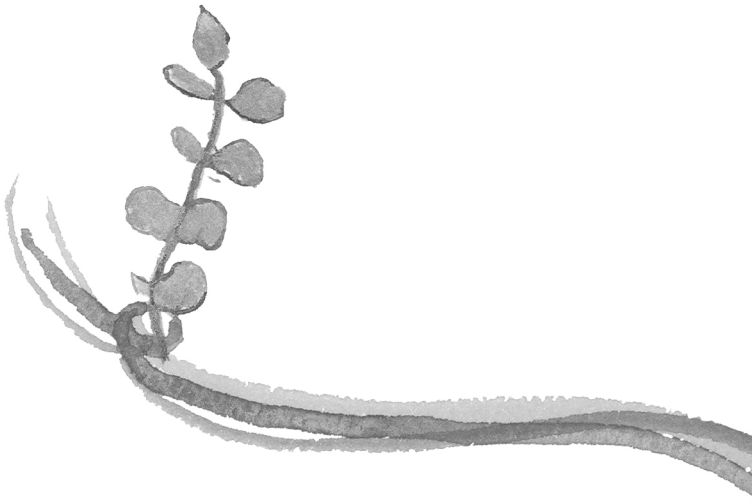
Inflammation as a target for treatment in hand osteoarthritis

Kroon, F.P.B.

CHAPTER 3

Efficacy and safety of non-pharmacological, pharmacological and surgical treatment for hand osteoarthritis: a systematic literature review informing the 2018 update of the EULAR recommendations for the management of hand osteoarthritis



Féline P.B. Kroon
Loreto Carmona
Jan W. Schoones
Margreet Kloppenburg

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ABSTRACT

To update the evidence on efficacy and safety of non-pharmacological, pharmacological and surgical interventions for hand osteoarthritis (OA), a systematic literature review was performed up to June 2017, including (randomised) controlled trials or Cochrane systematic reviews. Main efficacy outcomes were pain, function and hand strength. Risk of bias was assessed. Meta-analysis was performed when advisable. Of 7036 records, 127 references were included, of which 50 studies concerned non-pharmacological, 64 pharmacological and 12 surgical interventions. Many studies had high risk of bias, mainly due to inadequate randomisation or blinding. Beneficial non-pharmacological treatments included hand exercise and prolonged thumb base splinting, while single trials showed positive results for joint protection and using assistive devices. Topical and oral non-steroidal anti-inflammatory drugs (NSAIDs) proved equally effective, while topical NSAIDs led to less adverse events. Single trials demonstrated positive results for chondroitin sulfate and intra-articular glucocorticoid injections in interphalangeal joints. Pharmacological treatments for which no clear beneficial effect was shown include paracetamol, intra-articular thumb base injections of glucocorticoids or hyaluronic acid, low-dose oral glucocorticoids, hydroxychloroquine and anti-tumour necrosis factor. No trials compared surgery to sham or non-operative treatment. No surgical intervention for thumb base OA appeared more effective than another, although in general more complex procedures led to more complications. No interventions slowed radiographic progression. In conclusion, an overview of the evidence on efficacy and safety of treatment options for hand OA was presented and informed the task force for the updated European League Against Rheumatism management recommendations for hand OA.

INTRODUCTION

In 2007, the first European League Against Rheumatism (EULAR) recommendations for the management of hand osteoarthritis (OA) were published, based on expert opinion and an overview of the literature.[1] Many propositions, however, were based mainly on expert opinion, as evidence was lacking.

Despite it being a prevalent disease, for years, options to treat hand OA patients have been limited. In search of better alternatives for symptom relief, and in hopes of finding a disease-modifying anti-osteoarthritic drug, many clinical trials have been performed in the last decade, expanding the possible range of therapeutic options. At the same time, data has become available showing that some treatments which were believed to be beneficial do not appear to be efficacious after all. New evidence has emerged on various therapies, including but not limited to self-management, application of thumb base splints, topical non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, various intra-articular therapies and treatment with conventional and biological disease-modifying anti-rheumatic drugs (cs/bDMARDs), for example, hydroxychloroquine and tumour necrosis factor (TNF) inhibitors.

In light of the newly accrued data, it was therefore time to update the 2007 management recommendations. This paper presents the systematic literature review (SLR) that accompanies the update of the recommendations. The aim of this SLR was to inform the task force on the current evidence for efficacy and safety of all non-pharmacological, pharmacological and surgical treatments for hand OA.

METHODS

Search strategy

A systematic search was conducted in PubMed/MEDLINE, Embase and the Cochrane CENTRAL databases up to 6 June 2017. Additionally, conference abstracts of the EULAR, American College of Rheumatology (ACR) and OsteoArthritis Research Society International (OARSI) annual conferences of the last two years, and reference lists of included studies and other relevant SLRs were screened. The search strategy can be found in the online supplementary file 1. Eligible study types were randomised controlled trials (RCTs) and clinical controlled trials (CCTs). Observational longitudinal studies were considered to assess safety, and to assess efficacy of surgical interventions, but only if a comparator group was available and the number of participants per group was at least 50. Cochrane systematic reviews were also included. The following hierarchy of study design was adopted to assess the evidence for each intervention: Cochrane systematic reviews, RCTs, CCTs and lastly observational studies.

Research questions were formulated according to the PICO format: Participants, Interventions, Comparators, Outcomes.[2] Studies of any non-pharmacological, pharmacological or surgical intervention in adults diagnosed with hand OA were included. Studies including participants with other diagnoses were only eligible for inclusion if the results were presented separately for participants with hand OA. The comparator could be placebo, care-as-usual, any

other non-pharmacological, pharmacological or surgical intervention, or the same intervention in a different dose, formulation, regimen or treatment duration. Studies without a comparator were excluded. Other exclusion criteria were a total number of participants in non-surgical trials <20 and premature termination of the trial.

Efficacy outcomes were considered as proposed by the OMERACT core set for domains in clinical trials for hand OA.[3] Main efficacy outcomes were pain (preferably measured on visual analogue scale (VAS), numerical rating scale (NRS), or a validated questionnaire, eg, Australian/Canadian Hand Osteoarthritis Index (AUSCAN) or Michigan Hand Outcomes Questionnaire (MHQ)), hand function (validated questionnaire, eg, Functional Index for Hand OsteoArthritis (FIHOA), AUSCAN or MHQ), and hand strength (grip or pinch strength). Additional efficacy outcomes that were considered included patient global assessment (VAS or NRS), health-related quality of life (Short-Form 36, EuroQoL), structural damage, hand mobility (Hand Mobility in Scleroderma test, modified Kapandji index, fingertip-to-palm-distance) and the number of participants fulfilling the OMERACT-OARSI responder criteria.[4] The primary safety outcome was withdrawals due to adverse events (AEs). In addition, serious AEs and AEs broken up by bodily system (eg, gastrointestinal, cardiovascular) were assessed. Studies that did not assess any efficacy or safety outcomes were excluded.

Study selection, data extraction and risk of bias assessment

One reviewer (FK) screened titles and abstracts to determine eligibility for inclusion, according to predefined inclusion criteria, followed by full-text review where necessary. In case of doubt, a second reviewer was consulted (MK/LC). Relevant data on study characteristics, interventions, study population and the above-mentioned outcomes was extracted (FK). The risk of bias (RoB) was assessed with regard to random sequence generation, allocation concealment, blinding (participants, care provider, outcome assessor), incomplete outcome data, selective outcome reporting and other sources of bias according to the 'Cochrane tool' (FK).[5] Each item was judged as low (green colour), high (red) or unclear RoB (yellow; lack of information or uncertainty over potential bias). An 'overall assessment' for each study was based on the judgements for each RoB item. Selection bias (sequence generation, allocation concealment) and blinding were considered 'key domains', that is, the most important domains in a study's RoB.

Data analysis

Data were only pooled in case of sufficient clinical and statistical homogeneity. For continuous outcomes, data were summarised as mean difference (MD) with corresponding 95% CI, unless different measurement instruments were used to measure the same outcome, in which case standardised mean differences (SMDs) were calculated. A random effects model was used. Studies that could not be included in the meta-analysis are presented descriptively. Stata V.14.1 was used for meta-analysis.

RESULTS

The literature search yielded 5020 records (after de-duplication), of which 127 references were included in this review (see figure 1 and online supplementary table S1). Three studies were additionally excluded because of language (Turkish, Chinese). In total, 50 studies assessed benefits and harms of different non-pharmacological therapies, including one Cochrane review. Pharmacological interventions were investigated in 64 studies, including one observational study. Surgical interventions were assessed in 11 trials, all summarised in one Cochrane review.

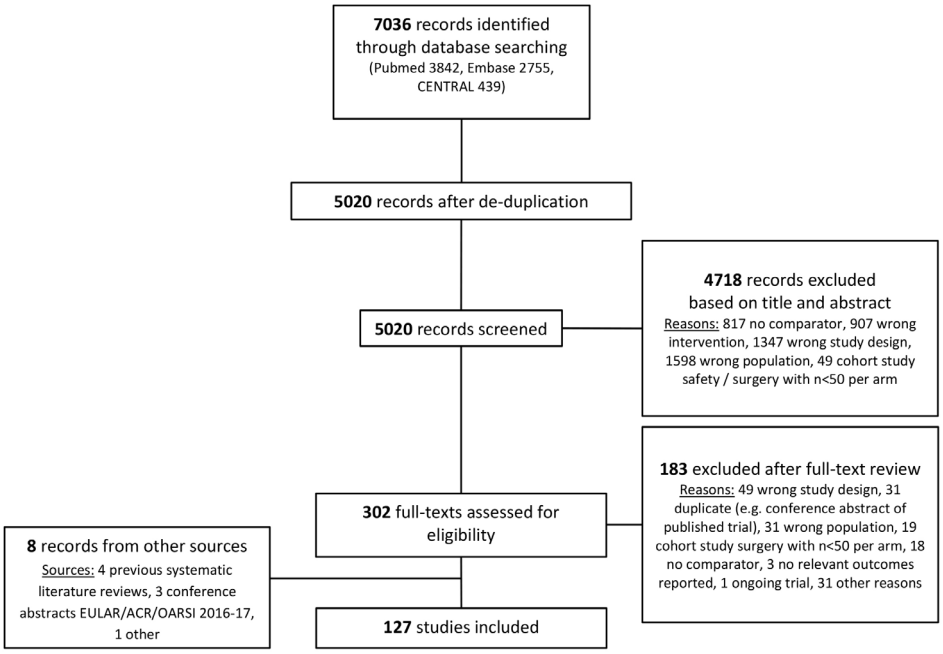

Figure 1. Flowchart of systematic literature review.

Non-pharmacological interventions

Table 1 presents an overview of the characteristics and RoB of the 28 studies of the most relevant non-pharmacological interventions to inform the 2018 update of the EULAR management recommendations for hand OA. The remaining trials studied thermal modalities (n=3), manual therapy (n=3), balneotherapy (n=6), low-level laser therapy (n=4), yoga (n=1), nuclear magnetic resonance (n=1), magnetotherapy (n=1), leeches (n=1) and alkalinisation of diet (n=1), and are described in online supplementary tables (3.1.5, 3.1.7, 3.1.9, 3.1.11).

The studies were heterogeneous, especially with respect to type of intervention, study duration (range: 1 week to 1 year, most up to 8 weeks) and assessed outcomes. Most were RCTs (n=19), and a minority CCTs (n=3) or cross-over trials (n=6). Many studies were small: 15 trials (54%) included 60 participants or less. All studies were judged to be at high or unclear RoB, most often due to lack of blinding. A detailed RoB assessment is presented in online supplementary tables 3.1.1-3.1.12.

Table 2 presents an overview of the main results of the most relevant non-pharmacological trials for which the outcomes pain, function, fulfilment of OARSI-OMERACT criteria[4] or grip strength could be assessed. Safety outcomes are presented in online supplementary table 4.1. If studies were pooled, results are also presented in forest plots (online supplementary figures S1-S8).

In summary, exercise leads to beneficial effects on hand pain, function, joint stiffness and grip strength, although effect sizes are small. Few (non-severe) AEs were reported, showing a signal for increased number of AEs in participants undergoing exercise therapy, in particular increased joint inflammation and hand pain (RR 4.6 (95% CI 0.5 to 39.3); online supplementary table 4.1).[6]

Joint protection led to a higher proportion of participants being classified as responder to treatment according to OARSI-OMERACT criteria after 6 months, though mean AUSCAN pain and function subscales did not differ between groups.[7]

On the short term, thumb base splinting did not lead to pain relief or functional improvement,[8-12] though studies assessing long-term use showed that this was associated with more pain relief and improved function (online supplementary figures S1-S4).[10,12] Studies assessed many different types of splints (eg, short or long, custom-made or prefabricated, neoprene or thermoplast or other material) and instructions for use (eg, during activities of daily living, at night, constantly). Only short versus long thumb base splints (ie, including only CMC joint vs both CMC and MCP joint) could formally be compared and were not associated with different clinical outcomes (online supplementary figures S5-S6).[13-15] For other splint types or instructions, no consistent benefit of one over another could be identified in RCTs/CCTs or cross-over studies.[16-20] A single study assessed night time DIP splinting specifically, but did not show improvements in pain, function or pinch strength after 3 months.[21]

Use of assistive devices led to small improvements in function, as measured with the patient-specific Canadian Occupational Performance Measure (COPM) and the AUSCAN function subscale, but not in pain.[22]

Several studies assessed different combination programmes of multiple non-pharmacological interventions.[7,15,23-28] Three trials compared a programme including education, joint protection and hand exercises to education alone, and though no formal meta-analysis could be performed, no between-group differences in pain, function or grip strength could be confirmed (online supplementary figures S7-8).[7,25,26] The other studies of combination programmes were more heterogeneous, especially in the type of intervention studied. Some reported positive effects of the combination versus non-combination interventions, especially on subjective measures like pain,[23,28] and not on more objective measures like hand strength,[24,28] though others reported no between-group differences.[15,27]

Furthermore, application of heat was assessed in three heterogeneous trials, both in design and type of intervention (high RoB). Two studies reported improvements in, for example, pain and grip strength in the intervention group compared with control,[29,30] and one cross-over trial reported no between-group differences.[31] Three studies (high RoB) focussed on different forms of manual therapy in elderly, severe CMC OA patients (mean age 81.4 years) and showed positive effects on pain sensitivity and hand strength in the intervention group compared with control, both in the treated, symptomatic hand, and in the contralateral non-treated non-symptomatic hand.[32-37] Finally, six studies (five high RoB, one unclear RoB) assessed different forms of balneotherapy to another active intervention,[38-40] sham intervention,[41,42] or usual care.[43] The studies comparing balneotherapy to another active intervention or to usual care all report positive effects of balneotherapy on pain, function and hand strength compared with the chosen control group.[38-40,43] However, balneotherapy (mud application or mineral thermal bath) was not convincingly better than a sham intervention.[41,42]

Pharmacological interventions

Table 3 presents an overview of the characteristics and RoB of the 33 trials of the most relevant pharmacological interventions to inform the 2018 update of the EULAR management recommendations for hand OA. Trials not listed in table 3 studied topical capsaicin (n=1), topical salicylates (n=2), paracetamol (n=4), glucosamine (n=1), diacerhein (n=1), different herbal formulations (n=3), anti-interleukin-1 (n=1), clodronate (n=1), several types of periarticular injections (n=3), intra-articular hyaluronic acid (n=9), other intra-articular therapies (n=2), folate/cobalamin supplementation (n=1), apremilast (n=1), galactosaminoglycuronglycan sulfate (n=1), and pregabalin and duloxetine (n=1). A description can be found in online supplementary tables (3.2.2, 3.2.4, 3.2.6, 3.2.10, 3.2.12, 3.2.15, 3.2.17, 3.2.22).

The longest trial lasted up to 3 years, though most trials had a duration of 3 weeks. Most studies focussed on clinical outcomes, while structure modification was the primary outcome of two trials.[44,45] The majority were RCTs (n=30), and few were set-up as CCTs (n=1) or cross-over trials (n=2). Seven trials specifically included participants with signs of "inflammatory OA", all investigating anti-inflammatory agents (ie, NSAIDs, glucocorticoids and anti-TNF).[45-51] Compared with non-pharmacological interventions, less studies were small (n≤60; 15 trials, 45%). Twelve studies (36%) were at low RoB. Reason to judge studies to be at high or unclear RoB was most often due to problems with randomisation or blinding, and for six studies only a conference abstract was available thus RoB remained unclear. The detailed RoB assessment is presented in online supplementary tables (3.2.1-3.2.23).

Table 4 presents an overview of the main results of the most relevant pharmacological trials for which the outcomes pain, function, fulfilment of OARSI-OMERACT criteria[4] or grip strength could be assessed. Safety outcomes are presented in online supplementary table 4.2. Forest plots of pooled results are presented in online supplementary figures S9-S20.

Topical pharmacological interventions

Topical diclofenac gel was shown to be superior to placebo in a large RCT (low RoB), leading to small improvements in pain and function, and not more AEs, after 8 weeks.[52] Topical NSAIDs led to similar pain relief as oral NSAIDs,[50,51] yet lower risk of any AE (RR 0.40 (95% CI 0.09

to 1.74)),[50,51] gastro-intestinal AEs (RR 0.64 (0.35 to 1.20)),[51] severe AEs (RR 0.54 (0.17 to 1.71)),[51] and withdrawals due to AEs (RR 0.15 (0.03 to 0.63)) (online supplementary table 5.2, figures S9-11).[51] Pooled safety data from two RCTs comparing topical diclofenac gel to placebo in patients with hand OA showed similar and low rates of AEs in subgroups at low versus high risk of NSAID-related AEs (ie, age ≥65 years, and with comorbid hypertension, type 2 diabetes or cerebrovascular or cardiovascular disease).[53] A trial (low RoB) comparing topical ibuprofen cream to arnica cream found no between-group differences.[54] Two studies (one high RoB, one unclear RoB) comparing topical NSAIDs with a non-pharmacological treatment reported superiority of the comparator.[39,55] Topical capsaicin was assessed in one RCT (unclear RoB), reporting better pain relief than placebo at the cost of increased risk of local AEs (burning and stinging sensation, RR 3.1 (95% CI 1.1 to 8.5)), which likely also compromised the trial's success of blinding.[56] A single application of topical salicylates was reported in two trials (high RoB) to lead to improvements in pain and stiffness, but also numerically more local AEs.[57,58]

Oral analgesics

Paracetamol was included as a treatment arm in three conference abstracts (unclear RoB) and one cross-over trial (high RoB), in various dosages and for different duration.[48,59-61] Three trials intended paracetamol to be the control group. One trial (unclear RoB) included a placebo arm, and reports no between-group difference in pain or morning stiffness.[59] Paracetamol was not superior to any of the active comparators.[48,60,61]

Oral NSAIDs lead to moderate improvements in pain and function compared with no intervention,[49] placebo[62-64] and other active interventions (glucosamine/chondroitin sulfate,[65] paracetamol[48]).

Nutraceuticals

The effectiveness of chondroitin sulfate was studied in two papers. One trial (low RoB) focused on clinical outcomes after six months, reporting beneficial effects on pain and function compared with placebo.[66] The other study (high RoB) assessed structural outcomes in two long-term trials (published in one paper), assessing chondroitin sulfate and chondroitin polysulphate.[44] Only for chondroitin polysulphate, a preparation not commercially available, less erosive damage after 3 years was reported, and not for chondroitin sulfate. The trials did not report higher risk of AEs in the intervention groups.

Glucosamine is reported to have beneficial effects on pain and function after 6 weeks in an RCT (unclear RoB) published as conference abstract (no raw data provided).[61]

Diacerhein was not better than placebo for pain relief or any of the other secondary outcomes in a study (unclear RoB) of Korean patients with hand OA, while more (mild) AEs were reported in the intervention group, especially discoloration of urine (88% vs 20%) and abdominal pain (31% vs 14%), but remarkably not diarrhoea (21% vs 20%).[67]

Intra-articular treatments

Several intra-articular therapies were assessed, of which glucocorticoids and hyaluronic acid are the most commonly used. Intra-articular injection of glucocorticoids in the thumb base was not more beneficial than placebo with respect to pain and function (online supplementary figures S12-13),[68-70] while in one study (low RoB) participants reported less pain during movement and soft swelling after intra-articular glucocorticoid injection in IP joints.[71] However, the latter study did not find beneficial effects on pain in rest or function.

Intra-articular injection of hyaluronic acid in the thumb base did not lead to improvements in pain or function compared with placebo (online supplementary figure S14).[68,69,72] Six trials (four high RoB, two unclear RoB) compared intra-articular thumb base injection of glucocorticoids to hyaluronic acid, but no consistent beneficial effect of one treatment over the other could be shown.[68,69,73-76] Single studies (two high RoB, two unclear RoB) assessed alternative dosages (ie, one, two or three hyaluronic acid injections,[77] low vs high molecular weight hyaluronic acid[78]) and therapies (ie, intra-articular infliximab,[79] dextrose[80]), and are not described in depth.

Glucocorticoids and conventional or biological DMARDs

Short-term treatment with low-dose oral glucocorticoids were evaluated in two RCTs (low RoB). Six-week treatment with prednisolone/dipyridamole led to more improvement in pain (MD 12.3 (95% CI 3.0 to 21.5) on 100 mm VAS), at the cost of more withdrawals due to AEs (38% vs 15%), mostly due to headache.[81] In a trial of 4-week treatment with prednisolone 5 mg, however, no between-group differences were observed (eg, 100 mm VAS pain 19.9 mm in prednisolone vs 16.8 mm in placebo group).[82] Results could not be combined due to clinical heterogeneity and remain inconclusive.

Three RCTs (unclear RoB), only published as conference abstracts, show that hydroxychloroquine does not have beneficial effects on pain (online supplementary figure S15), function, grip strength or radiographic progression (only assessed by Kingsbury *et al*).[59,83,84] One trial also included a paracetamol arm and found no between-group differences compared with hydroxychloroquine on pain (MD 2.5 (95% CI -9.9 to 14.9) on 100 mm VAS, in favour of paracetamol).[59]

Four studies (two unclear RoB, two low RoB) assessed the efficacy of different TNF inhibitors (adalimumab[45,46,85] and etanercept[47,86,87]), but no beneficial effect over placebo could be shown on pain, function or grip strength (online supplementary figures S16-20). Two studies (one unclear RoB, one low RoB) report less erosive radiological progression after 1 year in treated joints with soft tissue swelling at baseline (no data to pool).[45,47] One RCT (low RoB) and one cross-over trial (unclear RoB) report no between-group differences in MRI synovitis, while only the RCT found a decrease in bone marrow lesions and the cross-over trial did not.[46,87]

Table 1. Characteristics of studies of main non-pharmacological interventions (n=28 studies)

RoB	Study	Design	Intervention
Exercise			
	Østeras 2017[6]	SLR (6 RCT, 1 CO)	Hand exercise vs no exercise (N=6); different CMC exercise programmes (N=1)
Joint protection			
	Dziedzic 2015[7]	Factorial RCT	Group-based joint protection programme (incl. splints) (JP+, HEx-) Group-based exercise programme (HEx+, JP-) Group-based combination programme: education, joint protection (incl. splints), exercise (JP+, HEx+) Education alone (JP-, HEx-)
Splints			
	Adams 2014[8] (A)	RCT	Splint + occupational therapy Placebo splint + occupational therapy Occupational therapy only
	Arazpour 2016[9]	RCT	Splint (custom-made, thermoplast, CMC) No intervention
	Bani 2013[16]	CO (WA+)	Splint (custom-made, thermoplast) Splint (prefabricated, neoprene, CMC/MCP) No intervention
	Becker 2013[13]	RCT	Splint (custom-made, thermoplast, CMC/MCP) Splint (prefabricated, neoprene, CMC)
	Cantero-Tellez 2016[14]	CCT	Splint (custom-made, thermoplast, CMC/MCP) Splint (custom-made, thermoplast, CMC)
	Gomes-Carreira 2010[10]	RCT	Splint (custom-made, CMC/MCP) No intervention
	Hermann 2013[11]	RCT	Splint + hand exercises (prefabricated, fabrifoam, CMC/MCP) Hand exercises
	Rannou 2009[12]	RCT	Splint (custom-made, neoprene, CMC/MCP) Usual care
	Sillem 2011[17]	CO (WA+)	Splint (custom-made, neoprene, CMC/MCP) Splint (prefabricated, neoprene, IP to wrist)
	Wajon 2005[15]	RCT	Splint (custom-made, thermoplast, CMC) + abduction exercise regimen Splint (custom-made, thermoplast, CMC/MCP) + pinch exercise regimen
	Watt 2014[21]	CCT	Splint (custom-made, thermoplast, DIP) No intervention

	Frequency, duration (instructions)	N	OA location, definition	Women (%)	Age (years)	Primary outcome
	6 w to 12 mo	534	Hand (6) or CMC (1), ACR or clinical diagnosis	Median 90	Mean 60-81	-
	4 sessions in 4 w	62	ACR	69	65.5 (8.6)	OARSI-OMERACT responder
		65		63	64.5 (9.0)	
		65		71	66.0 (9.3)	
	4 w	65		62	67.2 (9.5)	
	4 w (NR)	9	CMC, NR	78	61.2 (9.4)	AUSCAN pain
		9				
		9				
	4 w (use during ADLs, not at night)	16	CMC, clinical diagnosis and E-L stage I-II	87	50.2 (5.7)	NR
		9		88	52.3 (6.4)	
	4 w (use during ADLs, not at night)	24	CMC, clinical diagnosis and E-L stage I-II	67	53.4	NR
				75	54.9	
	4 w	11		73	58.6	
	8-10 w (use as needed during ADLs and at night)	58	CMC, clinical diagnosis	80	62.8 (7.7)	DASH
		61		75	63.3 (8.5)	
	12 w (use during ADLs (3-4 h/d) and at night)	44	CMC, clinical and Rx diagnosis	93	59.7 (9.6)	NR
		40		90	60.5 (9.8)	
	12 w (NR)	20	CMC, clinical diagnosis and E-L stage II-III	100	62.8 (8.5)	VAS pain
		20		90	65.1 (10.1)	
	8 w (use as needed)	30	CMC, ACR, thumb pain	97	70.7 (7.3)	NRS pain
		29		100	70.2 (6.2)	
	1 y (use at night)	57	CMC, clinical and Rx diagnosis	93	63.0 (7.9)	VAS pain
		55		85	63.5 (7.6)	
	4 w (use when symptomatic, during heavy tasks, and at night if preferred)	56	CMC, clinical diagnosis	91	64.1 (8.6)	AUSCAN function
	2 w splint only, 4 w splint + exercise (use full-time)	19	CMC, clinical diagnosis and E-L stage I-III	74	59.7 (9.0)	NR
		21		81	61.2 (12.5)	
	12 w (use at night)	26	DIP, ACR, Rx damage DIP	88	63 (51-78)	NRS pain
		26				

Table 1. Continued

RoB	Study	Design	Intervention
	Weiss 2000[19]	CO (WA-)	Splint (custom-made, thermoplast, CMC) Splint (custom-made, thermoplast, CMC to wrist)
	Weiss 2004[20]	CO (WA-)	Splint (custom-made, thermoplast, CMC) Splint (prefabricated, neoprene, CMC/MCP)
	Van der Vegt 2017[18]	CO (WA+)	Splint (custom-made, thermoplast, CMC/MCP) Splint (prefabricated, semi-rigid, CMC)
Assistive devices			
	Kjeken 2011[22]	RCT	Provision of assistive devices + information Information alone
Combination programmes			
	Boustedt 2009[23]	RCT	Group-based combination programme: education, joint protection, exercise, splints Group-based joint protection programme
	Dziedzic 2015[7]	Factorial RCT	Group-based joint protection programme (incl. splints) (JP+, HEx-) Group-based exercise programme (HEx+, JP-) Group-based combination programme: education, joint protection (incl. splints), exercise (JP+, HEx+) Education alone (JP-, HEx-)
	Perez-Marmol 2017[24]	RCT	Fine motor skills occupational therapy Conventional occupational therapy
	Stamm 2002[25]	CCT	Individual combination programme: education, joint protection, exercise Education alone
	Stukstette 2013[26]	RCT	Group-based combination programme: education, joint protection (incl. splints), exercise Education alone
	Stukstette 2014[27] (A)	RCT	Group-based booster session after combination programme[26] No booster session after combination programme[26]
	Villafane 2013[28]	RCT	Individual combination programme: manual therapy, exercise Sham intervention (nontherapeutic ultrasound of the thumb region)
	Wajon 2005[15]	RCT	Splint (custom-made, thermoplast, CMC) + abduction exercise regimen Splint (custom-made, thermoplast, CMC/MCP) + pinch exercise regimen

Values are mean (SD) or median (min-max). Colours denote RoB (green: low, yellow: unclear, red: high). (A) indicates conference abstract. ACR, American College of Rheumatology; ADLs, activities of daily living; AUSCAN, Australian/Canadian Hand Osteoarthritis Index, CMC, first carpometacarpal joint; CO, cross-over trial; COPM, Canadian Occupational Performance Measure; d, day(s); DASH, Disabilities of the Arm, Shoulder and Hand; DIP, distal

	Frequency, duration (instructions)	N	OA location, definition	Women (%)	Age (years)	Primary outcome
	1 w (use when symptomatic)	26	CMC, clinical and Rx diagnosis	81	57 (36-88)	NR
	1 w (use when symptomatic)	25	CMC, clinical diagnosis and E-L stage I-II	84	NR	NR
	2 w (NR)	63	CMC, clinical and Rx diagnosis	70	60.1 (8.2)	VAS pain
	12 w (NR)	35	ACR	97	61.1 (6.0)	COPM
		35		97	59.9 (7.5)	
	10 sessions in 5 w	22	CMC, clinical and Rx diagnosis	100	61 (40-76)	NR
		20			61 (50-76)	
	4 sessions in 4 w	62	ACR	69	65.5 (8.6)	OARSI-OMERACT responder
		65		63	64.5 (9.0)	
		65		71	66.0 (9.3)	
	4 w	65		62	67.2 (9.5)	
	24 sessions in 8 w	25	Clinical diagnosis	84	82.8 (8.3)	DASH
		23		74	79.2 (10)	
	Single session, 3 mo	20	ACR	85	60.5 (8.3)	Grip strength
	3 mo	20		90	60.4 (6.4)	
	4 sessions in 12 w	76	ACR	82	60 (7)	AUSCAN function, OARSI-OMERACT responder
	12 w	75		84	58 (9)	
	Single session, 1 y	147	ACR	84	59 (8)	AUSCAN function, OARSI-OMERACT responder
	1 y					
	12 sessions in 4 w	30	CMC, clinical diagnosis and Rx damage	90	82 (2)	VAS pain
		30		80	83 (1)	
	2 w splint only, 4 w splint + excercise; use full-time	19	CMC, clinical diagnosis and E-L stage I-III	74	59.7 (9.0)	NR
		21		81	61.2 (12.5)	

interphalangeal joint; E-L, Eaton-Litter; FIHOA, Functional Index for Hand OsteoArthritis; h, hour(s); IP, interphalangeal joint; IQR, interquartile range; min, minute(s); N, number; NR, not reported; NRS, numerical rating scale; MCP, metacarpophalangeal; mo, month(s); OA, osteoarthritis; RCT, randomised controlled trial; RoB, risk of bias; Rx, radiography; SLR, systematic literature review; VAS, visual analogue scale; w, week(s); WA, wash-out period; y, year(s).

Table 2. Efficacy of main non-pharmacological interventions for hand osteoarthritis from RCTs/CCTs

Intervention	Control	Outcome	Number of participants (studies)	Duration
Exercise				
Hand exercise	No exercise	Pain	381 (5)	12 w
		Function	369 (4)	12 w
		OARSI-OMERACT responder	305 (3)	12 w
		Grip strength	362 (5)	12 w
Joint protection				
Joint protection	No joint protection	Pain	257 (1)	26 w
		Function	257 (1)	26 w
		OARSI-OMERACT responder	257 (1)	26 w
		Grip strength	257 (1)	26 w
Splints				
Thumb splint	Usual care or no intervention	Pain	221 (4)	4-8 w
		Pain	137 (2)	13-52 w
		Function	144 (3)	4 w
		Function	112 (1)	52 w
		Grip strength	95 (2)	6-8 w
		Grip strength	40 (1)	13 w
Long thumb splint (MCP + CMC joint)	Short thumb splint (only CMC joint)	Pain	185 (3)	2-12 w
		Function	146 (2)	9-12 w
DIP splint	No intervention	Pain	26 (1)	12 w
		Function	26 (1)	12 w
Assistive devices				
Assistive device	Information provision	Pain	70 (1)	12 w
		Function	70 (1)	12 w
Combination programmes				
Combination programme: education, joint protection, exercise	Education alone	Pain	321 (3)	12 w
		Function	321 (3)	12 w

	Quality of evidence	Effect estimate (95% CI)	References; Comments
	GRADE: Low	SMD -0.27 (-0.47;-0.07)*	[6]; Cochrane review
	GRADE: Low	SMD -0.28 (-0.58;0.02)*	idem
	Not reported	RR 2.8 (1.4;5.6)*	idem
	Not reported	SMD 0.34 (-0.01;0.69)*	idem
	RoB: High	MD -0.79 (-1.7;0.12) on AUSCAN pain scale (range 0-20)*	[7]; Adjusted for age, gender, social class, center, disease duration
	RoB: High	MD -0.6 (-1.9;1.1) on AUSCAN function scale (range 0-36)*	idem
	RoB: High	OR 2.1 (1.1;4.0)*	idem
	RoB: High	MD -0.47 (-1.9;0.94) kg†	idem
	RoB: High	MD -2.9 (-12.2;6.5) on 100 mm VAS*	[9-12]
	RoB: High	MD -17.4 (-25.6;-9.2) on 100 mm VAS*	[10,12]
	RoB: High	SMD 0.24 (-0.11;0.60)†	[8,9,12]; Effect estimate based on 2 trials (n=126)[9,12]
	RoB: High	MD -6.3 (-10.9;-1.7) on Cochin hand function scale (range 0-90)*	[12]
	RoB: High	SMD 0.39 (-0.35;1.1)*	[10,11]
	RoB: High	MD 0.8 (-3.1;4.7) kg*	[10]
	RoB: High	MD -0.85 (-5.1;3.4) on 100 mm VAS*	[13-15]; Wajon: results after splint period used for pooling
	RoB: High	MD 1.7 (-0.94;4.3)†	[13,14]
	RoB: High	Median difference -0.5 (range -7;3.5, p=0.53) on 10 cm VAS*	[21]; Outcome: average pain
	RoB: High	No between-group difference	[21]; No raw data presented
	RoB: High	MD 0.4 (-9.8;10.6) on 100 mm VAS†	[22]; Adjusted for baseline
	RoB: High	MD -0.3 (-0.6;0.01) on AUSCAN function scale (range 1-5)*	[22]; Adjusted for baseline, COPM scores (primary outcome) also significant improvements*
	RoB: High	MD 0.40 (-0.50;1.3) on AUSCAN pain scale (range 0-20)**	[7,25,26]; Effect estimate based on 1 trial (n=151)[26], adjusted for baseline
	RoB: High	MD 0.49 (-1.0;2.0) on AUSCAN function scale (range 0-36)*	[7,25,26]; Effect estimate based on 1 trial (n=151)[26], adjusted for baseline

Table 2. Continued

Intervention	Control	Outcome	Number of participants (studies)	Duration
		OARSI-OMERACT responder	281 (2)	12 w
		Grip strength	321 (3)	12 w
Quality of evidence:	GRADE: very low / low RoB: high	GRADE: moderate RoB: unclear	GRADE: high RoB: low	

*In favour of the intervention group, †In favour of the control group. AUSCAN, Australian/Canadian hand osteoarthritis index; CMC, first carpometacarpal; COPM, Canadian Occupational Performance Measure; DIP, distal interphalangeal joint; idem, same as above; MCP, metacarpophalangeal joint; MD, mean difference; OA, osteoarthritis; RoB, risk of bias; RR, risk ratio; SMD, standardised mean difference; VAS, visual analogue scale; w, week(s).

Table 3. Characteristics of studies of main pharmacological interventions (n=33 studies)

RoB	Study	Design	Intervention
Topical NSAIDs			
	Altman 2009[52]	RCT	Topical diclofenac gel 1% Topical placebo cream
	Graber 1997[39]	RCT	Topical ibuprofen cream Berthollet treatment (local steam bath and finger shower)
	Michalsen 2008[92]	RCT	Diclofenac gel 10mg/g Medicinal leeches
	Romero 2013[55]	RCT	Topical diclofenac gel 2% Topical herbal cream
	Talke 1985[50]	RCT	Topical etofenamate 100 mg/g Oral indomethacin 150 mg/d
	Widrig 2007[54]	RCT	Topical ibuprofen cream 5% Topical arnica cream 50%
	Zacher 2001[51]	RCT	Topical diclofenac gel 1% Oral ibuprofen 1200 mg/d
Oral NSAIDs			
	Dreiser 1993[62]	RCT	Ibuprofen 800 mg/d Placebo
	Grifka 2004[63]	RCT	Lumiracoxib 200 mg/d Lumiracoxib 400 mg/d Placebo
	Muratore 2004[65] (A)	RCT	Ketoprofen lysine salt 160 mg/d + glucosamine + chondroitin sulfate Glucosamine + chondroitin sulfate

	Quality of evidence	Effect estimate (95% CI)		References; Comments
	RoB: High	OR 0.82 (0.42;1.6)†		[7,26]; Effect estimate based on 1 trial (n=151)[26]
	RoB: High	SMD -0.21 (-0.49;0.08)†		[7,25,26]; Effect estimate based on 2 trials (n=186)[25,26]
		Effect estimate:	No effect	Between-group difference

	Frequency, duration	N	OA location, definition	Women (%)	Age (years)	Primary outcome
	4 per day, 8 w	198	ACR, Rx KL 1-3	77	63.6 (10.3)	VAS pain, AUSCAN, VAS patient global
		187		77	64.7 (9.6)	
	3 per day, 2 w	57	ACR or clinical diagnosis isolated CMC OA	91	65.8 (8.6)	FIHOA
	Daily, 3 w	59		86	63.2 (10.0)	
	2 per day, 4 w	16	CMC, clinical diagnosis and Rx damage	100	64.3 (9.1)	VAS pain
	Once in 4 w	16			64.1 (6.4)	
	3 per day, 4 w	65	ACR	86	62 (10.2)	NR
		65		95		
	3 per day, 3 w	30	IP, clinical diagnosis, "activated"	83	64.3 (13.5)	NR
	3 w	30		90	63.3 (11.0)	
	3 per day, 3 w	99	ACR	61	64 (11.4)	VAS pain, FIHOA
		105		67	64 (12.0)	
	4 per day, 3 w	165	IP, clinical diagnosis, "activated"	86	60.7 (9.4)	VAS pain improve ≥40%
	3 w	156		90	63.2 (9.4)	
	2 w	30	Rx damage, pain exacerbation	80	58.5 (1.7)	NR
		30		90	60.3 (2.0)	
	4 w	205	ACR	82	62.0 (12.1)	VAS pain
		193		83	61.0 (12.4)	
		196		83	62.7 (11.7)	
	20 d	30	Hand, NR	100	NR	NR
		28				

Table 3. Continued

RoB	Study	Design	Intervention
	Rovetta 2001-B[49]	CCT	Dexketoprofen-trometamol 50 mg/d No intervention
	Rovetta 2001-A[48]	CO (WA-)	Dexketoprofen-trometamol 50 mg/d Paracetamol 1000 mg/d
	Seiler 1983[64]	RCT	Meclofenamate socium 300 mg/d Placebo
	Talke 1985[50]	RCT	Oral indomethacin 150 mg/d Topical etofenamate 100 mg/g
	Zacher 2001[51]	RCT	Oral ibuprofen 1200 mg/d Topical diclofenac gel 1%
Chondroitin sulfate			
	Gabay 2011[66]	RCT	Chondroitin sulfate 800 mg/d Placebo
	Verbruggen 2002[44]	RCT	Chondroitin polysulphate 50 mg/d i.m Placebo i.m.
		RCT	Chondroitin sulfate 1200 mg/d Placebo
Intra-articular glucocorticoids			
	Bahadir 2009[73]	RCT	Glucocorticoid i.a. 20 mg/0.5 ml Hyaluronic acid i.a. 5 mg/ 0.5 ml
	Fuchs 2006[74]	RCT	Glucocorticoid i.a. 10 mg/1 ml Hyaluronic acid i.a. 10 mg/1 ml
	Heyworth 2008[68]	RCT	Glucocorticoids i.a. 1 ml Hyaluronic acid i.a. 8 mg/1 ml Placebo i.a. (1 ml, saline)
	Jahangiri 2014[93]	RCT	Gluocorticoid i.a. 40 mg/0.5 ml + 0.5 ml lidocaine Dextrose i.a. 100 mg/0.5 ml + 0.5 ml lidocaine
	Mandl 2012[69](A)	RCT	Glucocorticoid i.a. 40 mg/1 ml Hyaluronic acid i.a. 8 mg/1 ml Placebo i.a. (1 ml, bupivacaine)
	Meenagh 2004[70]	RCT	Glucocorticoid i.a. 5 mg/0.25 ml Placebo i.a. (0.25 ml, saline)
	Monfort 2014[75]	RCT	Glucocorticoid i.a. 3 mg/ 0.5 ml Hyaluronic acid i.a. 5 mg/0.5 ml

Frequency, duration	N	OA location, definition	Women (%)	Age (years)	Primary outcome
3 w	35	ACR, "active OA"	86	57.7 (3.4)	Morning stiffness (WOMAC)
	19		63		
13 d	36	ACR, "active OA"	NR	NR	Morning stiffness and pain (WOMAC)
4 w	22	Clinical diagnosis, ≥1 inflamed DIP and Rx damage	95	62.5 (34-77)	NR
	19		84	65.0 (49-80)	
3 w	30	IP, clinical diagnosis, "activated"	83	64.3 (13.5)	NR
3 per day, 3 w	30		90	63.3 (11.0)	
3 w	156	IP, clinical diagnosis, "activated"	90	63.2 (9.4)	VAS pain improve ≥40%
4 per day, 3 w	165		86	60.7 (9.4)	
6 mo	80	ACR	73	63.9 (8.5)	VAS pain, FIHOA
	82		76	63.0 (7.2)	
3 y	66	IP, clinical diagnosis and Rx damage	91	55.2 (6.7)	Rx progression
	64		97	56.1 (9.2)	
3 y	44	IP, clinical diagnosis and Rx damage	91	57.6 (7.1)	Rx progression
	48		88	55.9 (8.9)	
Once	20	CMC, Rx E-L stage II-III	100	62.9 (9.1)	NR
1 per w, 3 w	20			60.8 (7.3)	
1 per w, 3 w	28	CMC, clinical diagnosis and Rx KL >0	80	Median 61.0	NR
	28			Median 59.5	
Once + 1 i.a. placebo, 2 w	22	CMC, Rx E-L stage I-IV	90	60 (9.4)	NR
1 per w, 2 w	28		80	65 (10.6)	
1 per w, 2 w	18		89	64 (8.5)	
Once + 2 i.a. placebo, 3 w	30	CMC, clinical diagnosis and Rx E-L stage >I	70	63.3 (10.1)	VAS pain
1 per w, 3 w	30		77	63.9 (9.4)	
Once + 1 i.a. placebo, 2 w	65	CMC, clinical diagnosis and Rx KL >0	68	66.5 (45-89)	NR
1 per w, 2 w	62				
1 per w, 2 w	61				
Once	20	CMC, NR	95	60.6 (41-71)	VAS pain improve ≥20%
	20		85	59.3 (46-69)	
1 per w, 3w	40	CMC, clinical diagnosis and Rx KL 1-3	88	62.8 (8.7)	FIHOA
	48				

Table 3. Continued

RoB	Study	Design	Intervention
	Spolidoro 2015[71]	RCT	Glucocorticoid i.a. 4 mg/0.2 ml (DIP) or 6 mg/0.3 ml (PIP) + 0.1 ml lidocaine Placebo i.a. (0.1 ml, lidocaine)
	Stahl 2005[76]	RCT	Glucocorticoid i.a. 40 mg/1 ml Hyaluronic acid i.a. 15 mg/1 ml
Oral glucocorticoids			
	Kvien 2008[81]	RCT	Prednisone 3 mg/d + dipyridamole 200 mg/d Placebo
	Wenham 2012[82]	RCT	Prednisone 5 mg/d Placebo
Hydroxychloroquine			
	Basoski 2015[83](A)	RCT	Hydroxychloroquine 400 mg/d Placebo
	Kingsbury 2016[84](A)	RCT	Hydroxychloroquine 200-400 mg/d Placebo
	McKendry 2001[59] (A)	RCT	Hydroxychloroquine 400 mg/d Paracetamol 3900 mg/d Placebo
TNF inhibitors			
	Aitken 2017[46](A)	CO (WA+)	Adalimumab 40 mg sc. Placebo sc.
	Chevalier 2015[85]	RCT	Adalimumab 40 mg sc. Placebo sc.
	Kloppenburg 2016[47,86,87] (A)	RCT	Etanercept 25-50 mg sc. Placebo sc.
	Verbruggen 2012[45]	RCT	Adalimumab 40 mg sc. Placebo sc.

Values are mean (SD) or median (min-max). Colours denote RoB (green: low, yellow: unclear, red: high). (A) indicates conference abstract. ACR, American College of Rheumatology; AUSCAN, Australian/Canadian Hand Osteoarthritis Index, CCT, clinical controlled trial; CMC, first carpometacarpal joint; CO, cross-over trial; d, day(s); E-L, Eaton-Litter; FIHOA, Functional Index for Hand OsteoArthritis; i.a., intra-articular injection; IP, interphalangeal joint; IQR,

Frequency, duration	N	OA location, definition	Women (%)	Age (years)	Primary outcome
Once	30 30	IP, clinical diagnosis and Rx osteophyte	100 93	60.7 (9.1) 60.7 (7.3)	VAS pain, VAS joint swelling
Once	25 27	CMC, Rx E-L stage II	84 92.5	62 (50-91) 62 (37-80)	NR
6 w	42 41	ACR, Rx KL >1	93 93	61.1 (5.0) 59.6 (5.3)	AUSCAN pain
4 w	35 35	ACR, Rx KL >0	74 89	61.9 (6.6) 61.1 (9.0)	VAS pain
24 w	98 98	ACR	86	57	VAS pain
1 y	124 124	ACR	NR	NR	NRS pain
24 w	29 29 30	Hand, NR	NR	NR	NR
2 sc. per 2 w, 12 w	43	ACR, erosive (Rx erosion), MRI synovitis	77	61 (8.4)	AUSCAN pain
Once 2 sc., 2 w	42 43	ACR, Rx damage IPs	87 83	62.8 (6.9) 62.2 (7.0)	VAS pain improve ≥50%
1 sc. per w, 1 y	45 45	IP, ACR, erosive (Rx erosion IP)	82 80	59.4 (6.5) 60.1 (8.7)	VAS pain
1 sc. per 2 w, 1 y	30 30	IP, ACR, erosive (Rx erosion IP)	87 83	61.9 (6.1) 60.7 (6.9)	Rx progression

interquartile range; KL, Kellgren-Lawrence; NR, not reported; NRS, numerical rating scale; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; RCT, randomised controlled trial; RoB, risk of bias; Rx, radiography; sc., subcutaneous injection; TNF, tumour necrosis factor; VAS, visual analogue scale; w, week(s); WA, wash-out period; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; y, year(s).

Table 4. Efficacy of main pharmacological interventions for hand osteoarthritis from RCTs/CCTs

Intervention	Control	Outcome	Number of participants (studies)	Duration	Specific OA location or type
Topical NSAIDs					
Topical NSAID	Topical placebo	Pain	385 (1)	8 w	-
		Function	385 (1)	8 w	-
		OARSI-OMERACT response	385 (1)	8 w	-
Topical NSAID	Oral NSAID	Pain	381 (2)	3 w	"activated" IP OA
		Grip strength	381 (2)	3 w	"activated" IP OA
Oral NSAIDs					
Oral NSAID	Placebo	Pain	695 (3)	2-4 w	-
		Function	695 (3)	2-4 w	-
Chondroitin sulfate					
Chondroitin sulfate	Placebo	Pain	162 (1)	26 w	-
		Function	162 (1)	26 w	-
		Grip strength	162 (1)	26 w	-
Intra-articular therapies					
Intra-articular glucocorticoids	Intra-articular placebo	Pain	206 (3)	26 w	CMC
		Function	166 (2)	26 w	CMC
Intra-articular glucocorticoids	Intra-articular placebo	Pain	60 (1)	12 w	IP
		Function	60 (1)	12 w	IP
		Grip strength	60 (1)	12 w	IP
Intra-articular hyaluronic acid	Intra-articular placebo	Pain	235 (3)	26 w	CMC
		Function	235 (3)	26 w	CMC
Hydroxychloroquine					
Hydroxychloroquine	Placebo	Pain	503 (3)	24-52 w	-
		Function	444 (2)	24-52 w	-
		Grip strength	248 (1)	52 w	-

	Quality of evidence	Effect estimate (95% CI)	References; Comments
	RoB: Low	MD -5.9 (-11.7;-0.06) on 100mm VAS*	[52]
	RoB: Low	MD -7.3 (-12.9;-1.7) on AUSCAN function scale (range 0-36)*	[52]
	RoB: Low	RR 1.2 (0.99;1.4)*	[52]
	RoB: Low	SMD -0.05 (-0.27;0.17)*	[50,51]; Effect estimate based on 1 trial (n=321)[51]; same studies as previous SLR[1]
	RoB: Low	MD -0.01 (-0.03;0.01) bar*	[50,51]; Effect estimate based on 1 trial (n=321)[51]
	RoB: Low	SMD 0.40 (0.20;0.60)*	[62-64]; Effect estimate based on 2 trials with ibuprofen 800mg and lumiracoxib 200-400mg (n=654)[62,63]; same studies as previous SLR[1]
	RoB: Low	SMD 0.17 (-0.03;0.36)*	idem
	RoB: Low	MD -8.7 (p=0.016) on 100mm VAS*	[66]
	RoB: Low	MD -2.1 (p=0.008) on FIHOA (range 0-30)*	[66]
	RoB: Low	MD 1.9 (-0.02;3.8) kg*	[66]
	RoB: Low (1), unclear (1)	MD -3.6 (-13.9;6.8) on 100mm VAS*	[68-70]; Effect estimate based on 2 trials (n=166)[69,70]
	RoB: Unclear	MD -1.5 (-6.3;3.3) on DASH (range 0-100)*	[68,69]; Effect estimate based on 1 trial (n=126)[69]
	RoB: Low	MD -18.0 (-33.5;-2.6) on 100mm VAS*	[71]; Outcome: pain on movement; for pain in rest no between-group differences observed
	RoB: Low	MD -4.4 (-9.4;0.56) on AUSCAN function scale (range 0-36)*	[71]
	RoB: Low	MD 0.98 (-2.6;4.5) kg*	[71]
	RoB: Unclear	MD 3.3 (-5.2;11.8) on 100mm VAS†	[68,69,72]; Effect estimate based on 1 trial (n=123)[69]
	RoB: Unclear	MD -2.1 (-6.3;2.1) on DASH (range 0-100)*	idem
	RoB: Unclear	MD 2.9 (-3.4;9.2) on 100mm VAS†	[59,83,84]; Effect estimate based on 2 trials (n=307)[59,84]
	RoB: Unclear	MD -0.79 (-2.4;0.78) on AUSCAN function scale (range 0-36)†	[83,84]; Effect estimate based on 1 trial (n=248)[84]
	RoB: Unclear	MD 0.95 (-0.82;2.72) kg†	[84]

Table 4. Continued

Intervention	Control	Outcome	Number of participants (studies)	Duration	Specific OA location or type
TNF inhibitors					
TNF inhibitor	Placebo	Pain	235 (3)	24-52 w	Erosive OA (2/3 trials)
		Function	235 (3)	24-52 w	Erosive OA (2/3 trials)
		Grip strength	150 (2)	52 w	Erosive OA
Quality of evidence:	GRADE: very low / low RoB: high	GRADE: moderate RoB: unclear	GRADE: high RoB: low		

*In favour of the intervention group, †In favour of the control group. AUSCAN, Australian/Canadian hand osteoarthritis index; CMC, first carpometacarpal joint; DASH, Disabilities of the Arm, Shoulder and Hand; DIP, distal interphalangeal joint; idem, same as above; IP, interphalangeal joint; MD, mean difference; mm, millimetre; NSAID, non-steroidal anti-

Surgical interventions

A Cochrane review summarised all available trials of thumb base surgery.[88] No trials compared surgery to sham surgery or non-operative treatment. The trials all compared different surgical interventions for thumb base OA. Most trials compared trapeziectomy with and without ligament reconstruction tendon interposition (LRTI), but there was no difference in pain (three trials with 162 participants, MD -2.8 (95% CI -9.8 to 4.2) on 100 mm VAS) or function (three trials with 211 participants, SMD 0.01 (95% CI -0.30 to 0.32)), while the risk for more complications was increased in the trapeziectomy with LRTI groups (RR 1.9 (95% CI 0.96 to 3.7)). Single, low-quality studies compared other surgical interventions to each other, but did not show that one intervention was clearly superior over another in terms of efficacy or complication rate. Most importantly, compared with trapeziectomy, both arthrodesis (one trial, 37 participants) and joint replacement surgery (one trial, 26 participants) did not lead to different clinical outcomes. No studies of IP joint surgery could be included in our review.

DISCUSSION

This SLR summarises the current evidence for efficacy and safety of all non-pharmacological, pharmacological and surgical treatments for hand OA. Non-pharmacological treatments that were shown to result in symptom relief included hand exercise and prolonged splinting of the thumb base, while single trials showed positive results for joint protection and use of assistive devices. However, the RoB in most trials was high, mainly due to lack of blinding and effect sizes were modest. Pharmacological treatments that most evidently proved to be efficacious in relieving symptoms were NSAIDs, both topical and oral preparations, as assessed in high-quality trials. Single trials, also judged to be at low RoB, reported beneficial results for

	Quality of evidence	Effect estimate (95% CI)		References; Comments
	RoB: Low	MD -4.9 (-12.5;2.8) on 100mm VAS*		[45,85,86]; Effect estimate based on 2 trials (n=175)[85,86]
	RoB: Low (1), unclear (1)	SMD -0.02 (-0.35;0.32)*		[45,85,86]; Effect estimate based on 2 trials (n=145)[45,85]
	RoB: Low (1), unclear (1)	MD 0.70 (-0.59;2.0) kg*		[45,86]; Effect estimate based on 1 trial (n=60)[45]
	Effect estimate:	No effect	Between-group difference	

inflammatory drug; OA, osteoarthritis; OR, odds ratio; RoB, risk of bias; RR, risk ratio; SLR, systematic literature review; SMD, standardised mean difference; TNF, tumour necrosis factor; VAS, visual analogue scale; w, week(s).

chondroitin sulfate and intra-articular injections of glucocorticoids in interphalangeal OA. Also for pharmacological interventions, effect sizes were modest, as considered using the cut-offs proposed by Cohen *et al* (ie, 0.2 representing a small, >0.5 a moderate and >0.8 a large effect).[89] The effect of oral NSAIDs on pain, with an SMD of 0.4, was the largest effect. Taking an effect size of 0.37 as a minimal clinically important difference (MCID; based on the median MCID in four recent OA trials[90]), corresponding to 9 mm on a 100 mm VAS, only the effects of prolonged thumb base splinting, oral NSAIDs and intra-articular glucocorticoid injections in interphalangeal joints crossed the margin of clinical meaningful difference. Promising pharmacological treatments for which no clear beneficial effect was demonstrated include paracetamol, intra-articular injections of glucocorticoids or hyaluronic acid in the thumb base joint, low-dose oral glucocorticoids, hydroxychloroquine and TNF inhibitors. Disease-modifying properties, especially radiographic progression, were studied in only a few trials. No convincing effects were found for the formulations investigated, namely chondroitin sulfate (one trial) and TNF inhibitors (two trials). A signal for less erosive damage after 1 year of treatment with anti-TNF was reported in subgroup analyses of joints with clinical signs of inflammation at baseline in two separate trials, yet studies powered for this research question have not been performed to confirm this finding.

Safety was also evaluated in this SLR, though it should be noted that this outcome is best studied in large long-term observational studies with high-quality follow-up since RCTs are usually underpowered to assess this outcome and include a more selected population. Although we aimed to include observational studies for this purpose, we did not find any with our search strategy. Based on this SLR, it is therefore not possible to draw strong conclusions on the safety aspect of many of the assessed therapies. Importantly, the included trials of topical and oral NSAIDs showed that, while no difference in efficacy could be proven, topical NSAIDs were indeed associated with less AEs than oral NSAIDs. Furthermore, no increased risk of AEs was shown for topical NSAIDs compared with placebo. These observations support topical

NSAIDs as a useful option for first-line pharmacological treatment. Regarding surgical options, no specific intervention for thumb base OA appeared more effective than another, although in general more complex procedures led to more complications.

The trials included in this review were rather heterogeneous in many aspects, for example in the type of intervention, study duration, and assessed outcomes. This precluded meta-analysis in most instances. Some more recently published trials assessed more of the outcome measures summarised in the OMERACT core set for domains in clinical trials for hand OA.[3] A core set for the instruments best used to measure these core domains is still underway. It may be expected that such a core set of instruments will help to harmonise outcome assessment in future clinical trials, which will ultimately improve the assessment of new treatment options.

Despite the large increase in the amount of trials published in the field of hand OA since the previous EULAR management recommendations in 2007 (39 out of 50 and 43 out of 64 included trials of non-pharmacological and pharmacological therapies, respectively, were published in 2007 or later), some important questions remain. For example, placebo-controlled trials of thumb base splints, paracetamol, tramadol and surgery (both for thumb base and interphalangeal OA) are lacking. Moreover, while some trials specifically include a subset of participants with OA of the thumb base, or with "inflammatory" or "activated" (finger) OA, more trials targeting specific subsets of patients expected to respond to the investigated treatment are needed. Furthermore, many studies were assessed to be at high RoB, often due to lack of blinding or inadequate method of randomisation. So although the number of trials may have increased, their quality is not consistent. For some interventions, especially non-pharmacological therapies, it is difficult to perform a double-blind trial, and therefore the evidence currently available is probably the best we can get. Recently, the Consolidated Standards of Reporting Trials has issued a statement addressing methodological issues specific to trials of non-pharmacological treatments to provide more guidance in this respect.[91] However, other interventions, especially pharmacological therapies, are more easily studied in a double-blind fashion, and therefore, well-performed trials are needed and may change the conclusions of this review, for example for paracetamol.

This SLR has a few strengths, most importantly the methodological rigour with which it was performed, and the presentation of a comprehensive summary of the vast amount of data on the management of hand OA that has accrued so far. However, some limitations have to be acknowledged. Study selection and data extraction was performed by one review author, whereas this should ideally be performed by two independent persons. Many studies were only published as a conference abstract at the time of manuscript preparation, precluding an assessment of the RoB (now categorised as 'unclear').

In conclusion, this paper presents the current evidence on efficacy and safety of all non-pharmacological, pharmacological, and surgical treatments for hand OA, and was used to inform the task force for the 2018 update of the EULAR recommendations for the management of hand OA.

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