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Invited Review

Systematic Review of Non-surgical Therapies for Osteoarthritis of the Hand: An Update

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Abstract

Hand osteoarthritis is a common disease with significant morbidity. This review aimed to update our earlier systematic reviews which included all published randomized controlled trials evaluating pharmacological and non-pharmacological therapies in patients with hand osteoarthritis. A total of 133 randomized controlled trials evaluating pharmacological and nonpharmacological therapies in hand osteoarthritis were reviewed. Overall, the methodological quality of randomized controlled trials has improved since the last update. Almost all new studies described their methods for randomization, blinding, and allocation concealment. However, studies continued to underreport features specific to hand osteoarthritis, such as pattern of joint involvement and number of affected joints. Standardized outcome assessments for pain and function were commonly presented, but measures of other hand osteoarthritis specific outcomes, such as health-related quality of life and patient global assessments, continued to be underreported. Future trials should consistently report on hand osteo arthritis specific features and outcome assessments in order to make clinically relevant conclusions about the efficacy of the diverse treatment options available.

Keywords: Osteoarthritis, hand, therapy, systematic review

Introduction

Hand osteoarthritis (OA) is a common disease with an estimated prevalence of 38% in women over the age of 66 and 24.5% in men.[1] It is associated with significant morbidity, often causing pain, stiffness, and loss of function. Compiled data suggest that its effects on morbidity is comparable to rheumatoid arthritis.[2,3] Despite its prevalence and high burden of morbidity, hand OA has traditionally received less attention compared to OA of the hip and knee. There has recently been increased interest on pharmacologic and non-pharmacologic therapies for this disease. The objective of this article is to update our previous systematic reviews of non-surgical therapies for patients with hand OA with an emphasis on critically evaluating trial methodology.[4-6] Randomized control trials (RCTs) published between December 2015 and December 2020 were added in this update.

Methods

The inclusion and exclusion criteria were identical to those used in the original version of the systematic review.[4] Only RCTs that evaluated a therapeutic intervention in adult subjects with hand OA were included. The trial must have explicitly stated that a randomized method of allocation to a treatment group was used. Any non-surgical interventions were considered. Randomized control trials evaluating OA at multiple sites were only included if efficacy data were presented separately for the hand.

Exclusion criteria included: RCTs evaluating a surgical therapy, RCTs presented in duplicate, conference proceedings, unpublished RCTs, and non-English RCTs if their English abstracts did not contain sufficient details on trial methodology and outcomes.

The following electronic data sources were searched for this updated version of the systematic review: MEDLINE (1966 to December week 4, 2020), EMBASE (1980 to December week 4, 2020), AMED (1985 to December week 4, 2015), ClinicalTrials.gov (1960 to December week 4, 2020), and EBM reviews, including the Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effectiveness (DARE), ACP Journal Club, and the Central Cochrane Database (1980 to December week 4, 2020). Reference lists of all retrieved articles were also manually searched. A PRISMA diagram summarizing study identification and

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retrieval is shown in Fig. 1.[7] The search strategy was updated for this review. Two reviewers (HM and CO) independently screened retrieved records for inclusion, and discrepancies were adjudicated by a third reviewer (TT).

Data abstraction was completed by a single author (HM), and a standardized form was used to extract information pertaining to trial demographics, methodology, quality, and outcomes.[8,9] Study quality was evaluated by using Jadad's scoring checklist.[10] The final score ranged from 0 to 5, with a higher score reflecting higher methodological quality. Allocation concealment was specifically evaluated for each RCT. A formal meta-analysis was to be performed, if feasible.

Results

A total of 133 RCTs were analyzed in this systematic review.[11-142] These results are summarized in Table 1 and Table 2. Thirty-eight RCTs were added in this update. There were 2 RCTs published between 1970 and 1979, 5 between 1980 and 1989, 14 between 1990 and 1999, 34 between 2000 and 2009, 71 between 2010 and 2019, and 7 between January 2020 and December 2020. One hundred twenty-six RCTs were available as English full paper reports, 4 were non-English reports with English abstracts, and 3 were only available as English abstracts. Seventy-nine reports that evaluated therapies in hand OA were excluded from this review as they did not meet 1 or more of the stated inclusion criteria of this systematic review.

Of the 38 RCTs added in this update, a parallel, independent group study design was used in 35 RCTs, and 3 RCTs used a crossover design. Twenty-eight8 of the newly included RCTs evaluated symptom-modifying therapy, and 4 evaluated structural-modifying therapy. There were 6 RCTs evaluating both symptom- and structural-modifying therapy.

The median number of subjects randomized per study was 60, with a range of 5-5586. The median number of subjects completing the trials was 55, with a range of subjects completing trials of 5-3983. The median duration of the RCTs was 12 weeks, with a range of 2 hours to 260 weeks, and a mean of 22.39 weeks. Of subjects randomized, 73.85% were female. The mean age of randomized subjects was 62.35 years, with a range of 44.8-82.6 years. There were only 54 RCTs reporting duration of OA of subjects. The mean duration of OA was 6.5 years, with a range of 0.6-15.2 years.

Seventy-four of the 133 RCTs (56%) had a placebo group/arm. There were 30 multicenter RCTs, 14 of which were added in this update. The continent of origin was heterogeneous, with 84 RCTs from Europe, 24 from North America, 15 from Asia, 6 from South America, and 5 from Australia.

Features Specific to Hand Osteoarthritis Trials

There was no consistent definition of hand OA used in the RCTs, with most trials (N = 102) not explicitly distinguishing between primary (idiopathic) and secondary OA. Thirty RCTs exclusively evaluated subjects with primary hand OA, and one RCT explicitly evaluated subjects with both primary and secondary hand OA.[30] This remained inconsistently defined in recent RCTs. Twelve of the newly included RCTs explicitly evaluated patients with primary hand OA while the remaining 26 RCTs did not explicitly distinguish between primary and secondary OA.

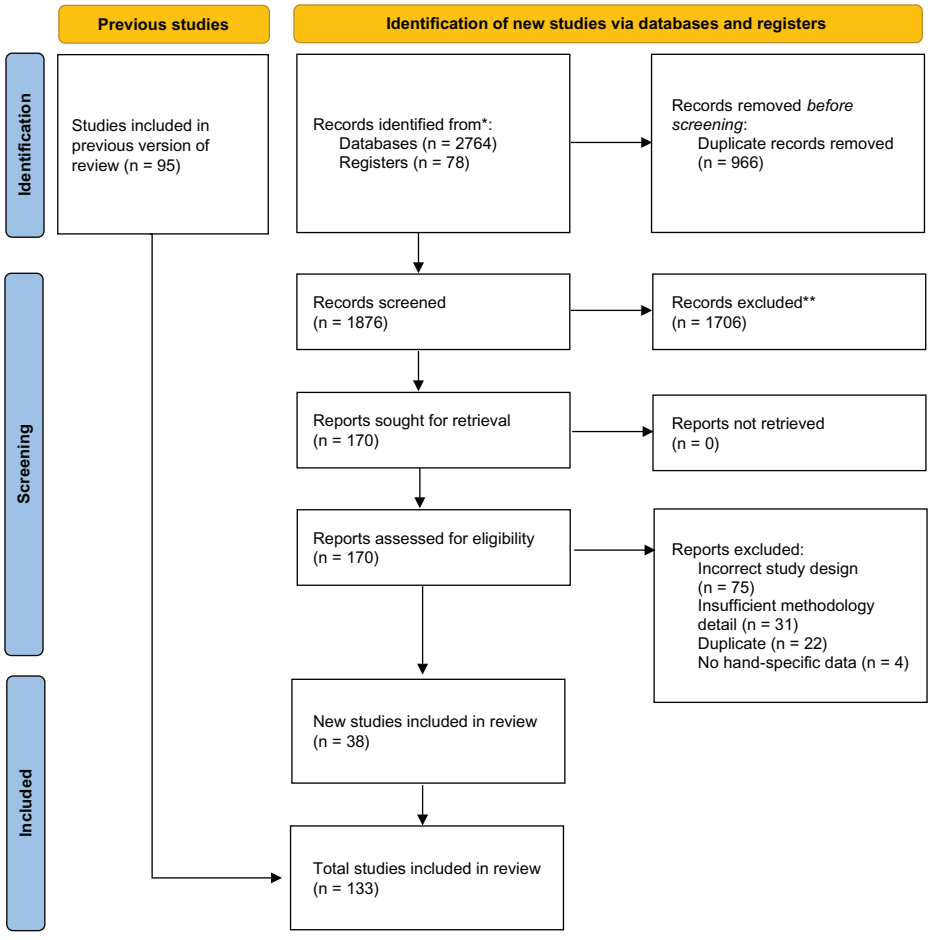

Figure 1. PRISMA diagram summarizing search strategy, study identification and retrieval.

Table 1. Published RCTs in OA of the hand – Pharmacologic Therapies (N = 60)

Study (authors and year)	Group	N randomized	N completed	Design	Duration (weeks)	Overall efficacy	Jadad score
NSAIDs							
Seiler, 1983[34]	Meclomen vs placebo	41	22	Parallel	4	Meclomen > placebo	4
Caruso et al., 1987[76]	S-adenosylmethionine vs naproxen vs placebo	51	NA*	Parallel	4	Equal	4
Sanders et al., 2015[31]	Naproxen vs placebo	23	20	Crossover	4	Naproxen > placebo	4
Dreiser et al., 1993[81]	Ibuprofen vs placebo	60	54	Parallel	2	Ibuprofen > placebo	3
Grifka et al., 2004[91]	Lumiracoxib vs placebo	594	559	Parallel	4	Lumiracoxib > placebo	3
Mibielli et al., 2009[52]	Diclofenac SR, vitamins B1, B6, and B12 vs placebo	80	80	Parallel	1	Diclofenac > placebo	2
Fleischmann et al., 2008[85]	Lumiracoxib 100 mg daily vs Lumiracoxib BID vs Celecoxib 200 mg daily	3036	1427	Parallel	52	Equal	5
Lisse et al., 2003[103]	Rofecoxib vs Naproxen	5586	3983	Parallel	12	Equal	4
Punzi et al., 1996[62]	Hydroxychloroquine (HCQ) vs NSAID/analgesics	15	15	Parallel	52	HCQ > NSAID + analgesic	2
Altman et al., 2009[66]	Diclofenac gel vs placebo	385	334	Parallel	8	Diclofenac > placebo	3
Thiesce and Dougados, 1995[45]	Topical diclofenac vs placebo	20	20	Cross-over	1.5	Equal	2
Zacher et al., 2001[26]	Topical diclofenac vs oral ibuprofen	321	NA*	Parallel	3	Equal	2
Rothacker et al., 1994[28]	Trolamine salicylate vs placebo	50	49	Cross-over	NA*	Trolamine > placebo	3
Rothacker et al., 1998[27]	Trolamine salicylate vs placebo	86	81	Parallel	0.01	Trolamine > placebo	3
Widrig et al., 2007[25]	Topical ibuprofen gel vs arnica gel	204	174	Parallel	3	Equal	2
Systemic therapy: Dietary supplements							
Gabay et al., 2011[88]	Chondroitin sulfate 800 mg OD vs placebo	162	139	Parallel	26	Chondroitin > placebo	5
Verbruggen et al., 2002[12]	Chondroitin polysulfate (CPS) vs placebo	130	92	Parallel	156	CPS > placebo	3
Verbruggen et al., 2002[12]	Chondroitin sulfate (CS) vs placebo	92	73	Parallel	156	CS > placebo	3
Rovetta et al., 2004[30]	CS and naproxen vs naproxen alone	24	24	Parallel	104	CS + naproxen > naproxen alone	2
Neogi et al., 2008[58]	Vitamin K supplement vs placebo	474	378	Parallel	156	Equal	4
Flynn et al., 1994[86]	Folate vs folate + B12 vs placebo	30	26	Cross-over	24	Folate + B12 > (placebo = folate)	4
Verbruggen and Veys, 1993[11]	GAGPS (Intramuscular) vs placebo	92	68	Parallel	260	GAGPS > placebo	2
Systemic therapy: Biologic therapy							
Verbruggen et al., 2012[13]	Adalimumab SC vs placebo	60	59	Parallel	52	Equal	2
Chevalier et al., 2015[77]	Adalimumab SC vs placebo	85	69	Parallel	26	Equal	5
Aitken et al., 2018[105]	Adalimumab SC vs placebo for 12 weeks followed by washout for 8 weeks, then crossover for 12 weeks	43	39	Crossover	32	Equal	5

(*Continued*)

Table 1. Published RCTs in OA of the Hand – Pharmacologic Therapies (N = 60) (*Continued*)

Study (authors and year)	Group	N randomized	N completed	Design	Duration (weeks)	Overall efficacy	Jadad score
Kloppenburg et al., 2018[120]	Etanercept 50mg SC x 24 weeks and 25mg SC thereafter vs placebo	91	68	Parallel	52	Equal	5
Kloppenburg et al., 2019[121]	Lutikizumab 200mg SC vs placebo	132	110	Parallel	24	Equal	5
Schett et al, 2020[139]	Otilimab vs placebo	44	39	Parallel	10	Equal	5
Richette et al, 2020[140]	Tocilizumab vs placebo	91	79	Parallel	8	Equal	5
Systemic therapy: Other							
Park et al, 2016[133]	GCSB-5 vs placebo	220	190	Paralel	12	GCSB-5 > placebo	5
Wang et al., 2017[123]	Xianlinggubao vs placebo	547	494	Parallel	26	Xianlinggubao > placebo	3
Sofat et al, 2017[127]	duloxetine vs pregabalin vs placebo	65	52	Parallel	12	Pregabalin > duloxetine or placebo	2
Davis et al, 2020[141]	Colchicine 0.5mg BID vs placebo	64	57	Parallel	12	Equal	5
Shin et al., 2013[35]	Diacerein 50 mg BID vs placebo	86	61	Parallel	12	Equal	5
Kvien et al., 2008[101]	CR-102 synergistic drug vs placebo	83	61	Parallel	6	CR-102 > placebo	4
Smith et al., 2010[37]	Sodium salicylate SC vs Sham injection	40	40	Parallel	13	Sodium salicylate > sham	4
Thorpe, 1970[46]	Fiorinal vs FIPA vs placebo	10	9	Cross-over	6	(Fiorinal = FIPA) > placebo	3
Saviola et al., 2012[32]	Clodronate IV + IM vs Hydroxychloroquine	38	29	Parallel	104	Clodronate > Hydroxychloroquine	2
Saviola et al., 2017[129]	Clodronate IM vs no intervention	40	31	Parallel	26	Clodronate > no intervention	2
Wenham et al., 2012[24]	Prednisolone 5 mg daily vs placebo	70	67	Parallel	12	Equal	5
Kroon et al., 2019[122]	Prednisolone 10mg x 6 weeks then taper vs placebo	92	84	Parallel	8	Prednisolone group > placebo at 6 weeks	5
Lee et al, 2015[131]	Hydroxychloroquine vs placebo	202	156	Parallel	24	Equal	5
Kingsbury et al., 2018[119]	Hydroxychloroquine vs placebo	248	232	Parallel	52	Equal	5
Intra-articular therapies							
Meenagh et al., 2004[51]	IA corticosteroid vs placebo	40	35	Parallel	24	Equal	5
Heyworth et al., 2008[95]	IA hylan vs IA corticosteroid vs placebo	60	60	Parallel	26	Equal	5
Paschoal et al., 2015[104]	IA triamcinolone and lidocaine vs lidocaine	60	60	Parallel	12	Triamcinolone and lidocaine > lidocaine	5
Ayhan et al., 2009[67]	Hylan GF 20 IA vs saline	33	31	Parallel	24	Hylan > saline	4
Stahl et al., 2005[38]	IA corticosteroid vs IA hyaluronate	52	52	Parallel	24	Equal	3
Monfort et al., 2015[55]	US IA hyaluronic acid vs US IA betamethasone	100	88	Parallel	26	Hyaluronic > betamethasone	3
Fuchs et al., 2006[86]	IA hyaluronate vs IA steroid	56	51	Parallel	26	Equal	1

(*Continued*)

Table 1. Published RCTs in OA of the Hand – Pharmacologic Therapies (N = 60) (*Continued*)

Study (authors and year)	Group	N randomized	N completed	Design	Duration (weeks)	Overall efficacy	Jadad score
Bahadir et al., 2009[68]	Triamcinalone IA vs hyaluronate	40	40	Parallel	52	Triamcinalone > hyaluronate	1
Jahangiri et al., 2014[97]	IA dextrose plus lidocaine vs IA 40 mg methylpred	60	55	Parallel	26	Dextrose > corticosteroid	4
Roux et al., 2007[29]	IA hyaluronate (once vs twice vs thrice)	42	37	Parallel	12	Equal	2
Pastinen et al., 1988[61]	Glycosaminoglycan polysulfate (GAGPS) intra-articular (IA) vs placebo	30	29	Parallel	52	GAGPS > placebo	4
Reeves and Hassanein, 2000[65]	Dextrose prolotherapy (DP) vs placebo	27	25	Parallel	24	DP > placebo	4
Malahias et al, 2018[136]	IA platelet rich plasma vs IA methylprednisolone and lidocaine	33	32	Parallel	52	IA PRP > IA methylprednisolone and lidocaine	4
Other topical therapies							
McCarthy and McCarty, 1992[50]	Capsaicin topical vs placebo	14	14	Parallel	4	Capsaicin > placebo	2
Schnitzer et al., 1994[33]	Capsaicin topical vs placebo	59	48	Parallel	9	Capsaicin > placebo	2
Talke et al., 1985[43]	Topical etofenamate vs oral indomethacin	NA*	NA*	Parallel	3	Equal	*
Dougados and Nguyen, 1995[81]	Topical niflumic acid vs placebo	186	186	Parallel	1	Equal	2

*Not available.

HCQ, hydroxychloroquine; NSAID, non-steroidal anti-inflammatory drug; CPS, chondroitin polysulfate; CS, chondroitin sulfate; GAGPS, glycosaminoglycan polysulfate; IA, intra-articular; DP, dextrose prolotherapy; PRP, platelet-rich plasma; IV, intravenous; IM, intramuscular; RCT, randomized controlled trial; OA, osteoarthritis; FIFA, Formulation of isobutylallylbarbituric acid, paracetamol, Aspirin, and caffeine; US, Ultrasound.

Sixty-one total RCTs, including 26 newly added RCTs, used a validated hand OA classification scheme for study entry, with the most common being the ACR classification criteria (N = 54). In 31 RCTs, hand OA was defined by the authors, and many did not offer further description. Two RCTs required diagnosis by a rheumatologist but did not specify if a validated scheme was used.[44,54] Three RCTs required diagnosis by a hand surgeon.[14,71,138]

Radiographs were taken at baseline in 77 RCTs, including 25 newly added RCTs. Sixty-nine of those RCTS detailed the x-ray criteria used. The most used x-ray criteria were Kellgren Lawrence (N = 25), Eaton (N = 23), and Verbruggen (N = 6). There were 26 RCTs that used both ACR hand OA classification and baseline radiographs.

The distribution of affected hand OA joints was variable and inconsistently described among the RCTs. Fifty-two RCTs did not specify which joints were being evaluated in the hand. Of the other RCTs, 38 exclusively evaluated subjects with first carpal metacarpal (CMC) joint OA, 17 evaluated subjects with interphalangeal joint OA (proximal and distal), and 18 evaluated subjects with involvement of all 3 joint areas (Proximal interphalangeal joint [PIP], distal interphalangeal joint [DIP], and first CMC).

There were 100 RCTs that used standardized outcome questionnaires. One hundred twenty-four RCTs used pain assessment as an outcome, 118 used functional assessments, 51 used patient global assessments, 36 used health-related quality of life, and 24 used physician global assessment. Of the RCTs that used a standardized evaluation questionnaire, the visual analog scale (VAS) for pain[143] was used in 46 RCTs and was the most used questionnaire. The Australian/Canadian Hand Osteoarthritis Index (AUSCAN)[144] was used in 37 RCTs, the Health Assessment Questionnaire Disability Index (HAQ-DI)[145] in 13, the Disability of the Arm, Shoulder and Hand (DASH)[146] in 12, Dreiser Functional Index[147] in 11, and the short-form-36[143] in 9. The Osteoarthritis Research Society International- Outcome Measures in Rheumatoid Arthritis Clinical Trials (OARSI-OMERACT)[148] and Functional Index of Hand Osteoarthritis (FIHOA)[149] were each used in 8 RCTs. Outcome variables were also used that have not been validated in OA trials. These variables included joint swelling, joint tenderness, need for OA-related surgery, analgesic usage, sleep quality, and range of motion.

Features of Trial Quality

Pre-randomization inclusion criteria were clearly specified in 125 RCTs. Pre-randomized exclusion criteria were clearly specified in 115 RCTs. Notably, all newly included RCTs had clearly specified pre-randomization inclusion criteria, and 36 had clearly specified pre-randomization exclusion criteria. Patients were blinded in 64 RCTs, while investigators were blinded in 84 RCTs. There were 43 RCTs associated with a pharmaceutical company or manufacturer. Forty-eight RCTs excluded subjects for protocol violation, while 4 RCTs had not reported if subjects were excluded for protocol violation. Forty-one RCTs excluded subjects due to adverse effects, and 3 RCTs

Table 2. Published RCTs in OA of the hand – Non-pharmacologic Therapies (N = 73)

Study (authors and year)	Group	N randomized	N completed	Design	Duration (weeks)	Overall efficacy	Jadad score
Splints/Gloves							
Arazpour et al, 2017[108]	1st CMC splint vs no intervention	25	25	Parallel	4	Splint > no intervention	2
Cantero-Tellez et al, 2018[109]	Ballena orthotic vs Colditz orthotic	84	84	Parallel	13	Equal	2
Cantero-Tellez et al, 2017[111]	Thumb orthosis with MCP vs Thumb orthosis without MCP	66	66	Parallel	1	Equal	2
van der Vegt et al, 2017[128]	Push ortho thumb brace vs personal custom thumb orthotic	63	59	Crossover	6	Equal	2
Can et al, 2020[138]	CMC-MCP splint and patient education vs patient education alone	80	63	Parallel	6	Splint and education > patient education alone	2
Adams et al, 2020[142]	Supported self-management programme (SSM) vs SSM and verum hand splints vs SSM and placebo splint	349	278	Parallel	8	Equal	3
Rannou et al., 2009[64]	Custom made neoprine splint vs usual care	112	98	Parallel	52	Custom splints > usual care	3
Sillem et al., 2011[36]	Prefabricated neoprine splint vs custom neoprine splint	56	54	Cross-over	9	Equal	3
Becker et al., 2013[71]	Neoprene vs custom thermoplast splint	119	65	Parallel	15	Equal	3
Weiss et al., 2004[22]	Neoprene splint (PFN) vs custom-made splint (CMS)	25	25	Cross-over	2	PFN > CMS	1
Swezey et al., 1979[42]	Pressure glove vs control glove vs no glove	5	5	Cross-over	6	Equal	3
Thiele et al., 2009[44]	Futuro fabric splint vs custom leather	30	25	Cross-over	5	Equal	3
Carreira et al., 2010[75]	Thermoplastic splint group vs control	40	40	Parallel	25.7	Thermoplastic splint > control	3
Kjeken et al., 2011[99]	Info plus splint/assistive device vs info	70	66	Parallel	12	Info splint > info	3
Bani et al., 2013[69]	Prefabricated vs custom made splint vs no splint	35	35	Cross-over	10	Custom > prefabricated > No splint	3
Hermann et al., 2014[94]	Exercise vs soft thumb base orthosis	59	55	Parallel	8	Equal	3
Buurke et al., 1999[74]	Uriel splint vs sporlastic splint vs gibortho splint	10	10	Cross-over	12	Uriel splint > others	2
Weiss et al., 2000[23]	Short splint vs long splint vs no splint	26	26	Cross-over	2	Short splint > long splint > no splint	2
Berggren et al., 2001[72]	OT vs OT + textile splint vs OT + leather splint	33	33	Parallel	28	All groups had less hand surgery	2
Wajon et al., 2005[21]	Thumb strap splint + exercise vs short opponens splint + exercise	40	34	Parallel	6	Equal	2

(*Continued*)

Table 2. Published RCTs in OA of the hand – Non-pharmacologic Therapies (N = 73) (*Continued*)

Study (authors and year)	Group	N randomized	N completed	Design	Duration (weeks)	Overall efficacy	Jadad score
Jamison et al, 2017[116]	Vibration glove vs no intervention	69	64	Parallel	13	Vibration glove > no intervention	2
Silva et al, 2020[137]	Night time orthosis and education vs education alone	56	55	Parallel	26	Orthosis and education > education alone	3
Exercises							
Davenport et al., 2012[79]	Stability vs general exercises	39	22	Parallel	26	Equal	5
Rogers et al., 2009[49]	Hand exercise program vs hand cream	76	46	Crossover	48	Equal	3
Osteras et al., 2014[59]	Group/home exercise vs usual care	130	119	Parallel	26	Equal	3
Dziedzic et al., 2015[83]	leaflet/advice vs joint protection vs hand exercise vs joint protection and hand exercise	257	219	Parallel	52	Equal	3
Hennig et al., 2015[93]	Informative leaflet + exercise vs informative leaflet	80	72	Parallel	12	Leaflet + home exercise > leaflet	3
Stamm et al., 2002[39]	Joint protection and exercise (JPE) vs info only	40	40	Parallel	12	JPE > info only	2
Lefler et al., 2004[102]	Strength training exercises vs control	19	18	Parallel	6	Strength training > control	2
Garfinkel et al., 1994[89]	Yoga vs no therapy	26	25	Parallel	10	Yoga > no therapy	0
Kang et al, 2018[117]	Finger exercise and paraffin bath vs paraffin bath alone	29	29	Parallel	8	Finger exercise and paraffin bath > paraffin bath alone	3
Srikesavan et al, 2016[126]	Computer games requiring finger exercises vs finger exercises	17	15	Parallel	6	Insufficient power	3
Perdersini et al, 2019[134]	Neurodynamic mobilization and hand stability exercises vs robot assisted passive movement and hand stability exercises alone	72	72	Parallel	4	Equal	3
Other therapies							
Stange-Rezende et al., 2006[40]	Infrared radiation (IRR) vs control	45	35	Cross-over	8	IRR > control	1
Minten et al, 2018[135]	Low dose radiation vs sham radiation	56	55	Parallel	13	Equal	5
Basford et al., 1987[70]	Helium neon laser vs placebo	81	81	Parallel	3	Equal	5
Brosseau et al., 2005[73]	Low level laser therapy vs placebo	88	86	Parallel	6	Equal	5
Paolillo et al., 2014[60]	US/low level laser vs placebo	45	43	Parallel	12	US/LLL > placebo	3
Cantero-Tellez et al, 2020[110]	High intensity laser vs placebo	43	43	Parallel	12	High intensity laser > placebo	5
Villafane et al., 2011[19]	Kaltenborn therapy vs detuned ultrasound	36	36	Parallel	4	Kaltenborn therapy > detuned ultrasound	3
Villafane et al., 2014[15]	Kaltenborn mobilization vs non-therapeutic ultrasound	29	29	Parallel	4	Kaltenborn > non-therapeutic ultrasound	3

(*Continued*)

Table 2. Published RCTs in OA of the hand – Non-pharmacologic Therapies (N = 73) (*Continued*)

Study (authors and year)	Group	N randomized	N completed	Design	Duration (weeks)	Overall efficacy	Jadad score
Villafane et al., 2012[20]	Maitland's mobilization vs detuned ultrasound	28	28	Parallel	5	Equal	3
Villafane et al., 2012[18]	Radial nerve mobilization vs detuned ultrasound	60	60	Parallel	12	mobilization > detuned ultrasound	1
Villafane et al., 2013[16]	Sliding mobilization of radial nerve vs sham ultrasound	60	60	Parallel	12	Equal	3
Villafane et al., 2013[17]	Passive accessory mobilization vs detuned ultrasound	28	28	Parallel	4	Equal	3
Villafane et al., 2013[14]	Multimodal treatment (mobilization + exercise) vs Sham ultrasound	60	60	Parallel	12	Multimodal > sham ultrasound	5
Cuperus et al., 2015[78]	Multidisciplinary vs phone program	158	139	Parallel	52	Equal	3
Moe et al., 2016[149]	Multidisciplinary program vs none	391	293	Parallel	52	Program > none	3
Stoffer-Marx et al, 2018[125]	Multidisciplinary combined intervention vs routine care and massage ball	153	151	Parallel	8	Multidisciplinary combined intervention > routine treatment	3
Gravas et al, 2019[113]	Occupational therapy vs information pamphlet	180	167	Parallel	13	Equal	3
Perez-Marmol et al, 2017[132]	Fine motor skills rehabilitation program vs conventional occupational therapy	48	42	Parallel	8	Equal	2
Amaral et al, 2018[128]	Assistive devices, group discussions and leaflets vs leaflets alone	39	37	Parallel	13	Assistive devices, group discussions and leaflets > leaflets alone	3
Nemes et al., 2013[57]	Medical plus rehab vs medical	587	390	Parallel	104	Meds plus rehab > meds	2
Stukstette et al., 2013[41]	30 min educational session vs multidisciplinary program	151	147	Parallel	13	Equal	3
Hansson et al., 2010[92]	Self efficacy sessions vs nothing	114	100	Parallel	26	Sessions > nothing	3
Aksoy et al, 2018[106]	Paraffin bath and exercise vs exercise alone	61	59	Parallel	2	Paraffin bath and exercise > exercise alone	2
Savas et al, 2019[130]	Flaxseed poultice and routine treatment vs hot compress and routine treatment vs routine treatment	82	82	Parallel	1	Flaxseed > warm compress = routine treatment	2
Fioravanti et al., 2013[84]	Daily mud packs and thermal baths vs routine care	60	60	Parallel	52	Spa therapy > routine care	3
Gyarmati et al, 2017[114]	Heviz mud vs Heviz mud on gloves	47	47	Parallel	3	Heviz mud > Heviz mud on gloves	3
Dilek et al., 2013[80]	Paraffin bath vs joint protection techniques	56	46	Parallel	12	Paraffin > joint protection	3
Myrer et al., 2011[56]	Paraffin baths vs Paraffin + 20% analgesic baths	35	30	Parallel	4	Paraffin + analgesic > Paraffin	2

(*Continued*)

Table 2. Published RCTs in OA of the hand – Non-pharmacologic Therapies (N = 73) (*Continued*)

Study (authors and year)	Group	N randomized	N completed	Design	Duration (weeks)	Overall efficacy	Jadad score
Graber-Duvemay et al., 1997[90]	Berthollet spa vs topical ibuprofen	116	107	Parallel	24	Spa > Ibuprofen	3
Horvath et al., 2012[96]	Balneotherapy (36 deg) vs Balneotherapy (38 deg) vs magnetotherapy	63	63	Parallel	16	Balneotherapy (38 deg) > Balneotherapy (36 deg) = magnetotherapy	3
Kovacs et al., 2012[100]	Balneotherapy vs warm tap water baths	47	45	Parallel	26	Equal	1
Farhadian et al, 2019[112]	Kinesio tape plus exercise vs exercise alone	38	38	Parallel	8	Kinesio tape and exercise > exercise alone	3
Richmond et al., 2009[48]	Standard wrist strap vs attenuated wrist strap vs demagnetized wrist strap vs copper bracelet	45	42	Cross-over	16	Equal	5
Randall et al., 2000[63]	Stinging nettle leaf topical vs placebo	27	24	Cross-over	12	Stinging nettle leaf > placebo	3
Michalsen et al., 2008[53]	Leeches vs topical diclofenac BID	32	31	Parallel	8.6	Leeches > diclofenac	3
Kanat et al., 2013[98]	Magnetotherapy plus exercises vs sham plus exercises	50	50	Parallel	1.43	Magnetotherapy > sham	1
Renklitepe et al., 1995[47]	Tens electrode glove vs carbon electrode	36	NA*	Parallel	0.7	Glove electrode > carbon electrode	*
Wade et al, 2018[127]	Therapeutic configuration of kinesio tape vs placebo kinesio tape	11	10	Parallel	3	Equal	3
Kasapoglu et al, 2017[118]	Peloid therapy and exercise vs exercise alone	63	55	Parallel	2	Peloid therapy and exercise > exercise alone	3
Barnard et al, 2020[115]	Acupuncture vs sham needling	74	70	Parallel	3	Equal	3

*Not available.
CMC, carpal metacarpal; SSM, supported self-management; PNF, neoprene splint; CMS, custom-made splint; IRR, infrared radiation; LLL, low-level laser; JPE, joint protection and exercise; RCT, randomized controlled trial; OA, osteoarthritis; OT, Occupational therapist.

did not report data on exclusion for adverse effects. One hundred four RCTs did not specify whether subjects had prior exposure to the test agents. Only 59 of the 133 RCTs controlled for supplemental analgesic use. Sixty-five RCTs described sample size calculations. Ninety-one RCTs described the method of randomization, and 66 described the method of blinding. There was an a priori main outcome variable described in 106 RCTs. The success of blinding was only evaluated at the end of the study in 4 RCTs.

One hundred one RCTs provided sufficient data for the reader to ensure the groups were comparable at baseline. One hundred nine RCTs used appropriate statistical analyses. Examples of inappropriate statistical analyses included: (1) using a parametric statistical test for non-parametric data, (2) stating that a marginally insignificant statistical test was still statistically "significant," (3) using a paired statistical test for independent groups, and (4) using multiple comparisons without employing any statistical correction. Eighty-three RCTs had either no withdrawals or used an intention-to-treat analysis. Only 44 RCTs adequately described the method used to ensure allocation concealment.

Methodological Quality Based on Jadad's Scores

The median Jadad score for the entire group of RCTs was 3, with a range of 0-5. The mean Jadad score for all entries was 3.08. Increasing Jadad scores were noted over time. The mean Jadad scores for the decades during which more than 5 RCTs were published were 2.14 in the 1990s, 2.91 in the 2000s, and 3.27 in 2010-2020.

Meta-Analysis

A formal meta-analysis was not performed for several reasons. Firstly, there is a limited number of high-quality RCTs for each intervention and significant clinical heterogeneity exists between these high-quality trials. Additionally, meta-analyses would involve comparisons of pain and function which are typically presented as continuous outcome variables in these RCT. This would require calculation

of the standardized mean difference using means and standardized deviations of these outcomes. These were not routinely reported in the available RCTs. Due to significant heterogeneity, limited quality, and quantity of data, a meta-analysis would not produce reliable and clinically applicable results. Lastly, the purpose of this review is to critically evaluate the methodology of included RCTs, as opposed to a detailed analysis and pooling of trial results. For these reasons, a meta-analysis was not performed.

Summary of Results of Therapy

Non-steroidal Anti-inflammatory Drug Therapies

There were no new RCTs evaluating non-steroidal anti-inflammatory drugs (NSAIDs) identified in this review. Of the 9 previously recorded studies, 5 RCTs compared systemic NSAIDs to placebo and was shown to be efficacious in all cases. Specific interventions included meclomen 100 mg Three times a day (TID),[34] ibuprofen 800 mg per os (PO) twice a day (BID),[82] lumiracoxib 200 mg and 400 mg daily,[91] and naproxen 250 mg PO TID[31] and 500 mg PO BID,[76] all of which resulted in decreased pain compared to placebo after 2-4 weeks of therapy. Four trials compared topical NSAIDs to placebo and demonstrated superiority in 3 trials.[27,28,66] Topical diclofenac was found to be equal in efficacy to placebo by Thiesce and Dougadous[45] in 1995. However, this trial was limited by its crossover design and small population of 20 patients.

Despite its efficacy, NSAIDs should be used judiciously and can be associated with adverse events with chronic use. For example, systemic NSAIDs can lead to worsening hypertension, renal dysfunction, and gastrointestinal bleeding.[31] Topical NSAIDs have lower systemic absorption but may be associated with contamination of other body surfaces such as the eyes.

Biologic Therapies

Biologic medications were unsuccessful in the treatment of erosive hand OA. Tumor necrosis factor-α inhibitors, including adalimumab and etanercept, were investigated in 4 RCTS, all of which showed no difference in their primary endpoint of pain control compared to placebo.[13,77,105,120] Lutikizumab is an anti-interleukin-1α/β dual variable domain immunoglobulin and was not found to be effective in reducing pain or imaging outcomes in patients with erosive hand OA in a recent phase IIa, placebo-controlled RCT.[121] Otilimab is a novel monoclonal antibody against granulocyte–macrophage colony-stimulating factor that was compared against placebo for treatment of hand OA by Schett et al[139] in 2020. Results of this phase IIa, exploratory trial showed a non-statistically significant trend toward reduction in pain and functional impairment. Lastly, tocilizumab, an interleukin-6 receptor antagonist, did not show a reduction in pain VAS compared to placebo according to a single RCT.[140] Along with this inconclusive data, the prevalent risks of biologic medication including risk of immunosuppression, cytopenia, infection, and infusion reactions limit the utilization of biologic therapy in the management of hand OA.[113,77,120,121,139]

Hydroxychloroquine

Two recent RCTs compared hydroxychloroquine to placebo. In the study by Lee et al.[131] there was no difference between hydroxychloroquine 400 mg daily and placebo for pain and function at 24 weeks. This was consistent with the findings of the RCT by Kingsbury et al.[119] In this study, synovitis detected by ultrasound was not associated with a difference in treatment response. Adverse events associated with hydroxychloroquine described in these trials include prolonged QT interval and rash.[119,131] Other well-known side effects of hydroxychloroquine include retinal toxicity and myotoxicity.

Oral Corticosteroids

One new RCT evaluating oral prednisolone use was identified in this review. Kroon et al[147] compared prednisolone 10 mg PO daily to placebo in patients with radiographic features of DIP/PIP joint inflammation and found that prednisolone treatment led to substantial improvement in pain and function at 6 weeks. This stands in contrast to Wenham et al's[24] 2012 placebo-controlled RCT which showed no difference in pain and function after 4 weeks of treatment with 5 mg of prednisolone. A trial comparing a formulation of dipyridamole–prednisolone was found to be efficacious for pain but caused significant adverse effects including headache.[101] Other well-described adverse effects of systemic steroids include hypertension, hyperglycemia, immunosuppression, and osteoporosis with chronic use. Overall, these findings suggest that prednisolone at a dose of 10 mg may improve pain in selected patients with inflammatory hand OA.

Intra-articular Therapies

One new RCT evaluating intra-articular therapies was identified in this review. Malahias et al[136] compared platelet-rich plasma to injections of methylprednisolone and lidocaine in patients with trapeziometacarpal OA. They found no difference in pain and function at 3 months but observed significant, sustained improvement at 12 months in the platelet-rich plasma arm. Previous RCTs have compared intra-articular steroids and hyaluronate against placebo, often with conflicting results.

Orthotics and Splints

Twenty-two RCTs in total, including 8 new RCTs since our last review, studied the use of orthotics. Fifteen trials intervened only on the first CMC joint. The remaining RCTs intervened on different combinations of first CMC, Metacarpal phalangeal (MCP) joint, and interphalangeal (IP) joints, while 3 RCTs did not specify the active joint. Of the RCTs evaluating the first CMC, outcomes were heterogenous, with 8 RCTs showing improvements in pain compared to the control group[22,23,64,69,74,75,108,135] and 7 showing no difference.[21,36,71,72,94,109,142] The median Jadad score in this group was 2 compared to a median of 3 for all RCTs in this review, owing largely to the lack of double blinding with these interventions.

Other Therapies

The following pharmacologic therapies demonstrated efficacy across multiple RCTs: intramuscular and intravenous clodronate, topical capsaicin, topical trolamine salicylate, and oral chondroitin sulfate. Non-pharmacologic therapies that demonstrated efficacy across multiple studies include joint strengthening exercises, mobilization, paraffin baths, and multidisciplinary combined intervention. The remainder of the therapies had mixed or negative results, were compared to other therapies in single studies, or efficacy compared to placebo was only demonstrated in a single study.

Discussion

The results of this systematic review were consistent with the recommendations from the European Alliance of Associations for Rheumatology (EULAR) 2018[150] and American College of Rheumatology (ACR) 2019[151] guidelines for the management of hand OA. Both societies strongly recommend NSAIDs as first-line therapies for hand OA, with weaker recommendations for other analgesics such as acetaminophen and chondroitin sulfate. These have uniformly shown efficacy in RCTs included in this systematic review.

In terms of non-pharmacologic therapy, both societies strongly recommend orthotics for first CMC joint OA. However, RCTs supporting this recommendation identified in this review demonstrated heterogenous conclusions and were comparatively of lower quality as

evidenced by lower Jadad scores. This stems from the inherent difficulties of blinding patients to interventions. Furthermore, there is insufficient evidence to direct the type of orthotic that should be used, and it remains unclear whether these findings can be applied to patients with OA in joints outside of the first CMC. Additional standardized, high-quality RCTs are necessary to strengthen this recommendation.

Further trends can be gleaned from the results of this systematic review. Thirty-eight new RCTs have been published from December 2015 to December 2020. Many new RCTs have studied biologic Disease Modifying Antirheumatic Drugs (DMARDs), with 5 of the 7 total RCTs performed thus far conducted within the past 5 years. Two recent, high-quality RCTs showed that hydroxychloroquine was inefficacious at improving pain or functioning in hand OA compared to placebo. It is expected that research in this field will expand in the future. However, current evidence does not support the use of anti-malarials or biologic DMARDs in the treatment of hand OA.

Since the previous update, there has been an overall improvement to the methodology of RCTs in terms of allocation concealment, intention-to-treat analysis, and description of randomization and blinding. This is reflected by improvements in the mean Jadad score from 3.08 in all trials to 3.37 in the 38 new trials evaluated in this review.

Although trial quality has improved from our previous review, important information specific to hand OA trials continue to be underreported. As described in the OARSI Consensus Guidelines for the Design and Conduct of Trials in Subjects with Hand OA, these include the use of validated diagnostic criteria during patient enrollment, description of hand OA phenotype, and pattern of joint involvement and radiographic disease state, all of which are inconsistently reported in recent trials.[152] Additionally, both the OARSI Consensus Guidelines and the OMERACT working group[153] have described key domains and outcome measures specific to hand OA trials. While measures of pain and function were routinely described, additional key outcomes including patient global assessment, health-related quality of life, and joint strength continue to be reported in less than half of recent studies. These should be assessed in all future RCTs evaluating hand OA therapies.

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