EXTENDED REPORT

EULAR evidence based recommendations for the management of hand osteoarthritis: Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT)

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Appendices 1 and 2 giving details of the search strategies for hand OA and the study designs can be found at http://ard.bmj.com/supplemental

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Objectives: To develop evidence based recommendations for the management of hand osteoarthritis (OA).
Methods: The multidisciplinary guideline development group comprised 16 rheumatologists, one physiatrist, one orthopaedic surgeon, two allied health professionals, and one evidence based medicine expert, representing 15 different European countries. Each participant contributed up to 10 propositions describing key clinical points for management of hand OA. Final recommendations were agreed using a Delphi consensus approach. A systematic search of Medline, Embase, CINAHL, Science Citation Index, AMED, Cochrane Library, HTA, and NICE reports was used to identify the best available research evidence to support each proposition. Where possible, the effect size and number needed to treat were calculated for efficacy. Relative risk or odds ratio was estimated for safety, and incremental cost effectiveness ratio was used for cost effectiveness. The strength of recommendation was provided according to research evidence, clinical expertise, and perceived patient preference.
Results: Eleven key propositions involving 17 treatment modalities were generated through three Delphi rounds. Treatment topics included general considerations (for example, clinical features, risk factors, comorbidities), non-pharmacological (for example, education plus exercise, local heat, and splint), pharmacological (for example, paracetamol, NSAIDs, NSAIDs plus gastroprotective agents, COX-2 inhibitors, systemic slow acting disease modifying drugs, intra-articular corticosteroids), and surgery. Of 17 treatment modalities, only six were supported by research evidence (education plus exercise, NSAIDs, COX-2 inhibitors, topical NSAIDs, topical capsaicin, and chondroitin sulphate). Others were supported either by evidence extrapolated from studies of OA affecting other joint sites or by expert opinion. Strength of recommendation varied according to level of evidence, benefits and harms/costs of the treatment, and clinical expertise.
Conclusion: Eleven key recommendations for treatment of hand OA were developed using a combination of research based evidence and expert consensus. The evidence was evaluated and the strength of recommendation was provided.

Hand osteoarthritis (OA) is a common condition,[1 2] though its prevalence varies according to the definition used. For example, most people aged 55 years and over have radiographic changes of OA affecting at least one hand joint,[3] and about one fifth of this population have symptomatic hand OA.[4] The correlation between symptoms and radiographic change is even less for hand OA than for OA of the hip or knee. Although many people affected by hand OA may never seek medical advice,[5 6] its impact and associated disability are significant.[3 4 6] Importantly, many of the clinical consequences of hand OA are site-specific (for example, interference with grip and fine precision pinch, dissatisfaction with cosmetic appearance) and distinct from those of knee and hip OA. Furthermore, compared with large joint OA, the small size and accessibility of hand joints make them amenable to a different range of interventions. Owing to differences in anatomy, function, risk factors, and outcomes, OA at different sites may also show a different response to the same treatment. Therefore interventions for OA need to be examined in a site-specific fashion.

After developing separate evidence based recommendations for management of knee and hip OA[7–9] the EULAR OA Task Force was commissioned in 2005 to examine the management of hand OA. As before, it was agreed that recommendations should be developed using an evidence based format that involves both a systematic review of research evidence and expert consensus.

METHODS

Participants

A multidisciplinary guideline development group was commissioned by the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Twenty one experts in the field of OA (16 rheumatologists, one physiatrist, one orthopaedic surgeon, two allied health professionals, and

Abbreviations: ASU, avocado soybean unsaponifiables; CI, confidence interval; CT, controlled trial; CV, cardiovascular; ES, effect size; GI, gastrointestinal; MeSH, medical subject heading; NNT, number needed to treat; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; QALY, quality of life year; OA, osteoarthritis; OR, odds ratio; RCT, randomised controlled trial; RR, relative risk; SOR, strength of recommendation; SYSADOAs, symptomatic slow acting drugs for osteoarthritis; VAS, visual analogue scale

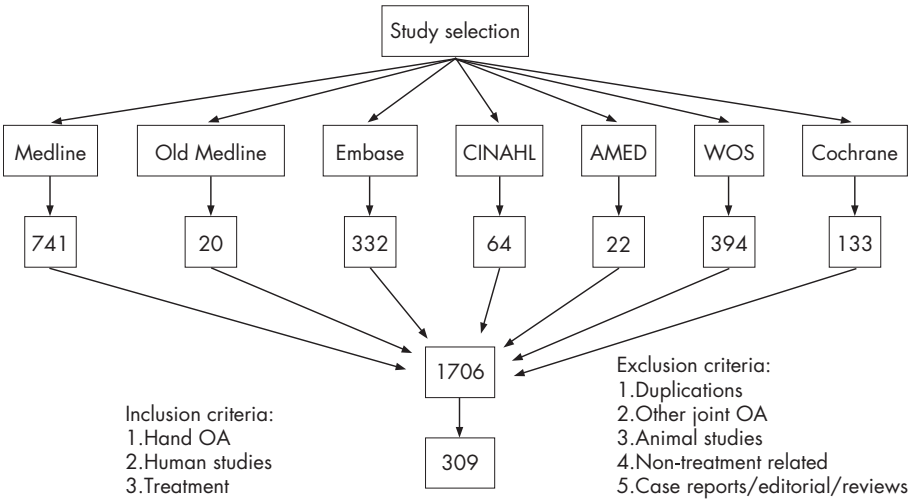

Figure 1 Literature search and study selection.

one evidence based medicine expert) representing 15 European countries agreed to take part in the study. The objectives were (1) to agree key propositions relating to the management of hand OA; (2) to identify and critically appraise research evidence for the effectiveness and cost effectiveness of relevant treatments; and (3) to generate recommendations based on a combination of the best available evidence and expert opinion.

Experts' consensus

Each participant was asked to contribute independently up to 10 propositions relating to key clinical aspects in the management of hand OA. Consensus about the propositions was reached using the Delphi technique. The initial propositions were collated into a single list by a co-chair who was not involved in the generation of propositions (MD). Where necessary, the propositions were edited for English grammar and phrasing, and similar, substantially overlapping propositions were combined. The edited list was then returned to the experts and they were asked to select the 10 most important from the list. Propositions were accepted if over half of the participants accepted them in any round, whereas propositions receiving only one to three votes were removed. Propositions receiving less than 50% of the votes but more than three votes entered the next Delphi round. The Delphi exercise was stopped when no further propositions had between three votes and 50% of the votes. There was no predetermined limit to the number of final propositions selected.

Systematic literature search

A systematic search of the literature published between January 1945 and January 2006 was undertaken using Medline (1966-), Old Medline (1950-), Embase (1980-), CINAHL (1980-), Science Citation Index through Web of Science (WOS; 1945-), Allied Complementary Medicine (AMED; 1985-), and Cochrane Library databases (1996-present). The search in the Cochrane Library included the Cochrane Reviews, Abstracts of Quality Assessed Systematic Reviews, The Cochrane Controlled Trial Register, NHS Economic Evaluation Databases, Health Technology Assessment Database, and NHS Economic Evaluation Bibliography Details Only. The search included both a general search and a proposition-specific search. The general search strategy consisted of two basic components: hand OA in whatever possible terms in the databases (Appendix 1, available at http:www.annrheumdis.com/supplemental); and types of research in the forms of systematic review/meta-analysis, randomised controlled trial (RCT)/controlled trial (CT), uncontrolled trial, cohort study, case-control study, cross-sectional study, and economic evaluation (Appendix 2, http:www.annrheumdis.com/supplemental). The two components were combined to search for the current available research evidence from published reports. Summary results of the search were reported to the committee before the Delphi exercise.

After the Delphi exercise, the proposition-specific search was undertaken to identify evidence for each specific proposition. The search strategy included the terms for hand OA (Appendix 1) and any possible terms for the specific component of each proposition. For example, ''paracetamol'', ''acetaminophen'', and ''simple analgesics'' were used for paracetamol. The results of the general search and the proposition-specific search were then combined and duplications excluded. A medical subject heading (MeSH) search, together with a key word search was used whenever possible. All MeSH search terms were exploded. The reference lists within reviews or systematic reviews were examined, and any additional studies meeting the inclusion criteria were included.

Inclusion/exclusion criteria

Only studies concerning treatment and clinical outcomes of hand OA were included as direct evidence. Studies that examined an intervention for OA at several sites were included if data were presented separately for hand OA. The main focus of interest was on systematic reviews/meta-analyses, RCTs/CTs, uncontrolled trials (for example, one group intervention, quasi-experimental study, etc), cohort studies, case-control studies, cross-sectional studies, and economic evaluations. Case reports, review articles, editorials, and commentaries were excluded. Studies on healthy subjects or animals were excluded (fig 1).

Table 1 Level of evidence

Category	Evidence from:
Ia	Meta-analysis of RCTs
Ib	RCT
IIa	Controlled study without randomisation
IIb	Quasi-experimental study
III	Non-experimental descriptive studies, such as comparative, correlation, and case-control studies
IV	Expert committee reports or opinion or clinical experience of respected authorities, or both

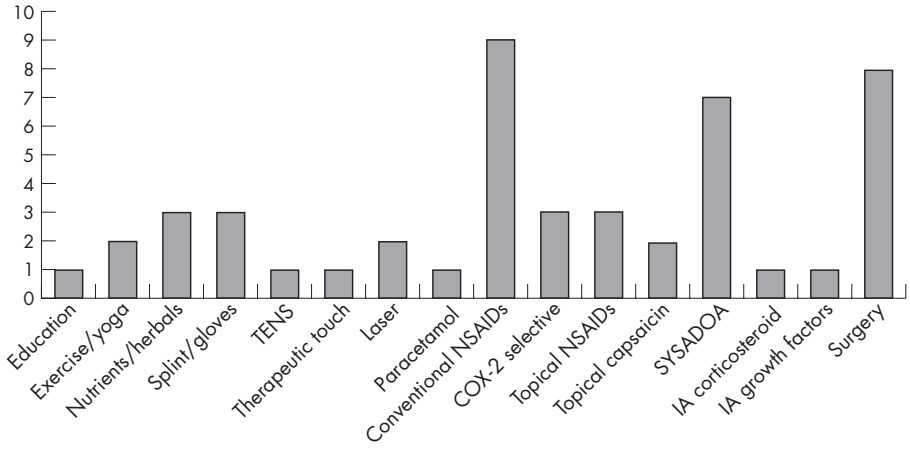

Figure 2 Treatment modalities investigated by RCTs or CTs.

Level of evidence

Evidence for efficacy was categorised according to the design characteristics of available studies using an established hierarchy (table 1).[10] Questions were answered using the best available evidence. For example, if a question on the effect of an intervention could be answered by level Ia evidence (that is, systematic review of RCTs) then studies of a weaker design (RCT, level Ib) were not reviewed. Results of the latest systematic review containing the largest number of studies were used if there was more than one systematic review for the same question. However, questions on adverse effects were answered using both RCTs and observational studies irrespective of hand OA because RCTs are not necessarily the best method to assess adverse effects, and hand OA is not necessarily the target condition for which the side effects of a particular intervention are assessed. Questions of cost effectiveness were answered according to the outcome measure of effectiveness. For example, if the effectiveness was measured as "pain relief" only, studies for hand OA were eligible. If the effectiveness was measured as "adverse events averted", any study for the proposed intervention was included.

In the absence of direct evidence for hand OA, any evidence for treatment of OA at other joint sites was examined. However, in such cases support for the proposition was categorised as expert opinion (IV); we did not directly extrapolate and report for hand OA the category of evidence for OA at other sites.

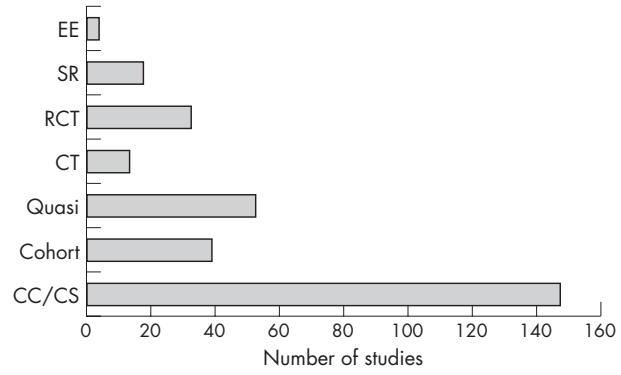

Figure 3 Type of evidence for hand OA. EE, economic evaluation; SR, systematic review; RCT, randomised controlled trial; CT, controlled trial; Quasi, quasi experiments; Cohort, cohort studies; CC/CS, case-control or cross-sectional study.

Outcome measures

Efficacy

For treatment efficacy, effect size (ES) compared with placebo or active control as specified within the propositions was calculated for continuous outcomes such as pain scores. ES is the standard mean difference—that is, the mean difference between a treatment and a control group divided by the standard deviation of the difference. It is therefore free of units and comparable across interventions. Clinically, an ES of 0.2 is considered small, 0.5 is moderate, and >0.8 is large.[11] For dichotomous data, such as the percentage of patients with more than 50% pain relief, the number needed to treat (NNT) was estimated.[12] The NNT is the estimated number of patients that need to be treated to achieve a specified target treatment effect. The 95% confidence interval (CI) of the NNT was calculated by Altman's method.[13]

Adverse effects

For adverse effects, the relative risk (RR) was calculated from RCTs or cohort studies for incident risk, and from cross-sectional studies for prevalent risk, whereas the odds ratio (OR) was calculated from case-control studies.[14] Both present how many times more likely (or less likely) a subject who is exposed to the drug/intervention has adverse events than a subject who is not exposed. RR or OR = 1 indicates no increased risk, whereas RR or OR >1 or <1 indicates an increased or decreased risk, respectively.

Economic evaluation

For economic evaluations the incremental cost effectiveness ratio was calculated as the difference in cost between two treatments divided by their difference in effectiveness. When available, quality of life years (QALYs) were used for the measurement of effectiveness, otherwise disease-specific outcomes such as pain relief and functional improvement were used. In addition, study design, comparator, perspective, time horizon, discounting, total costs, and effectiveness were critically appraised.

The outcomes are presented with the point estimate (for example, mean) and 95% CI unless otherwise stated. Statistical pooling was undertaken as appropriate[15] when there was more than one study and a systematic review was not available.

Strength of recommendation

The strength of recommendation (SOR) was graded using the EULAR visual analogue scale (VAS) and ordinal scale.[9 16] Participants were asked to score their SOR for each proposition using both a 0–100 mm VAS (0 mm = not recommended at all,

Table 2 Experts' propositions developed through three Delphi rounds—order according to topic (general, non-pharmacological, pharmacological, invasive, and surgical)

No	Proposition	SOR (95% CI) VAS100	A-B (%)
1	Optimal management of hand OA requires a combination of non-pharmacological and pharmacological treatment modalities individualised to the patient's requirements	95 (92 to 98)	100
2	Treatment of hand OA should be individualised according to localisation of OA; risk factors (age, sex, adverse mechanical factors); type of OA (nodal, erosive, traumatic); presence of inflammation; severity of structural change; level of pain, disability and restriction of quality of life; comorbidity and co-medication (including OA at other sites); and the wishes and expectations of the patient	84 (76 to 92)	92
3	Education concerning joint protection (how to avoid adverse mechanical factors) together with an exercise regimen (involving both range of motion and strengthening exercises) are recommended for all patients with hand OA	59 (45 to 74)	38
4	Local application of heat (for example, paraffin wax, hot pack), especially before exercise, and ultrasound are beneficial treatments		
	Overall	56 (40 to 71)	33
	Heat	77 (69 to 85)	77
	Ultrasound	25 (15 to 36)	0
5	Splints for thumb base OA and orthoses to prevent/correct lateral angulation and flexion deformity are recommended	67 (57 to 77)	69
6	Local treatments are preferred over systemic treatments, especially for mild to moderate pain and when only a few joints are affected. Topical NSAIDs and capsaicin are effective and safe treatments for hand OA	75 (68 to 83)	86
7	Because of its efficacy and safety paracetamol (up to 4 g/day) is the oral analgesic of first choice and, if successful, is the preferred long term oral analgesic	87 (78 to 96)	92
8	Oral NSAIDs should be used at the lowest effective dose and for the shortest duration in patients who respond inadequately to paracetamol. The patient's requirements and response to treatment should be re-evaluated periodically. In patients with increased gastrointestinal risk, non-selective NSAIDs plus a gastroprotective agent, or a selective COX-2 inhibitor (coxib) should be used. In patients with increased cardiovascular risk, coxibs are contraindicated and non-selective NSAIDs should be used with caution	81 (74 to 88)	100
9	SYSADOA (for example, glucosamine, chondroitin sulphate, avocado soybean unsaponifiables, diacerhein, intra-articular hyaluronan) may give symptomatic benefit with low toxicity, but effect sizes are small, suitable patients are not defined and clinically relevant structure modification, and pharmacoeconomic benefits have not been established	63 (48 to 76)	69
10	Intra-articular injection of long-acting corticosteroid is effective for painful flares of OA, especially trapeziometacarpal joint OA.	60 (47 to 74)	46
11	Surgery (for example, interposition arthroplasty, osteotomy or arthrodesis) is an effective treatment for severe thumb base OA and should be considered in patients with marked pain and/or disability when conservative treatments have failed	68 (56 to 79)	62

SOR, strength of recommendation; VAS, visual analogue scale; OA, osteoarthritis; NSAIDs, non-steroidal anti-inflammatory drugs; SYSADOAs, symptomatic slow acting drugs for osteoarthritis.

100 mm = fully recommended) and an A-E ordinal scale (A = fully recommended, B = strongly recommended, C = moderately recommended, D = weakly recommended, and E = not recommended). Participants were asked to determine their scores by taking into account both the research evidence (efficacy, safety, and cost effectiveness) and their clinical expertise (logistics, patient perceived acceptance, and tolerability). The mean VAS and 95% CI and the percentage of strongly to fully recommended (A-B) were calculated.

Future research agenda

Each participant was asked to propose up to 10 topics for the future research agenda based on current available evidence and clinical experience in the management of hand OA. Similar, substantially overlapping propositions were combined by an independent co-chair uninvolved in generating propositions (MD), and then a Delphi approach was used to reach a consensus on up to 10 most important topics. The same criteria as those used to select management propositions were employed (that is, accepted if more than 50% votes; removed if fewer than three votes; next round if less than 50% but more than three votes).

RESULTS

Treatment modalities and types of evidence

The general literature search yielded 1706 hits. Of these, 309 met inclusion and exclusion criteria (fig 1). Forty eight of the 309 studies were RCTs or CTs in which a variety of treatment modalities were examined, including non-pharmacological (for example, education and exercise), pharmacological (for example, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs)), and surgical treatments (for example, trapeziectomy with interposition arthroplasty versus trapeziectomy) (fig 2). Evidence in the form of systematic reviews and economic evaluations was also identified. However, a large number of studies had non-experimental designs such as case-control and cross-sectional studies (fig 3).

Experts' consensus

The experts were informed of the results of the general literature search and then the Delphi exercise was undertaken. One hundred and fifty eight propositions were produced initially, and 11 final propositions were agreed after three anonymous Delphi rounds (table 2).

Assessment of propositions

The proposition-specific search was then undertaken and the additional studies that were identified were added to the database to evaluate each proposition or modalities within each proposition. The following propositions are grouped by topic (general, non-pharmacological, pharmacological, invasive, and surgical) with no weighting according to order.

1. Optimal management of hand OA requires a combination of non-pharmacological and pharmacological treatment modalities individualised to the patient's requirements

Level of evidence: IV.

Strength of recommendation (95% CI): 95 (92 to 98).

Although this statement is logical and represents recognised good clinical practice, there are no direct comparisons or scientific evidence from appropriately designed clinical trials

Table 3 Evidence of efficacy—pooled effect size (ES) and number needed to treat (NNT) for hand OA

Intervention*	Studies: Level*	No of studies (patients)	Duration	ES_{pain} (95% CI)	$ES_{function}$ (95% CI)	NNT (95% CI)	References
Education+exercise *v* OA information	Ib	1 (40)	3 months	–	–	2 (1 to 6)	19
Splint (full *v* half)	Ia	2 (47)	1 week	0.64 (0.02 to 1.26)	–	4 (2 to 13)	21, 22
NSAIDs	Ia	2 (654)	2–4 weeks	0.40 (0.20 to 0.60)	0.17 (−0.03 to 0.36)	3 (2 to 6)	23, 24
Topical NSAIDs	Ia	2 (131)	2–3 hours	0.77 (0.32 to 1.22)	–	NS	25
Topical capsaicin	Ia	2 (318)	4 weeks	–	–	3 (2 to 5)	26
Chondroitin sulphate	Ib	1 (92)	3 years	–	–	NS	27
Chondroitin polysulphate	Ib	1 (130)	3 years	–	–	8 (4 to 166)	27
IA corticosteroid	Ib	1 (40)	24 weeks	NS	NS	NS	28
Surgery	Ia	7 (384)	3–66 months				
T+LRTI/IA *v* T				−0.17 (−0.57 to 0.24)	0.03 (−0.37 to 0.44)	NS	29
TJR *v* T+IA				−0.3 (−1.07 to 0.47)	–	–	29

*Compared with placebo, unless otherwise stated; †see table 1 for definitions
No, number of studies; ES, effect size of treatment compared with placebo unless otherwise stated; NNT, number needed to treat to obtain moderate to excellent (more than 50%) pain relief or symptomatic improvement; –, not available; NS, not significant; T, trapeziectomy; LRTI, ligament reconstruction and tendon interposition; IA, interposition arthroplasty; TJR, total joint replacement.

using either factorial or pragmatic designs to inform this statement. The statement is supported by expert opinion alone (level IV).

2. Treatment of hand OA should be individualised according to localisation of OA; risk factors (age, sex, adverse mechanical factors); type of OA (nodal, erosive, traumatic); presence of inflammation; severity of structural change; level of pain, disability, and restriction of quality of life; comorbidity and co-medication (including OA at other sites); and the wishes and expectations of the patient

Level of evidence: IV.
Strength of recommendation (95% CI): 84 (76 to 92).

This statement includes a number of factors derived from patient assessment that may be relevant in guiding clinical decisions. However, although it has considerable commonsense face validity, there is little experimental evidence to support it. RCTs predominantly investigate the efficacy of one or two specific monotherapies in highly selected homogeneous populations of otherwise fit subjects with hand OA. The evidence obtained from such experimental studies, therefore, may not be directly applicable to the whole population of subjects with hand OA, especially those with comorbidities. In addition, because of exclusion of many variables that may influence efficacy it is often difficult to determine predictors of outcome (positive or negative). Any management plan requires consideration of patient beliefs and expectations and a holistic approach that takes into account comorbidity and other treatment requirements.[17 18]

In conclusion, this statement is a pragmatic attempt to apply the best care to the individual patient but is one supported by expert opinion alone (level IV).

3. Education concerning joint protection (how to avoid adverse mechanical factors) together with an exercise regimen (involving both range of motion and strengthening exercises) are recommended for all patients with hand OA

Level of evidence: IV.
Strength of recommendation (95% CI): 59 (45 to 74).

One RCT has compared a joint protection programme plus home based hand exercise (range of motion) versus hand OA information alone in 40 patients with hand OA.[19] The NNT for improvement in patient global function was 2 (95% CI 1 to 6), suggesting significant clinical benefit from the combined treatment (table 3). However, the comparison group was not an ideal control to examine this proposition and because the two elements of treatment were not directly compared we do not know whether the benefit was derived from the range of motion exercise, the joint protect programme, or both; further study using a factorial design and larger sample size is required to answer this. Furthermore, "joint protection" is usually given as part of a broader education intervention and whether any benefit is directly attributable to avoidance of adverse mechanical factors remains unproved. Education concerning joint protection is better studied, and reported to be of benefit, in patients with rheumatoid arthritis,[20] but whether this is generalisable to non-inflammatory OA is unclear. Strengthening exercises for hand OA have not been studied directly.

Nevertheless, both education and exercise are well established treatment modalities for many chronic painful conditions, including OA. Two well conducted systematic reviews have demonstrated that in patients with OA affecting various sites education significantly relieves pain (ES = 0.06, 95% CI 0.02 to 0.10) and improves function (ES = 0.02, 95% CI 0.02 to 0.10),[30 31] though both these effects are small. In contrast, exercise provides a larger ES for pain relief (0.32, 95% CI 0.23 to 0.42) and functional improvement (0.32, 95% CI 0.23 to 0.41).[32]

In conclusion, direct evidence for education or exercise alone in the treatment of hand OA is lacking. Robust evidence for the combination therapy of these two modalities has yet to be determined. Therefore the proposition is supported predominantly by expert opinion (level IV).

4. Local application of heat (for example, paraffin wax, hot pack), especially before exercise, and ultrasound are beneficial treatments

Level of evidence: IV.
Strength of recommendation (95% CI)—overall: 56 (40 to 71); heat: 77 (69 to 85); ultrasound: 25 (15 to 36).

There are no clinical trials of heat or ultrasound specifically for hand OA. A Cochrane systematic review has been undertaken on thermotherapy for OA in general.[33] However, only three RCTs were included, none were for hand OA, and only one investigated the adjuvant effects of local application of hot packs (or cold packs) to physiotherapy for knee OA. This study showed that at 3 weeks there was no difference between combined hot packs plus physiotherapy, combined cold packs plus physiotherapy, and physiotherapy alone. Whether pre-application of heat or cold would assist exercise was not

Table 4 Evidence of safety—pooled relative risk (RR) or odds ratio (OR)* and 95% confidence interval (CI)

Intervention†	Adverse events	RR/OR (95% CI)	Evidence	References
Paracetamol	GI discomfort	0.80 (0.27 to 2.37)	RCTs	48
	GI perforation/bleed	3.60 (2.60 to 5.10)	Case-control study	49
	GI bleeding	1.2 (0.8 to 1.7)	Case-control studies	50
	Renal failure	2.5 (1.7 to 3.6)	Case-control study	51
	Renal failure	0.83 (0.50 to 1.39)	Cohort study	52
Topical NSAIDs	GI events	0.81 (0.43 to 1.56)	RCTs	25
	GI bleed/perforation	1.45 (0.84 to 2.50)	Case-control	42
Glucosamine sulphate preparations	Any	0.97 (0.88 to 1.08)	RCTs	53
Diacerhein	Diarrhoea	3.98 (2.90 to 5.47)	RCTs	54, 55
NSAIDs	GI perforation/ulcer/bleed	5.36 (1.79 to 16.10)	RCTs	56
	GI perforation/ulcer/bleed	2.70 (2.10 to 3.50)	Cohort studies	56
	GI perforation/ulcer/bleed	3.00 (2.70 to 3.70)	Case-control studies	56
GI protective strategies versus NSAID alone				
H2 blocker+NSAID	Serious GI complications	0.33 (0.01 to 8.14)	RCTs	57
	Symptomatic ulcers	1.46 (0.06 to 35.53)	RCTs	57
	Serious CV or renal events	0.53 (0.08 to 3.46)	RCTs	57
PPI+NSAID	Serious GI complications	0.46 (0.07 to 2.92)	RCTs	57
	Symptomatic ulcers	0.09 (0.02 to 0.47)	RCTs	57
	Serious CV or renal events	0.78 (0.10 to 6.26)	RCTs	57
Misoprostol+NSAID	Serious GI complications	0.57 (0.36 to 0.91)	RCTs	57
	Symptomatic ulcers	0.36 (0.20 to 0.67)	RCTs	57
	Serious CV or renal events	1.78 (0.26 to 12.07)	RCTs	57
	Diarrhoea	1.81 (1.52 to 2.61)	RCTs	58
COX-2 selective	Serious GI complications	0.61 (0.34 to 1.10)	RCTs	57
	Symptomatic ulcers	0.41 (0.26 to 0.65)	RCTs	57
	Serious CV or renal events	0.95 (0.55 to 1.66)	RCTs	57
COX-2 specific (coxibs)	Serious GI complications	0.55 (0.38 to 0.80	RCTs	57
	Symptomatic ulcers	0.49 (0.38 to 0.62)	RCTs	57
	Serious CV or renal events	1.19 (0.80 to 1.75)	RCTs	57
Surgery				
T+LRTI/IA *v* T	Any	2.12 (1.24 to 3.60)	RCTs	29
TJR *v* T+IA	Any	5.00 (0.26 to 95.02)	RCTs	29

*RR was calculated for an RCT or cohort study and OR was for a case-control study. RR (or OR) = 1: no difference between treatment and control; RR (or OR)>1: more risky with treatment; RR <1: less risky with treatment. The results were pooled if more than one study was involved; †compared with placebo/non-exposure unless otherwise stated.
H_2-blockers, histamine type 2 receptor antagonists; PPIs, proton pump inhibitors; GI, gastrointestinal; CV, cardiovascular; CNS, central nervous system; T, trapeziectomy; LRTI, ligament reconstruction and tendon interposition; IA, interposition arthroplasty; TJR, total joint replacement.

examined. Although local heat application is generally considered an effective and safe means of relieving pain, evaluating its efficacy is problematic in a blinded controlled design.

Ultrasound has not been studied directly for hand OA but has been investigated in large joint OA. A Cochrane systematic review of three RCTs demonstrated that ultrasound had no benefit over placebo or short wave diathermy for people with hip or knee OA.[34]

In conclusion, direct research evidence for the benefit of local application of heat or ultrasound as a pretreatment or in combination with other physical therapies for hand OA is lacking, and there is no positive research evidence for efficacy of ultrasound for hip or knee OA. Therefore the proposition is currently based on expert opinion alone (level IV).

5. Splints for thumb base OA and orthoses to prevent/correct lateral angulation and flexion deformity are recommended

Level of evidence: IV

Strength of recommendation (95% CI): 67 (57 to 77)

There are no placebo or non-splint controlled RCTs to support this statement. Two small (n = 26, n = 21) head to head RCTs with a crossover design have compared the treatment effects of a full splint (covering both thumb base and wrist) versus a half split (only protecting the thumb base) in patients with first carpometacarpal OA.[21 22] The results showed more pain relief from the full splint than from the half splint (ES = 0.64, 95% CI 0.02 to 1.26). The pooled NNT for the improvement of patient daily life activity was 4 (95% CI 2 to 13) (table 3). Unfortunately, the studies did not examine the effects of the splints on lateral angulation and flexion deformity. Another small crossover trial compared different types of full splint and found no clinical differences.[35]

In conclusion, apart from expert opinion, placebo controlled or non-splint controlled research evidence is still required (level IV). However, splint protection for thumb base OA may need to consider inclusion of a wrist component to increase the clinical effect (level Ia).

6. Local treatments are preferred over systemic treatments, especially for mild to moderate pain and when only a few joints are affected. Topical NSAIDs and capsaicin are effective and safe treatments for hand OA

Level of evidence: Ia.

Strength of recommendation (95% CI): 75 (68 to 83).

Topical NSAIDs were first suggested as an alternative to oral NSAIDs in 1982 when the first placebo controlled RCT demonstrated that trolamine salicylate cream was effective in the treatment of knee OA.[36] Since then, two placebo controlled and two head to head RCTs have been published for hand OA.[37–40] In a systematic review of topical NSAIDs in 2005,[25] a subgroup analysis for hand OA demonstrated that topical NSAIDs were effective for pain relief (ES = 0.77, 95% CI 0.32 to 1.22) and that this efficacy was equal to oral NSAID (ES = −0.05, 95% CI −0.27 to 0.17). Furthermore, topical NSAIDs appeared to have no more gastrointestinal (GI) side effects than placebo (RR = 0.81, 95% CI 0.43 to 1.56). These GI safety data were supported by another systematic review of RCTs for musculoskeletal pain, where topical NSAIDs were

shown to have fewer GI events than oral NSAIDs.[41] In addition, a population based case-control study comparing previous exposure to oral or topical NSAIDs in 1101 patients with upper GI bleeding and perforation and 6593 age and sex matched controls from a community in Tayside, Scotland[42] showed that GI bleeding and perforation were significantly associated with the use of oral NSAIDs (adjusted OR 2.59, 95% CI 2.12 to 3.16) but not with the use of topical NSAIDs (adjusted OR 1.45, 95% CI 0.84 to 2.50).

A systematic review of topical capsaicin in the treatment of chronic painful disorders including OA[26] contained two placebo controlled RCTs for hand OA.[43 44] The results showed that topical capsaicin was more effective than placebo in obtaining clinical improvement (NNT = 3, 95% CI 2 to 5) in 4 weeks (table 4). Topical capsaicin may not be available from some countries such as France.

In conclusion, both topical NSAIDs and capsaicin are effective for hand OA (Ia). Apart from minor local skin reactions; these topical agents appear to cause no more systematic side effects than placebo.

7. Because of its efficacy and safety paracetamol (up to 4 g/day) is the oral analgesic of first choice and, if successful, is the preferred long term oral analgesic

Level of evidence: IV.

Strength of recommendation (95% CI): 87 (78 to 96).

Although paracetamol has been used to treat hand OA for decades there are no placebo controlled trials. Head to head comparisons of NSAIDs and paracetamol in patients with hand OA have all shown the superiority of NSAIDs over paracetamol,[45 46] but whether paracetamol is effective for hand OA remains unclear. Evidence to support its use are mainly extrapolated from studies of OA at other joints, such as the hip or knee.[7 9] For example, two recent systematic reviews have demonstrated that paracetamol is effective in relieving pain due to OA of any joint, with an ES of 0.21 (95% CI 0.02 to 0.41), and NNT of 2 (95% CI 1 to 3), although the efficacy is inferior to that of NSAIDs.[47 48]

However, clinical decision is not based solely on strength of efficacy but also on other issues such as side effects and cost. For serious GI side effects, it is well known that paracetamol is much safer than NSAIDs and less expensive for each GI complication averted.[9] There are a few reports suggesting possible GI side effects from paracetamol.[49] However, these have not been replicated,[50] suggesting chance or ''channelling'' bias whereby, because of its known GI safety, paracetamol is preferentially prescribed to patients with higher GI risk. A recent meta-analysis of RCTs, which avoids channelling bias, showed no more GI symptoms from paracetamol than from placebo (table 4).[48] However, GI discomfort defined by this study must be differentiated from serious GI events such as bleeding, perforation or obstruction; although endoscopic studies show no acute mucosal injury from paracetamol, an adequately powered outcome trial would be required to decide this issue.

Although some have voiced concerns about the possible renal toxicity of paracetamol, evidence to support this is sparse (table 4).[51 52] Concern has been raised also over hepatic toxicity. However, although acute poisoning due to self administered overdoses of paracetamol is potentially lethal, at recommended therapeutic doses hepatic toxicity from paracetamol is not a problem. In contrast, there is no controversy over the cardiovascular (CV) and cerebrovascular safety of paracetamol. There are no reports of CV harm from paracetamol, whereas several studies have found CV toxicity from COX-2 inhibitors such as rofecoxib,[59 60] valdecoxib,[61] and celecoxib.[62] More recently, traditional NSAIDs (non-selective COX-2 inhibitors) have also been shown to have potential CV side effects.[63] Therefore paracetamol retains a good balance between benefit and harm and is a first line oral analgesic for patients with many chronic painful conditions, including OA.

In conclusion, the efficacy of paracetamol for hand OA has not been determined directly. The proposition is supported by evidence extrapolated from studies of OA at other joint sites (Ia) and by expert opinion (IV). Although the analgesic effect of paracetamol is inferior to that of NSAIDs, it is safer and cheaper and therefore the first choice oral analgesic for people with hand OA. Therefore, overall this proposition is supported primarily by expert opinion (IV).

8. Oral NSAIDs should be used at the lowest effective dose and for the shortest duration in patients who respond inadequately to paracetamol. The patient's requirements and response to treatment should be re-evaluated periodically. In patients with increased gastrointestinal risk, non-selective NSAIDs plus a gastroprotective agent, or a selective COX-2 inhibitor should be used. In patients with increased cardiovascular risk, coxibs are contraindicated and non-selective NSAIDs should be used with caution

Level of evidence: Ia.

Strength of recommendation (95% CI): 81 (74 to 88).

In contrast to numerous RCTs for hip and knee OA,[7 9] only three placebo controlled trials of NSAIDs in hand OA met our inclusion/exclusion criteria. These trials examined the efficacy of meclofenamate (100 mg three times a day for 4 weeks in 41 patients), ibuprofen (800 mg/day for 2 weeks in 60 patients) or lumiracoxib (200 mg or 400 mg/day for 4 weeks in 594 patients from four countries).[23 24 64] All three trials demonstrated the superiority of NSAIDs over placebo. Two provided data for reanalysis[23 24] showing for pain relief an ES of 0.40 (95% CI 0.20 to 0.60) and an NNT of 3 (95% CI 2 to 6) (table 3). Lumiracoxib 200 mg/day was as effective as 400 mg/day, supporting use of this lower dose for hand OA.

The major concern over NSAIDs is GI toxicity (table 4).[56] Because the risk of serious GI toxicity is dose dependent and increases with age [50] the use of NSAIDs for treating OA, an age associated condition with common comorbidity, is limited.[7 9] Several GI protective strategies have been proposed to optimise NSAID use: NSAIDs plus proton pump inhibitors (PPIs); NSAIDs plus H2 antagonists; NSAIDs plus misoprostol; and selective COX-2 inhibitors (including COX-2 selectives and COX-2 specifics—''coxibs''). Evidence that these strategies reduce the risk of endoscopic ulcers is well documented.[65] A recent systematic review of 112 RCTs (total 74 666 participants) that included the three largest outcome studies—CLASS (n = 8059),[66] VIGOR (n = 8076),[59] and TARGET (n = 18325),[67]—provided further evidence, particularly in relation to serious GI complications and symptomatic ulcers (table 4).[57] Except for co-prescription with H2-antagonists, co-prescription of PPIs or misoprostol or use of selective COX-2 inhibitors reduces NSAID associated symptomatic ulcers by 50–90% (table 4). However, care must be taken in applying these strategies because they may have their own toxicity—for example, increased risk of diarrhoea with misoprostol[58] or potential cardiorenal toxicity with coxibs.[60–62] In addition, the unexpected extra CV and cerebrovascular events associated with naproxen use in the ADAPT trial (Alzheimer's Diseases Anti-inflammatory Prevention Trial),[63] has heightened concern that cardiorenal toxicity may be a class related side effect of NSAIDs rather than a specific side-effect of coxibs. Just as the level of risk reduction for GI events varies between different agents within the coxib class, their relative risk of cardiorenal toxicity may also vary. Further evidence is still needed, though

pragmatic advice on current clinical use of these agents has been published by the European Medicines Agency (EMEA; http://www.emea.eu.int (accessed 11 December 2006)) and the U.S. Food and Drug Administration (FDA; http//www.fda.gov (accessed 11 December 2006)).

A consideration of the costs shows that the cost for each GI event averted (perforation, ulcer or bleed) may be less with coxibs than with co-prescribed GI protectors,[9] whereas co-prescription of GI protectors may be more cost effective for cost/QALY.[68] Nevertheless, all strategies require additional costs in order to gain additional benefits compared with conventional oral NSAIDs, but they are more cost effective for the high risk population who have GI bleeding.

Use of NSAIDs varies across Europe. In some countries, such as the UK, NSAIDs are recommended only for patients who obtain insufficient pain control with paracetamol, whereas in others, such as Austria, NSAIDs are more commonly used as a first line treatment for OA. Given their benefits and harms, the decision to use oral NSAIDs should be based on individual patient characteristics (propositions 1 and 2), and this decision must only be made after full and open discussion with the patient.

In conclusion, NSAIDs are effective for treating symptoms of hand OA (Ia). However, they cause serious GI side effects (Ia). Although most GI protective strategies (co-prescription with either PPI or misoprostol and selective COX-2 inhibitors) can effectively reduce NSAID associated GI side effects by 50–90% (Ia), their overall safety profiles remain unclear (Ib). Additional costs are incurred should they be used, though they are more cost effective in patients with high GI risk.

9. SYSADOA (for example, glucosamine, chondroitin sulphate, avocado soybean unsaponifiables, diacerhein, intra-articular hyaluronan) may give symptomatic benefit with low toxicity, but effect sizes are small, suitable patients are not defined, and clinically relevant structure modification and pharmacoeconomic benefits have not been established

Level of evidence: Ib-IV for different SYSADOAs.
Strength of recommendation (95% CI): 63 (48 to 76).

Evidence for symptomatic slow acting drugs for osteoarthritis (SYSADOAs) predominantly derives from RCTs in knee OA,[7] and data for OA at other sites are sparse.[9] For example, in a recent systematic review of 15 placebo controlled RCTs for glucosamine 12 studies were in knee OA, one in hip/knee OA, and two did not specify the index joints.[53] Glucosamine sulphate preparations were the major agents in this review (14/15), with only one trial investigating glucosamine hydrochloride. The results demonstrated that glucosamine sulphate preparations were effective for pain relief but ineffective in improving physical function or stiffness. Two placebo controlled RCTs in knee OA also demonstrated a small but statistically significant effect of glucosamine sulphate preparations on structural change, and the agents appeared safe with no side effects apparent during 3-year treatment periods (RR = 0.97, 95% CI 0.88 to 1.08).[69 70]

Two trials of chondroitin sulphate have been undertaken in hand OA: one a placebo controlled RCT,[27] the other a non-RCT comparing chondroitin sulphate plus naproxen versus naproxen alone in erosive interphalangeal OA.[71] The placebo controlled RCT was a report of two independent trials comparing chondroitin sulphate with placebo and chondroitin polysulphate with placebo (table 3). The results showed that over a 3-year period chondroitin sulphate was no more beneficial than placebo (NNT = 15 (95% CI −12 to 5), whereas chondroitin polysulphate was more effective than placebo in preventing radiographic progression (that is, development of ''erosive OA'' change) (NNT = 8, 95% CI 4 to 166).[27] No data on symptoms and functions were reported so whether this effect had any clinical impact and whether chondroitin sulphate and polysulphate formulations have different effects remains unknown. In addition, the non-RCT showed that over a 2-year treatment period, chondroitin sulphate plus naproxen was no better than naproxen alone in preventing radiographic changes of erosive OA.

No studies in hand OA have examined possible clinical or structure modifying effects of avocado soybean unsaponifiables (ASU). In a systematic review of RCTs of ASU undertaken for hip/knee OA,[72] it was concluded that ASU were effective in relieving pain and improving function, with better efficacy in hip OA than knee OA, though there were no quantitative data to support this. In contrast, pooling of two RCTs undertaken in patients with hip OA gave an ES for pain relief that did not reach significance,[9] although these were long term (over 24 weeks) and one was designed primarily to investigate structure modifying effects at 2 years.[73 74]

There are no studies of diacerhein in hand OA. Five placebo controlled RCTs have been conducted in hip and/or knee OA.[54 55 75–77] The results of these trials were heterogeneous with a pooled ES of 0.22 (95% CI 0.01 to 0.42) for pain relief and 0.03 (95% CI −0.11 to 0.16) for improvement in function. The two trials that investigated structure modifying effects of diacerhein obtained different results: a significant structure modifying effect was observed for hip OA,[54] but no effect was seen for knee OA.[55] The trials had different treatment periods (3 years for hip OA,1 year for knee OA) and whether longer term treatment might be beneficial for knee OA needs further study. Nevertheless, both trials identified diarrhoea as a significant side effect (pooled RR = 3.98, 95% CI 2.90 to 5.47).

While intra-articular hyaluronan has been investigated in knee and hip OA,[78–86] the evidence in hand OA is sparse. In one uncontrolled trial 16 men with OA of the trapeziometacarpal joint were injected with sodium hyaluronate (10 mg in 1 ml) once a week for 5 weeks.[87] After 5 months their pain score was decreased 46% at rest and 27% on movement. One active controlled RCT comparing intra-articular injections of hyaluronan and corticosteroid for trapeziometacarpal joint OA suggested that hyaluronan was as effective as corticosteroid for pain relief and may have more prolonged benefit.[88]

In conclusion, chondroitin sulphate has been examined in hand OA for structure modifying effects (Ib), but the results are inconclusive. Intra-articular hyaluronan may be useful in treating trapeziometacarpal OA (IIb). The use of other SYSADOAs is entirely based on evidence extrapolated from hip or knee OA and is therefore primarily supported by expert opinion (IV). Care must be taken with diacerhein since it may cause diarrhoea (Ia).

10. Intra-articular injection of long-acting corticosteroid is effective for painful flares of OA, especially trapeziometacarpal joint OA

Level of evidence: Ib (inconclusive).
Strength of recommendation (95% CI): 60 (47 to 74).

One small placebo controlled RCT (n = 40) was identified for this proposition.[28] Forty hospital referred patients with symptomatic trapeziometacarpal joint OA were randomly assigned to intra-articular injection of either 5 mg triamcinolone hexacetonide (0.25 ml) or 0.9% saline (0.25 ml); a painful flare was not a required entry criterion. Clinical assessments undertaken at 4, 12, and 24 weeks included pain, stiffness, and patient and physician global assessment. There were no statistically significant differences between groups for all outcomes at any time points. Unfortunately, data were not available to calculate

Table 5 Future research agenda

No	Proposition
1	Clinical trials on hand OA should separately consider the localisation (thumb base, interphalangeal joints) and the stage or type of OA (non-erosive, erosive, nodal) and examine clinical predictors of response
2	Thorough evaluation is required of physical treatments, such as ultrasound, laser, TENS, and local application of heat (for example, paraffin wax, hot pack)
3	Studies are required to determine the most appropriate form or combination of exercise (for example, strengthening, range of movement) for the different subsets of hand OA
4	Further studies are required to better evaluate the symptom and structure modifying effects of SYSADOA
5	The benefits of intra-articular injection of either corticosteroid or hyaluronan should be determined both for thumb base and interphalangeal OA
6	Existing slow acting antirheumatic drugs and biological agents (especially anti-tumour necrosis factor therapy) should be investigated in erosive interphalangeal OA, to determine possible symptom benefits and structure modifying effects
7	The efficacy and safety (both short and long term) of paracetamol, weak opioids, and oral NSAIDs need to be assessed and compared
8	The potential benefits of surgery compared with conservative management, and the most appropriate surgical procedure for thumb base OA, remain to be determined

ES and NNT. In contrast, one uncontrolled trial demonstrated that intra-articular corticosteroid significantly reduced pain due to trapeziometacarpal joint OA at one month but not at 3, 6, or 12 months after injection.[89]

In conclusion, the short term treatment effects of intra-articular corticosteroid in patients with symptomatic trapezio-metacarpal joint OA reported in one uncontrolled trial was not supported in one RCT (Ib). However, that RCT was under-powered. Whether this treatment is effective for a more acute flare of pain has not been investigated. Therefore the proposition is supported mainly by expert opinion (IV).

11. Surgery (for example, interposition arthroplasty, osteotomy or arthrodesis) is an effective treatment for severe thumb base OA and should be considered in patients with marked pain and/or disability when conservative treatments have failed

Level of evidence: III.

Strength of recommendation (95% CI): 68 (56to 79).

Although placebo controlled RCTs have not been conducted because of methodological and ethical constraints, numerous studies support surgery as a clinically effective treatment for severe thumb base OA when symptoms are refractory to conventional treatments. A number of surgical procedures are now available for thumb base OA, including arthrodesis, trapeziectomy alone or with synthetic or biological interpositions, osteotomy, and total joint replacement. Each intervention has particular benefits and harms and choosing the appropriate technique can be challenging. Two recent systematic reviews have been undertaken of surgery of thumb base OA,[29 90] the latest, a review by the Cochrane Musculoskeletal Group, that includes seven RCTs/CTs with 383 patients with thumb base OA. The review compared a combination of surgical procedures (for example, trapeziectomy + ligament reconstruction and tendon interposition or interposition arthroplasty) with a single procedure (for example, trapeziectomy). The results showed that the combination was no better than the single intervention for pain relief (ES = −0.17 95% CI −0.57 to 0.24), and functional improvement (ES = 0.03, 95% CI −0.37 to 0.44). Furthermore, the combination caused more side effects (for example, tendon rupture/adhesion, scar tenderness, sensory change, neurological complications, instability, complex regional pain syndrome) than the single surgical procedure (RR = 2.12 (1.24 to 3.60). In addition, total joint replacement was no better than the combined approach.[29]

The second systematic review included 18 studies (two RCTs, one prospective and 15 retrospective studies). Quantitative data were not available, but the results concurred with the Cochrane review in showing no advantage, but more complications from a combined surgical approach.[90]

In conclusion, surgery is a clinically effective treatment for patients with severe thumb base OA refractory to conventional treatment (III). The combination of two surgical procedures appears to offer no advantages but a higher complication rate and therefore should be avoided.

Future research agenda

After three Delphi rounds eight propositions for future research were developed (table 5).

DISCUSSION

These are the first recommendations for the management of hand OA to be developed by EULAR. As with the previous EULAR recommendations for management of knee OA[7 8] and hip OA,[9] we used an evidence based format that presents both research evidence and expert opinion, with clear separation between the two. We employed a Delphi technique to generate propositions and to reach consensus in an unbiased democratic fashion, and undertook a systematic evidence based medicine approach to identity and appraise the research evidence. The EULAR VAS scale was employed to show the strength of recommendation and the level of concordance within the Task Force for each proposition. This is based not just on the research evidence but also on the opinion of each expert, taking into account efficacy, safety, availability, logistical issues, and perceived patient acceptability. Although evidence based methodology continues to evolve, we consider that this current system of generating and presenting recommendations has much to commend it.

To our knowledge these are the first recommendations for management of hand OA to be developed by an international multidisciplinary group. The usual focus of published recommendations for OA is on management of large joint OA, specifically OA of the knee or the hip, or both. This is despite the high prevalence of symptomatic hand OA in the community.[1–6] Most OA recommendations have been developed and led by rheumatologists and the focus on knee and hip OA possibly represents the bias of this specialty, the perceived greater impact on the individual patient of large joint OA, and the success of surgical large joint replacement. There are important differences between hands, knees, and hips and the way that OA impacts at each site—for example, variation in the anatomy, function, risk factors for OA, natural history and outcome of OA, suitability for certain interventions (for

example, topical applications, injections), and even varying response to the same treatment (for example, NSAIDs).[91] For these reasons it is impossible to extrapolate clinical trial results between sites and to give a single recommendation for OA irrespective of site. For these multiple reasons EULAR has developed separate treatment recommendations for OA of the knee,[7 8] hip[9] and, now, hand.

The OA Task Force identified fewer clinical trials and systematic reviews for hip OA than for knee OA.[7–9] However, there is a real paucity of clinical trials to guide recommendations for hand OA,[92 93] resulting in many of the propositions being supported by category IV evidence alone. Furthermore, many of the trials that we did identify had a poor study design and were of inadequate power, and such major caveats limited their interpretation and generalisability to a clinical practice setting. Recent recommendations for the design and conduct of clinical trials in hand OA have been published,[94] and it is hoped that this will assist in improving the quality of future studies. The discussion around the current management propositions, as well as the propositions for the future research agenda, both highlight topics that might be prioritised by future studies.

There are a number of limitations to these recommendations. Firstly, the aforementioned paucity of research evidence for hand OA limits the weight of support for some of the treatments that are proposed. Secondly, rather than undertaking an exhaustive review of all possible treatments we developed and highlighted a limited number of key propositions. The recommendations are not necessarily comprehensive, therefore, and certain, less commonly used treatments may have been omitted. Thirdly, as with any search strategy, it is possible that some relevant studies were missed. Against this, however, is the fact that the Task Force experts were unaware of additional studies that were not identified by this means. Fourthly, we had representation from several health professions but no general practitioners on the Task Force. Because many people with hand OA are managed in primary care the generalisability of the propositions may be reduced. Finally, evidence based practice should synthesise information from three key sources with equal weighting: research evidence, expert opinion, and patient perspectives.[95] As with previous EULAR recommendations, patient opinion was omitted. For future projects ESCISIT is considering appropriate ways in which European patient opinion can be included.

During the Task Force discussions it was apparent that there are a number of important concerns about the clinical diagnosis of hand OA and the occurrence of several subsets of hand OA that may differ in outcome and treatment requirements. These diagnostic issues will be examined by the Task Force during 2006–7 and reported in 2007.

In conclusion, we have developed 11 recommendations involving 17 treatment modalities for the management of hand OA based on both clinical practice and the best available research evidence. For many treatments we found a paucity of research evidence specific to hand OA, highlighting the need for further well conducted clinical trials. We trust that these recommendations will lift the profile of hand OA and act as a catalyst for discussion between all health professionals concerned with the management of people with hand OA.

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