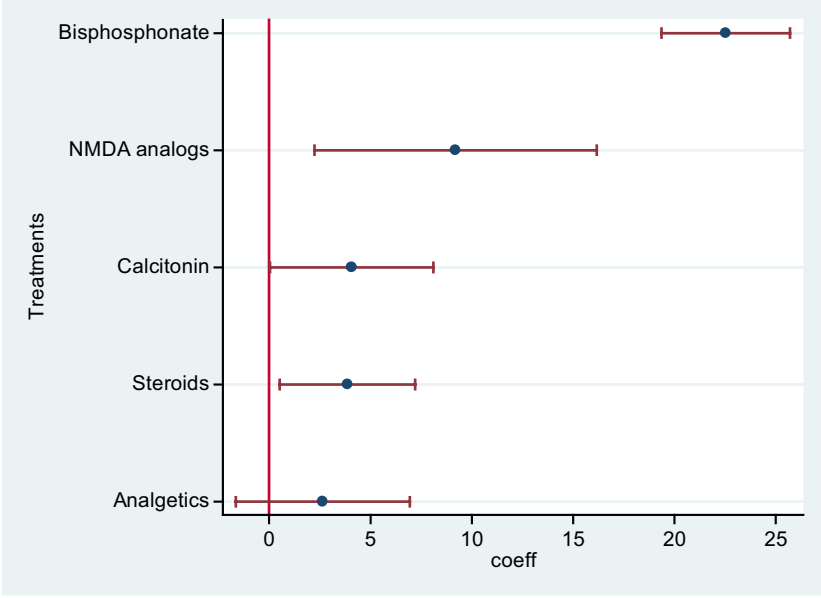

Figure 3 Summary of results in mean symptom duration less than 12 months.
Coefficient, effect size, and 95% confidence intervals in the regression model between placebo and intervention.

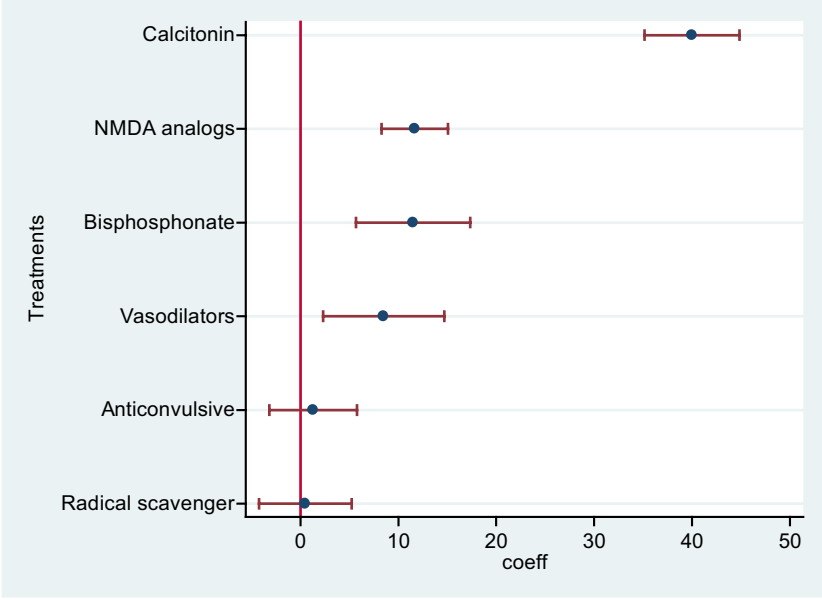

Figure 4 Summary of results in mean disease duration 12 months and more.
Coefficient, effect size, and 95% confidence intervals in the regression model between placebo and intervention.

in short- and long-term CRPS 1. Short-term effects were seen in several medications including calcitonin, radical scavenger, NMDA analogs, bisphosphonates, analgesics, and steroids, while long-term efficacy was only present in bisphosphonates, NMDA analogs, and vasodilators. This is in agreement with the findings of a recently published RCT, and therefore not yet included in this analysis, that showed good efficacy for bisphosphonates in patients with CRPS 1 of less than 4-months duration [31].

Strength and Limitation

To our knowledge, this is the first network meta-analysis providing a comprehensive evaluation of currently available pharmaceutical treatment strategies in patients with CRPS 1. In particular, the network approach allowed us to provide a rank ordering of drug classes and allowed us to explore the temporal aspect of drug efficacy in more detail. The review was conducted according to modern methodological standards, searches were comprehensive, no language limitations were imposed, a thorough bibliographic search was conducted in order to include all relevant studies, and the extraction process was done carefully.

While the network meta-analysis is an exciting and promising technique that allows for comparison between treatments where no head-to-head comparison is available,

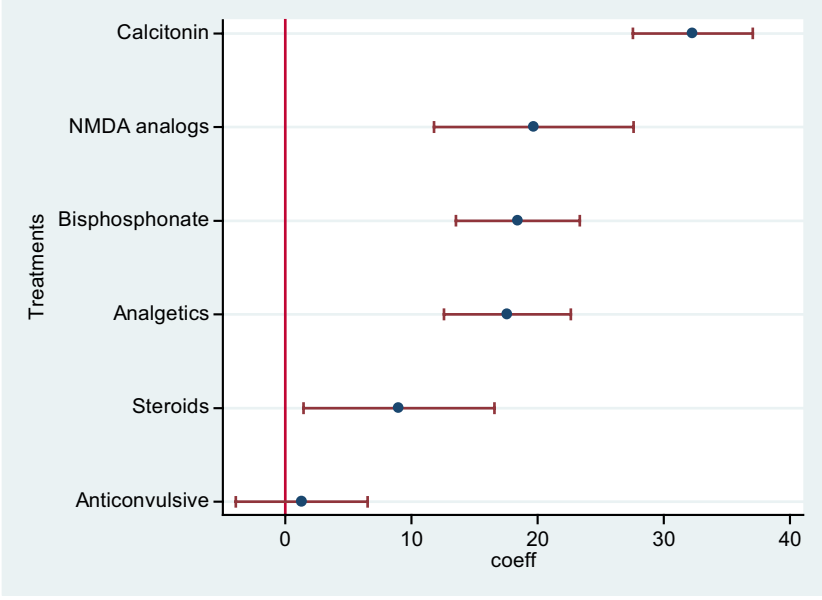

Figure 5 Results of follow-up less than 2 months.
Coefficient, effect size, and 95% confidence intervals in the regression model between placebo and intervention.

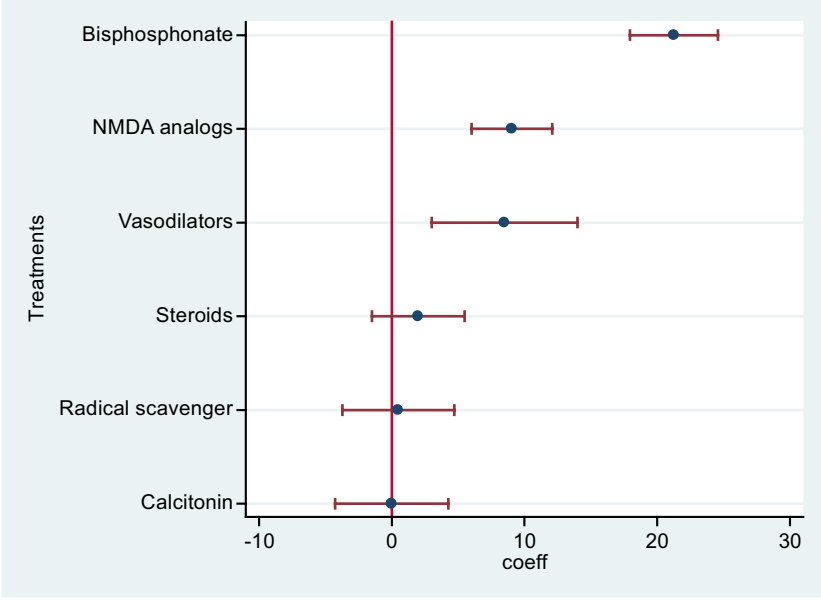

Figure 6 Results of follow-up 2 months and more.
Coefficient, effect size, and 95% confidence intervals in the regression model between placebo and intervention.

the findings are as robust as the quality of the RCTs they are based on. The majority of studies included only a small group of patients and for some drug classes assessed, the number on included studies was small for most, and in a number of cases, only one drug in a drug class was assessed. Further, although we aimed at investigating pharmaceutical efficacy on disability outcomes as well, presentation of results (heterogeneity on the level of outcome measurement and reporting) impeded us from conducting efficacy analysis beyond pain outcome measures. Therefore, the findings have to be interpreted with caution, and further research is needed to understand the underlying mechanism.

Implication for Research

Further research should aim at clarifying the role of calcitonin and bisphosphonates in short- and long-term CRPS 1 in terms of short-term and long-term pain control and disability.

Moreover, the analgesic effects of bisphosphonates remain incompletely understood. We are aware of a few studies on animals and humans postulating potential pathophysiologic pathways of action [32]. However, further investigations should aim at exploring these further.

Quite similarly, the analgesic properties of calcitonin remain unclear. A few, often uncontrolled studies postulated a central nervous involvement, which was independent from an effect on osteoclastic bone resorption [33–35].

Based on our current pathophysiologic understanding of CRPS [36], treatment regimens should distinguish between early (neurogenic inflammation, vasomotor dysfunction) and chronic (neuroplastic changes in the central nervous system) illness stages. Further research should take this aspect into account.

From a more methodological viewpoint, initiatives aiming at reaching a consensus regarding relevant outcome measures and their quantification, particularly to assess function restoration, should be encouraged [37].

Implication for Practice

Our findings encourage using bisphosphonates as a first-line treatment for pain control in early CRPS and calcitonin as a short-term addition to bisphosphonates in later stages (after 12 months of symptom duration). Our findings endorse a recent warning to limit the calcitonin treatment period to 6 weeks in maximum, after finding a potential association with cancer incidence of various types [38].

Conclusion

Based on an efficacy network meta-analysis of 16 RCTs, a rational pharmacological choice for pain management should consider illness duration and should either contain bisphosphonates (disease duration less than 12 months, follow-up 2 months and more) or short-term calcitonin (for disease duration 12 months and more, follow-up less than 2 months). While most medications showed some efficacy on short-term follow-up, only bisphosphonates, NMDA analogs and vasodilators showed better long-term pain reduction than placebo. Further studies are warranted exploring the analgesic effects of bisphosphonates in more detail.

Authors' Contributions

All authors discussed the results and commented on the manuscript. F.B., A.G.H.K., and L.M.B. designed the

study. M.M.W. and F.B. performed the literature search. M.M.W., F.B., A.G.H.K., R.S.G.M.P., and L.M.B. analyzed the data and interpreted the results. M.M.W., F.B., R.S.G.M.P., and L.M.B. wrote the manuscript. F.B. oversaw the execution of the project.

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Appendices

Appendix I

Search strategies for Medline and Embase

Ia) Medline (1990–January 2013/week 2) (OvidSP)

The Medline search was from 1990 to January 2013/week 2 and identified 906 references.

No.	Search	Results
1	Randomized controlled trial.pt	342,334
2	Controlled clinical trial.pt.	85,694
3	Random$.ab	572,469
4	Placebo.ab	136,550
5	Drug therapy.fs.	1,588,363
6	Random$.ti.	94,252
7	Trial.ab.	253,825
8	Groups.ab.	1,145,730
9	or/1–8	3,070,837
10	Animals/ not (animals/ and humans/)	3,720,385
11	9 not 10	2,608,039
12	Complex regional pain syndromes/ or reflex sympathetic dystrophy/	3,791
13	(CRPS or complex regional pain syndrome$ or RND or CRPS1).ti,ab.	2,140
14	Posttrauma$ dystroph$ or post trauma$ dystroph$ or reflex$ neurovascular dystroph$).ti,ab.	58
15	(Reflex$ sympathetic dystroph$ or sudeck$ atroph$ or algodystroph$ or algoneurodystroph$).ti,ab.	2,099
16	(Algo dystroph$ or algo neurodystroph$).ti,ab.	12
17	(Shoulder hand syndrom$ or shoulder hand dystroph$).ti,ab.	175
18	Cervical sympathetic dystroph$.ti,ab.	0
19	or/12–18	5,383
20	11 and 19	1,167
21	Limit 20 to year = “1990–Current”	906

Based on the following trials filter:
Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Ib) Embase (1990–2013/week 2) (OvidSP)

The Embase search was from 1990 to 2013/week 2 and identified 1406 references.

No.	Search	Results
1	Random.tw. or clinical trial.mp. or exp treatment outcome/	1,814,870
2	Animal/	1,802,202
3	Animal experiment/	1,554,445
4	(Rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp.	5,230,067
5	or/2–4	5,230,067
6	Exp human/	14,036,759
7	Human experiment/	307,990
8	or/6–7	14,038,153
9	5 not (5 and 8)	4,134,417
10	1 not 9	1,753,891
11	Complex regional pain syndrome/ or exp complex regional pain syndrome type i/	6,240
12	(CRPS1 or CRPS or complex regional pain syndrome$ or RND).ti,ab	3,173

Appendix I Continued

No.	Search	Results
13	(Posttrauma$ dystroph$ or post trauma$ dystroph$ or reflex$ neurovascular dystroph$).ti,ab.	62
14	(Reflex$ sympathetic dystroph$ or sudeck$ atroph$ or algodystroph$ or algoneurodystroph$).ti,ab.	2,767
15	(Algo dystroph$ or algo neurodystroph$).ti,ab.	12
16	(Shoulder hand syndrom$ or shoulder hand dystroph$).ti,ab.	231
17	Cervical sympathetic dystroph$.ti,ab.	0
18	or/11–17	8,153
19	10 and 18	1,423
20	Limit 19 to year = "1990–Current"	1,406

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association 2006;94(1):41–7.

Appendix II

Summary of study quality according to the Jadad score quality assessment [8]

Author	Year	Randomization	Randomization Correct	Double Blind	Blinding Adequate?	Drop Out Described?	Score
Adami et al. [15]	1997	1	−1	1	1	1	3
Bickerstaff and Kanis [16]	1991	1	1	1	1	1	5
Frade et al. [28]	2005	1	1	1	1	0	4
Groeneweg et al. [21]	2008	1	1	1	1	1	5
Gustin et al. [22]	2010	1	−1	1	1	1	3
Hamamci et al. [23]	1996	1	−1	0	−1	0	0
Lukovic et al. [14]	2006	1	−1	0	−1	0	0
Manicourt et al. [17]	2004	1	1	1	1	1	5
Perez et al. [25]	2008	1	1	1	1	1	5
Robinson et al. [26]	2004	1	−1	1	−1	1	1
Sahin et al. [18]	2006	1	−1	0	−1	0	0
Schwartzman et al. [19]	2009	1	1	1	1	1	5
Sigtermans et al. [27]	2009	1	1	1	1	1	5
Taskaynatan et al. [29]	2004	1	1	1	1	1	5
van de Vusse et al. [24]	2004	1	1	1	1	1	5
Varenna et al. [20]	2000	1	1	1	1	1	5

Jadad Scoring system: methodological quality high ≥3 points; increased risk for bias in <3 points.
Scoring: 1 point if adequately described, 0 point if not adequately described. Give 1 additional point if for question 1, the method to generate the sequence of randomization was described and it was appropriate (table of random numbers, computer generated, etc.) AND/OR if for question 2, the method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.). Deduct 1 point if for question 1, the method to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.) AND/OR for question 2, the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs injection with no double dummy).

Appendix III

Budapest Clinical Diagnostic Criteria, 2003	Bruehl, 1999	IASP-Orlando, 1994	Veldman, 1993	Kozin, 1981	Steinbrocker, 1958
1. Continuing pain, which is disproportionate to any inciting event	1. Continuing pain, which is disproportionate to any inciting event	1. Develops after an initiating noxious event (type I) or after a nerve injury (type II)	1. 4 or 5 of: • Unexplained diffuse pain • Difference in skin color relative to other limb • Diffuse edema • Difference in skin temperature relative to other limb • Limited active range of motion	Definite: • Pain and tenderness in the distal extremity • Signs and/or symptoms of vasomotor instability • Swelling in the extremity—often with periarticular prominence (dystrophic skin changes usually present)	Stage 1 (“acute”): • Severe pain, burning or aching quality, increased by dependency of the affected part, physical contact or emotional upset. • Edema • Hyperthennia or hypothermia • Increased hair and nail growth occurs in the affected part • Bony changes may be present on roentgenograms
2. Must report at least one symptom in three of the four following categories: • Sensory: reports of hyperesthesia and/or allodynia • Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry • Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry • Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)	2. Must report at least one symptom in each of four following categories • Sensory: reports of hyperesthesia • Vasomotor: reports of temperature asymmetry and/or skin color change and/or skin color asymmetry • Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry • Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)	2. Spontaneous pain or allodynia/hyperalgesia that is not limited to the territory of a single peripheral nerve and is disproportionate to the inciting event	2. Occurrence or increase of above signs and symptom after use	Probable: • Pain and tenderness • Vasomotor instability or swelling (dystrophic skin changes often present)	Stage 2 (“dystrophic” stage): • Dystrophic changes and the persistence of pain and disability. The edematous tissue becomes indurated and the skin is cool and hyperhidrotic. • Roentgenograms may reveal diffuse osteoporosis.

3. Must display at least one sign at time of evaluation in two or more of the following categories: • Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement) • Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry • Sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry • Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)	3. Must display at least one sign in two or more of the following categories: • Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch) • Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry • Sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry • Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)	3. There is or has been evidence of edema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event.	3. Above signs and symptoms present in an area larger than the area of primary injury or operation and including the area distal to the primary injury	Possible • Vasomotor instability and/or swelling • No pain, but mild moderate tenderness may be present (dystrophic skin changes occasionally present)	Stage 3 (“atrophic” stage): • Progressive skin and subcutaneous tissue atrophy, and occasionally proximal spread of pain. The skin is thin and shiny, the fascia becomes thickened, and flexion or Dupuytren’s contractures may occur. • Roentgenograms show masked demineralization and ankylosis.
4. There is no other diagnosis that better explains the signs and symptoms.		4. There is no other diagnosis that better explains the degree of pain and dysfunction. Note: Criteria 2–4 must be satisfied		Doubtful • Unexplained pain and tenderness in an extremity	