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REVIEW

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

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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.

Key messages

What is already known about this subject?

► The first European League Against Rheumatism (EULAR) recommendations for the management of hand osteoarthritis were published in 2007, based on expert opinion and available literature at that time.

What does this study add?

► Since 2007 many new trials were published in the hand osteoarthritis field.

► This systematic literature review provides an updated overview of the current evidence on efficacy and safety of non-pharmacological, pharmacological and surgical treatment options for hand osteoarthritis.

How might this impact on clinical practice?

► This systematic literature review informed the task force for the 2018 update of the EULAR recommendations for the management of hand osteoarthritis.

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 patients with hand OA 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 have 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 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.

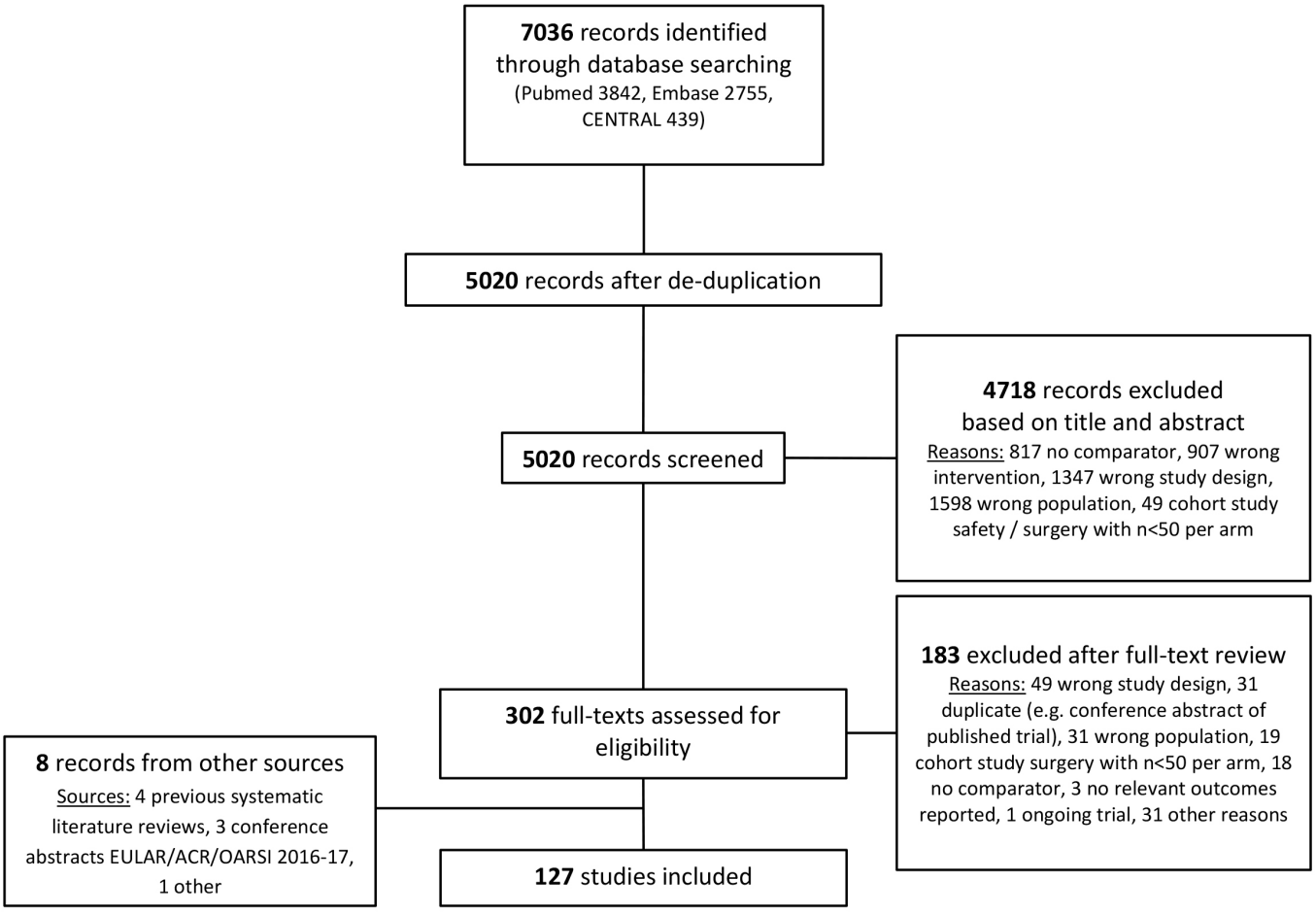

Figure 1 Flow chart of systematic literature review. ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; OARSI, Osteoarthritis Research Society International.

Pharmacological interventions were investigated in 64 studies, including one observational study. Surgical interventions were assessed in 11 trials, all summarised in one Cochrane 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]

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

RoB	Study	Design	Intervention	Frequency, duration (instructions)	N	OA location, definition	Women (%)	Age (years)	Primary outcome
Exercise									
	Østeras *et al* 2017[6]	SLR (6 RCT, 1 CO)	Hand exercise vs no exercise (N=6); different CMC exercise programme (N=1)	6–12 months	534	Hand (6) or CMC (1), ACR or clinical diagnosis	Median 90	Mean 60–81	–
Joint protection									
	Dziedzic *et al* 2015[7]	Factorial RCT	Group-based joint protection programme (including splints) (JP+, HEx–)	4 sessions in 4 weeks	62	ACR	69	65.5 (8.6)	OARSI-OMERACT responder
			Group-based exercise programme(HEx+, JP–)		65		63	64.5 (9.0)	
			Group-based combination programme: education, joint protection (including splints), exercise (JP+, HEx+)		65		71	66.0 (9.3)	
			Education alone (JP–, HEx–)	4 weeks	65		62	67.2 (9.5)	
Splints									
	Adams *et al* 2014[8] (A)	RCT	Splint+occupational therapy	4 weeks (NR)	9	CMC, NR	78	61.2 (9.4)	AUSCAN pain
			Placebo splint+occupational therapy		9				
			Occupational therapy only		9				
	Arazpour *et al* 2016[9]	RCT	Splint (custom-made, thermoplast, CMC)	4 weeks (use during ADLs, not at night)	16	CMC, clinical diagnosis and E-L stage I–II	87	50.2 (5.7)	NR
			No intervention		9		88	52.3 (6.4)	
	Bani *et al* 2013[16]	CO (WA+)	Splint (custom-made, thermoplast)	4 weeks (use during ADLs, not at night)	24	CMC, clinical diagnosis and E-L stage I-II	67	53.4	NR
			Splint (prefabricated, neoprene, CMC/MCP)				75	54.9	
			No intervention	4 weeks	11		73	58.6	
	Becker,*et al* 2013[13]	RCT	Splint (custom-made, thermoplast, CMC/MCP)	8–10 weeks (use as needed during ADLs and at night)	58	CMC, clinical diagnosis	80	62.8 (7.7)	DASH
			Splint (prefabricated, neoprene, CMC)		61		75	63.3 (8.5)	
	Cantero-Tellez *et al* 2016[14]	CCT	Splint (custom-made, thermoplast, CMC/MCP)	12 weeks (use during ADLs (3–4 hours/day) and at night)	44	CMC, clinical and Rx diagnosis	93	59.7 (9.6)	NR
			Splint (custom-made, thermoplast, CMC)		40		90	60.5 (9.8)	
	Gomes-Carreira 2010[10]	RCT	Splint (custom-made, CMC/MCP)	12 weeks (NR)	20	CMC, clinical diagnosis and E-L stage II–III	100	62.8 (8.5)	VAS pain
			No intervention		20		90	65.1 (10.1)	

Continued

Table 1 Continued

RoB	Study	Design	Intervention	Frequency, duration (instructions)	N	OA location, definition	Women (%)	Age (years)	Primary outcome
	Hermann *et al* 2013[11]	RCT	Splint+hand exercises (prefabricated, fabrifoam, CMC/MCP)	8 weeks (use as needed)	30	CMC, ACR, thumb pain	97	70.7 (7.3)	NRS pain
			Hand exercises		29		100	70.2 (6.2)	
	Rannou *et al* 2009[12]	RCT	Splint (custom-made, neoprene, CMC/MCP)	1 year (use at night)	57	CMC, clinical and Rx diagnosis	93	63.0 (7.9)	VAS pain
			Usual care		55		85	63.5 (7.6)	
	Sillem *et al* 2011[17]	CO (WA+)	Splint (custom-made, neoprene, CMC/MCP)	4 weeks (use when symptomatic, during heavy tasks and at night if preferred)	56	CMC, clinical diagnosis	91	64.1 (8.6)	AUSCAN function
			Splint (prefabricated, neoprene, IP to wrist)						
	Wajon *et al* 2005[15]	RCT	Splint (custom-made, thermoplast, CMC)+abduction exercise regimen	2 weeks splint only, 4 weeks splint +exercise (use full-time)	19	CMC, clinical diagnosis and E-L stage I–III	74	59.7 (9.0)	NR
			Splint (custom-made, thermoplast, CMC/MCP)+pinch exercise regimen		21		81	61.2 (12.5)	
	Watt *et al* 2014[21]	CCT	Splint (custom-made, thermoplast, DIP)	12 weeks (use at night)	26	DIP, ACR, Rx damage DIP	88	63 (51–78)	NRS pain
			No intervention		26				
	Weiss *et al* 2000[19]	CO (WA–)	Splint (custom-made, thermoplast, CMC)	1 week (use when symptomatic)	26	CMC, clinical and Rx diagnosis	81	57 (36–88)	NR
			Splint (custom-made, thermoplast, CMC to wrist)						
	Weiss *et al* 2004[20]	CO (WA–)	Splint (custom-made, thermoplast, CMC)	1 week (use when symptomatic)	25	CMC, clinical diagnosis and E-L stage I–II	84	NR	NR
			Splint (prefabricated, neoprene, CMC/MCP)						
	Van der Vegt *et al* 2017[18]	CO (WA+)	Splint (custom-made, thermoplast, CMC/MCP)	2 weeks (NR)	63	CMC, clinical and Rx diagnosis	70	60.1 (8.2)	VAS pain
			Splint (prefabricated, semirigid, CMC)						
Assistive devices									
	Kjeken *et al* 2011[22]	RCT	Provision of assistive devices+information	12 weeks (NR)	35	ACR	97	61.1 (6.0)	COPM
			Information alone		35		97	59.9 (7.5)	
Combination programme									
	Boustedt 2009[23]	RCT	Group-based combination programme: education, joint protection, exercise, splints	10 sessions in 5 weeks	22	CMC, clinical and Rx diagnosis	100	61 (40–76)	NR
			Group-based joint protection programme		20			61 (50–76)	
	Dziedzic,*et al* 2015[7]	Factorial RCT	Group-based joint protection programme (including splints) (JP+, HEx–)	4 sessions in 4 weeks	62	ACR	69	65.5 (8.6)	OARSI-OMERACT responder
			Group-based exercise programme (HEx+, JP–)		65		63	64.5 (9.0)	
			Group-based combination programme: education, joint protection (including splints), exercise (JP+, HEx+)		65		71	66.0 (9.3)	
			Education alone (JP–, HEx–)	4 weeks	65		62	67.2 (9.5)	
	Perez-Marmol *et al* 2017[24]	RCT	Fine motor skills occupational therapy	24 sessions in 8 weeks	25	Clinical diagnosis	84	82.8 (8.3)	DASH
			Conventional occupational therapy		23		74	79.2 (10)	
	Stamm *et al* 2002[25]	CCT	Individual combination programme: education, joint protection, exercise	Single session, 3 months	20	ACR	85	60.5 (8.3)	Grip strength
			Education alone	3 months	20		90	60.4 (6.4)	
	Stukstette *et al* 2013[26]	RCT	Group-based combination programme: education, joint protection (including splints), exercise	4 sessions in 12 weeks	76	ACR	82	60 (7)	AUSCAN function, OARSI-OMERACT responder
			Education alone	12 weeks	75		84	58 (9)	

Continued

Table 1 Continued

RoB	Study	Design	Intervention	Frequency, duration (instructions)	N	OA location, definition	Women (%)	Age (years)	Primary outcome
	Stukstette *et al* 2014[27](A)	RCT	Group-based booster session after combination programme[26]	Single session, 1 year	147	ACR	84	59 (8)	AUSCAN function, OARSI-OMERACT responder
			No booster session after combination programme[26]	1 year					
	Villafane 2013[28]	RCT	Individual combination programme: manual therapy, exercise	12 sessions in 4 weeks	30	CMC, clinical diagnosis and Rx damage	90	82 (2)	VAS pain
			Sham intervention (non-therapeutic ultrasound of the thumb region)		30		80	83 (1)	
	Wajon 2005[15]	RCT	Splint (custom-made, thermoplast, CMC)+abduction exercise regimen	2 weeks splint only, 4 weeks splint+excercise; use full-time	19	CMC, clinical diagnosis and E-L stage I–III	74	59.7 (9.0)	NR
			Splint (custom-made, thermoplast, CMC/MCP)+pinch exercise regimen		21		81	61.2 (12.5)	

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; DASH, Disabilities of the Arm, Shoulder and Hand; DIP, distal interphalangeal joint; E-L, Eaton-Littler; FIHOA, Functional Index for Hand OsteoArthritis; IP, interphalangeal joint; MCP,metacarpophalangeal; N, number; NR, not reported; NRS, numerical rating scale; OA, osteoarthritis; RCT, randomised controlled trial; RoB, risk of bias; Rx, radiography; SLR, systematic literature review; VAS, visual analogue scale; WA, wash-out period.

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-S8).[7 25 26] The other studies of combination programme 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) focused on different forms of manual therapy in elderly, severe CMC patients with OA (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]

Table 2 Efficacy of main non-pharmacological interventions for hand osteoarthritis from randomised controlled trials/clinical controlled trials

Intervention	Control	Outcome	Participants (studies), n	Duration	Quality of evidence	Effect estimate (95%CI)	References; comments
Exercise							
Hand exercise	No exercise	Pain	381 (5)	12 weeks	GRADE: low	SMD −0.27 (−0.47 to −0.07)*	6; Cochrane review
		Function	369 (4)	12 weeks	GRADE: low	SMD −0.28 (−0.58 to 0.02)*	Idem
		OARSI-OMERACT responder	305 (3)	12 weeks	Not reported	RR 2.8 (1.4 to 5.6)*	Idem
		Grip strength	362 (5)	12 weeks	Not reported	SMD 0.34 (−0.01 to 0.69)*	Idem
Joint protection							
Joint protection	No joint protection	Pain	257 (1)	26 weeks	RoB: high	MD −0.79 (−1.7 to 0.12) on AUSCAN pain scale (range 0–20)*	7; adjusted for age, gender, social class,centre, disease duration
		Function	257 (1)	26 weeks	RoB: high	MD −0.6 (−1.9 to 1.1) on AUSCAN function scale (range 0–36)*	Idem
		OARSI-OMERACT responder	257 (1)	26 weeks	RoB: high	OR 2.1 (1.1 to 4.0)*	Idem
		Grip strength	257 (1)	26 weeks	RoB: high	MD −0.47 (−1.9 to 0.94) kg†	Idem
Splints							
Thumb splint	Usual care or no intervention	Pain	221 (4)	4–8 weeks	RoB: high	MD −2.9 (−12.2 to 6.5) on 100 mm VAS*	9–12
		Pain	137 (2)	13–52 weeks	RoB: high	MD −17.4 (−25.6 to −9.2) on 100 mm VAS*	10 12
		Function	144 (3)	4 weeks	RoB: high	SMD 0.24 (−0.11 to 0.60)†	8 9 12; effect estimate based on two trials (n=126)9 12
		Function	112 (1)	52 weeks	RoB: high	MD −6.3 (−10.9 to −1.7) on Cochin hand function scale (range 0–90)*	12
		Grip strength	95 (2)	6–8 weeks	RoB: high	SMD 0.39 (−0.35 to 1.1)*	10 11
		Grip strength	40 (1)	13 weeks	RoB: high	MD 0.8 (−3.1 to 4.7) kg*	10
Long thumb splint (MCP+CMC joint)	Short thumb splint (only CMC joint)	Pain	185 (3)	2–12 weeks	RoB: high	MD −0.85 (−5.1 to 3.4) on 100 mm VAS*	13–15; Wajon: results after splint period used for pooling
		Function	146 (2)	9–12 weeks	RoB: high	MD 1.7 (−0.94 to 4.3)†	13 14
DIP splint	No intervention	Pain	26 (1)	12 weeks	RoB: high	Median difference 0.5 (range −7 to 3.5, p=0.53) on 10 cm VAS*	21; outcome: average pain
		Function	26 (1)	12 weeks	RoB: high	No between-group difference	21; no raw data presented
Assistive devices							
Assistive device	Information provision	Pain	70 (1)	12 weeks	RoB: high	MD 0.4 (−9.8 to 10.6) on 100 mm VAS†	22; adjusted for baseline
		Function	70 (1)	12 weeks	RoB: high	MD −0.3 (−0.6 to 0.01) on AUSCAN function scale (range 1–5)*	22; adjusted for baseline, COPM scores (primary outcome) also significant improvements*
Combination programme							

Continued

Table 2 Continued

Intervention	Control	Outcome	Participants (studies), n	Duration	Quality of evidence	Effect estimate (95%CI)	References; comments
Combination programme: education, joint protection, exercise	Education alone	Pain	321 (3)	12 weeks	RoB: high	MD 0.40 (−0.50 to 1.3) on AUSCAN pain scale (range 0–20)†	7 25 26; effect estimate based on one trial (n=151),26adjusted for baseline
		Function	321 (3)	12 weeks	RoB: high	MD 0.49 (−1.0 to 2.0) on AUSCAN function scale (range 0–36)*	7 25 26; effect estimate based on one trial (n=151),26adjusted for baseline
		OARSI-OMERACT responder	281 (2)	12 weeks	RoB: high	OR 0.82 (0.42 to 1.6)†	7 26; effect estimate based on one trial (n=151)26
		Grip strength	321 (3)	12 weeks	RoB: high	SMD −0.21 (−0.49 to 0.08)†	7 25 26; effect estimate based on two trials (n=186)25 26
Quality of evidence:	GRADE: very low/low RoB: high	GRADE: moderate RoB: unclear	GRADE: high RoB: low		Effect estimate:	No effect	Between-group difference

*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.

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 focused 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 (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] gastrointestinal 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-S11).[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

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

RoB	Study	Design	Intervention	Frequency, duration	N	OA location, definition	Women (%)	Age (years)	Primary outcome
Topical NSAIDs									
	Altman *et al* 2009[52]	RCT	Topical diclofenac gel 1%	4 per day, 8 weeks	198	ACR, Rx KL1–3	77	63.6 (10.3)	VAS pain, AUSCAN, VAS patient global
			Topical placebo cream		187		77	64.7 (9.6)	
	Graber *et al* 1997[39]	RCT	Topical ibuprofen cream	3 per day, 2 weeks	57	ACR or clinical diagnosis isolated CMC OA	91	65.8 (8.6)	FIHOA
			Berthollet treatment (local steam bath and finger shower)	Daily, 3 weeks	59		86	63.2 (10.0)	
	Michalsen *et al* 2008[92]	RCT	Diclofenac gel 10 mg/g	2 per day, 4 weeks	16	CMC, clinical diagnosis and Rx damage	100	64.3 (9.1)	VAS pain
			Medicinal leeches	Once in 4 weeks	16			64.1 (6.4)	
	Romero *et al* 2013[55]	RCT	Topical diclofenac gel 2%	3 per day, 4 weeks	65	ACR	86	62 (10.2)	NR
			Topical herbal cream		65		95		
	Talke *et al* 1985[50]	RCT	Topical etofenamate 100 mg/g	3 per day, 3 weeks	30	IP, clinical diagnosis, 'activated'	83	64.3 (13.5)	NR
			Oral indomethacin 150 mg/day	3 weeks	30		90	63.3 (11.0)	
	Widrig *et al* 2007[54]	RCT	Topical ibuprofen cream 5%	3 per day, 3 weeks	99	ACR	61	64 (11.4)	VAS pain, FIHOA
			Topical arnica cream 50%		105		67	64 (12.0)	
	Zacher *et al* 2001[51]	RCT	Topical diclofenac gel 1%	4 per day, 3 weeks	165	IP, clinical diagnosis, 'activated'	86	60.7 (9.4)	VAS pain improve≥40%
			Oral ibuprofen 1200 mg/day	3 weeks	156		90	63.2 (9.4)	
Oral NSAIDs									
	Dreiser *et al* 1993[62]	RCT	Ibuprofen 800 mg/day	2 weeks	30	Rx damage, pain exacerbation	80	58.5 (1.7)	NR
			Placebo		30		90	60.3 (2.0)	
	Grifka *et al* 2004[63]	RCT	Lumiracoxib 200 mg/day	4 weeks	205	ACR	82	62.0 (12.1)	VAS pain
			Lumiracoxib 400 mg/day		193		83	61.0 (12.4)	
			Placebo		196		83	62.7 (11.7)	
	Muratore *et al* 2004[65] (A)	RCT	Ketoprofen lysine salt 160 mg/ day+glucosamine+chondroitin sulfate	20 days	30	Hand, NR	100	NR	NR
			Glucosamine+chondroitin sulfate		28				
	Rovetta *et al*,2001-B[49]	CCT	Dexketoprofen-trometamol 50 mg/day	3 weeks	35	ACR, 'active OA'	86	57.7 (3.4)	Morning stiffness (WOMAC)
			No intervention		19		63		
	Rovetta *et al*, 2001-A[48]	CO (WA-)	Dexketoprofen-trometamol 50 mg/day	13 days	36	ACR, 'active OA'	NR	NR	Morning stiffness and pain (WOMAC)
			Paracetamol 1000 mg/day						
	Seiler 1983[64]	RCT	Meclofenamate sodium 300 mg/day	4 weeks	22	Clinical diagnosis,≥1 inflamed DIP and Rx damage	95	62.5 (34–77)	NR
			Placebo		19		84	65.0 (49–80)	
	Talke 1985[50]	RCT	Oral indomethacin 150 mg/day	3 weeks	30	IP, clinical diagnosis, 'activated'	83	64.3 (13.5)	NR
			Topical etofenamate 100 mg/g	3 per day, 3 weeks	30		90	63.3 (11.0)	
	Zacher *et al* 2001[51]	RCT	Oral ibuprofen 1200 mg/day	3 weeks	156	IP, clinical diagnosis,'activated'	90	63.2 (9.4)	VAS pain improve≥40%
			Topical diclofenac gel 1%	4 per day, 3 weeks	165		86	60.7 (9.4)	
Chondroitin sulfate									

Continued

Table 3 Continued

RoB	Study	Design	Intervention	Frequency, duration	N	OA location, definition	Women (%)	Age (years)	Primary outcome
	Gabay *et al* 2011[66]	RCT	Chondroitin sulfate 800 mg/day	6 months	80	ACR	73	63.9 (8.5)	VAS pain, FIHOA
			Placebo		82		76	63.0 (7.2)	
	Verbruggen 2002[44]	RCT	Chondroitin polysulphate 50 mg/day intramuscularly	3 years	66	IP, clinical diagnosis and Rx damage	91	55.2 (6.7)	Rx progression
			Placebo intramuscularly		64		97	56.1 (9.2)	
		RCT	Chondroitin sulfate 1200 mg/day	3 years	44	IP, clinical diagnosis and Rx damage	91	57.6 (7.1)	Rx progression
			Placebo		48		88	55.9 (8.9)	
Intra-articular glucocorticoids									
	Bahadir*et al* 2009[73]	RCT	Glucocorticoid i.a. 20 mg/0.5 mL	Once	20	CMC, Rx E-L stage II–III	100	62.9 (9.1)	NR
			Hyaluronic acid i.a. 5 mg/0.5 mL	1 per week, 3 weeks	20			60.8 (7.3)	
	Fuchs *et al* 2006[74]	RCT	Glucocorticoid i.a. 10 mg/1 mL	1 per week, 3 weeks	28	CMC, clinical diagnosis and Rx KL>0	80	Median 61.0	NR
			Hyaluronic acid i.a. 10 mg/1 mL		28			Median 59.5	
	Heyworth *et al* 2008[68]	RCT	Glucocorticoids i.a.1 mL	Once+1 i.a. placebo, 2 weeks	22	CMC, Rx E-L stage I–IV	90	60 (9.4)	NR
			Hyaluronic acid i.a. 8 mg/1 mL	1 per week, 2 weeks	28		80	65 (10.6)	
			Placebo i.a. (1 mL, saline)	1 per week, 2 weeks	18		89	64 (8.5)	
	Jahangiri 2014[93]	RCT	Gluocorticoid i.a. 40 mg/0.5 mL+0.5 mL lidocaine	Once+2 i.a. placebo, 3 weeks	30	CMC, clinical diagnosis and Rx E-L stage>I	70	63.3 (10.1)	VAS pain
			Dextrose i.a. 100 mg/0.5 mL+0.5 mL lidocaine	1 per week, 3 weeks	30		77	63.9 (9.4)	
	Mandl,*et al* 2012[69](A)	RCT	Glucocorticoid i.a. 40 mg/1 mL	Once+1 i.a. placebo,2 weeks	65	CMC, clinical diagnosis and Rx KL>0	68	66.5 (45–89)	NR
			Hyaluronic acid i.a. 8 mg/1 mL	1 per week, 2 weeks	62				
			Placebo i.a. (1 mL, bupivacaine)	1 per week, 2 weeks	61				
	Meenagh *et al* 2004[70]	RCT	Glucocorticoid i.a. 5 mg/0.25 mL	Once	20	CMC, NR	95	60.6 (41–71)	VAS pain improve≥20%
			Placebo i.a. (0.25 mL, saline)		20		85	59.3 (46–69)	
	Monfort *et al* 2014[75]	RCT	Glucocorticoid i.a. 3 mg/0.5 mL	1 per week, 3 weeks	40	CMC, clinical diagnosis and Rx KL1–3	88	62.8 (8.7)	FIHOA
			Hyaluronic acid i.a. 5 mg/0.5 mL		48				
	Spolidoro,*et al* 2015[71]	RCT	Glucocorticoid i.a.4 mg/0.2 mL (DIP) or 6 mg/0.3 mL(PIP)+0.1 mL lidocaine	Once	30	IP, clinical diagnosis and Rx osteophyte	100	60.7 (9.1)	VAS pain, VAS joint swelling
			Placebo i.a. (0.1 mL, lidocaine)		30		93	60.7 (7.3)	
	Stahl *et al* 2005[76]	RCT	Glucocorticoid i.a. 40 mg/1 mL	Once	25	CMC, Rx E-L stage II	84	62 (50–91)	NR
			Hyaluronic acid i.a. 15 mg/1 mL		27		92.5	62 (37–80)	
Oral glucocorticoids									
	Kvien *et al* 2008[81]	RCT	Prednisone 3 mg/day+dipyridamole 200 mg/day	6 weeks	42	ACR, Rx KL>1	93	61.1 (5.0)	AUSCAN pain
			Placebo		41		93	59.6 (5.3)	
	Wenham *et al* 2012[82]	RCT	Prednisone 5 mg/day	4 weeks	35	ACR, Rx KL>0	74	61.9 (6.6)	VAS pain
			Placebo		35		89	61.1 (9.0)	

Continued

Table 3 Continued

RoB	Study	Design	Intervention	Frequency, duration	N	OA location, definition	Women (%)	Age (years)	Primary outcome
Hydroxychloroquine									
	Basoski *et al* 2015[83](A)	RCT	Hydroxychloroquine 400 mg/day	24 weeks	98	ACR	86	57	VAS pain
			Placebo		98				
	Kingsbury,*et al* 2016[84](A)	RCT	Hydroxychloroquine 200–400 mg/day	1 year	124	ACR	NR	NR	NRS pain
			Placebo		124				
	McKendry *et al* 2001[59](A)	RCT	Hydroxychloroquine 400 mg/day	24 weeks	29	Hand, NR	NR	NR	NR
			Paracetamol 3900 mg/day		29				
			Placebo		30				
TNF inhibitors									
	Aitken *et al* 2017[46](A)	CO (WA+)	Adalimumab 40 mg subcutaneously	2 subcutaneously per 2 weeks,12 weeks	43	ACR, erosive (Rx erosion), MRI synovitis	77	61 (8.4)	AUSCAN pain
			Placebo subcutaneously						
	Chevalier *et al* 2015[85]	RCT	Adalimumab 40 mg subcutaneously	Once 2 subcutaneously,2 weeks	42	ACR, Rx damage IPs	87	62.8 (6.9)	VAS pain improve≥50%
			Placebo subcutaneously		43		83	62.2 (7.0)	
	Kloppenburg *et al* 2016[47] [86 87] (A)	RCT	Etanercept 25–50 mg subcutaneously	1 subcutaneously per week, 1 year	45	IP, ACR, erosive (Rx erosion IP)	82	59.4 (6.5)	VAS pain
			Placebo subcutaneously		45		80	60.1 (8.7)	
	Verbruggen *et al* 2012[45]	RCT	Adalimumab 40 mg subcutaneously	1 subcutaneously per 2 weeks, 1 year	30	IP, ACR, erosive (Rx erosion IP)	87	61.9 (6.1)	Rx progression
			Placebo subcutaneously		30		83	60.7 (6.9)	

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 trials; CMC, first carpometacarpal; CO, cross-over trial; FIHOA, Functional Index for Hand OsteoArthritis; i.a., intra-articular; IP, interphalangeal joint; NR, not reported; NRS, numerical rating scale; NSAID, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; RCT, randomised controlled trial; TNF, tumour necrosis factor; VAS, visual analogue scale; WA, wash-out period; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 4 Efficacy of main pharmacological interventions for hand osteoarthritis from randomised controlled trials/clinical controlled trials

Intervention	Control	Outcome	Participants (studies), n	Duration	Specific OA location or type	Quality of evidence	Effect estimate (95%CI)	References; comments
Topical NSAIDs								
Topical NSAID	Topical placebo	Pain	385 (1)	8 weeks	–	RoB: low	MD −5.9 (−11.7 to −0.06) on 100 mm VAS*	52
		Function	385 (1)	8 weeks	–	RoB: low	MD −7.3 (−12.9 to −1.7) on AUSCAN function scale (range 0–36)*	52
		OARSI-OMERACT response	385 (1)	8 weeks	–	RoB: low	RR 1.2 (0.99 to 1.4)*	52
Topical NSAID	Oral NSAID	Pain	381 (2)	3 weeks	'Activated' IP OA	RoB: low	SMD −0.05 (−0.27 to 0.17)*	50 51; effect estimate based on one trial (n=321)51; same studies as previous SLR1
		Grip strength	381 (2)	3 weeks	'Activated' IP OA	RoB: low	MD −0.01 (−0.03 to 0.01) bar*	50 51; effect estimate based on one trial (n=321)51
Oral NSAIDs								
Oral NSAID	Placebo	Pain	695 (3)	2–4 weeks	–	RoB: low	SMD 0.40 (0.20 to 0.60)*	62–64; effect estimate based on two trials with ibuprofen 800 mg and lumiracoxib 200–400 mg (n=654)62 63; same studies as previous SLR1
		Function	695 (3)	2–4 weeks	–	RoB: low	SMD 0.17 (−0.03 to 0.36)*	Idem
Chondroitin sulfate								
Chondroitin sulfate	Placebo	Pain	162 (1)	26 weeks	–	RoB: low	MD −8.7 (p=0.016) on 100 mm VAS*	66
		Function	162 (1)	26 weeks	–	RoB: low	MD −2.1 (p=0.008) on FIHOA (range 0–30)*	66
		Grip strength	162 (1)	26 weeks	–	RoB: low	MD 1.9 (−0.02 to 3.8) kg*	66
Intra-articular therapies								
Intra-articular glucocorticoids	Intra-articular placebo	Pain	206 (3)	26 weeks	CMC	RoB: low (1), unclear (1)	MD −3.6 (−13.9 to 6.8) on 100 mm VAS*	68–70; effect estimate based on two trials (n=166)69 70
		Function	166 (2)	26 weeks	CMC	RoB: unclear	MD −1.5 (−6.3 to 3.3) on DASH (range 0–100)*	68 69; effect estimate based on one trial (n=126)69

Continued

Table 4 Continued

Intervention	Control	Outcome	Participants (studies), n	Duration	Specific OA location or type	Quality of evidence	Effect estimate (95%CI)	References; comments
Intra-articular glucocorticoids	Intra-articular placebo	Pain	60 (1)	12 weeks	IP	RoB: low	MD −18.0 (−33.5 to −2.6) on 100 mm VAS*	71; outcome: pain on movement; for pain in rest no between-group differences observed
		Function	60 (1)	12 weeks	IP	RoB: low	MD −4.4 (−9.4 to 0.56) on AUSCAN function scale (range 0–36)*	71
		Grip strength	60 (1)	12 weeks	IP	RoB: low	MD 0.98 (−2.6 – to 4.5) kg*	71
Intra-articular hyaluronic acid	Intra-articular placebo	Pain	235 (3)	26 weeks	CMC	RoB: unclear	MD 3.3 (−5.2 to 11.8) on 100 mm VAS†	68 69 72; effect estimate based on one trial (n=123)69
		Function	235 (3)	26 weeks	CMC	RoB: unclear	MD −2.1 (6.3 to 2.1) on DASH (range 0–100)*	Idem
Hydroxychloroquine								
Hydroxychloroquine	Placebo	Pain	503 (3)	24–52 weeks	–	RoB: unclear	MD 2.9 (−3.4 to 9.2) on 100 mm VAS†	59 83 84; Effect estimate based on two trials (n=307)59 84
		Function	444 (2)	24–52 weeks	–	RoB: unclear	MD −0.79 (−2.4 to 0.78) on AUSCAN function scale (range 0–36)†	83 84; effect estimate based on one trial (n=248)84
		Grip strength	248 (1)	52 weeks	–	RoB: unclear	MD 0.95 (−0.82 to 2.72)kg†	84
TNF inhibitors								
TNF inhibitor	Placebo	Pain	235 (3)	24–52 weeks	Erosive OA (2/3 trials)	RoB: low	MD −4.9 (−12.5 to 2.8) on 100 mm VAS*	45 85 86; effect estimate based on two trials (n=175)85 86
		Function	235 (3)	24–52 weeks	Erosive OA (2/3 trials)	RoB: low (1), unclear (1)	SMD −0.02 (−0.35 to 0.32)*	45 85 86; effect estimate based on two trials (n=145)45 85
		Grip strength	150 (2)	52 weeks	Erosive OA	RoB: low (1), unclear (1)	MD 0.70 (−0.59 to 2.0)kg*	45 86; effect estimate based on one trial (n=60)45
Quality of evidence:	GRADE: very low/low RoB: high	GRADE: moderate RoB: unclear	GRADE: high RoB: low		Effect estimate:	No effect	Between-group difference	

*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; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; RoB, risk of bias; RR, risk ratio; SLR, systematic literature review; SMD, standardised mean difference; TNF, tumour necrosis factor; VAS, visual analogue scale.

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 6 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 sAEs 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 inflximab,[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]

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 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 reviewer 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').

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