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OARSI recommendations for the management of hip and knee osteoarthritis Part III: changes in evidence following systematic cumulative update of research published through January 2009

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SUMMARY

Objective: To update evidence for available therapies in the treatment of hip and knee osteoarthritis (OA) and to examine whether research evidence has changed from 31 January 2006 to 31 January 2009.
Methods: A systematic literature search was undertaken using MEDLINE, EMBASE, CINAHL, AMED, Science Citation Index and the Cochrane Library. The quality of studies was assessed. Effect sizes (ESs) and numbers needed to treat were calculated for efficacy. Relative risks, hazard ratios (HRs) or odds ratios were estimated for side effects. Publication bias and heterogeneity were examined. Sensitivity analysis was undertaken to compare the evidence pooled in different years and different qualities. Cumulative meta-analysis was used to examine the stability of evidence.
Results: Sixty-four systematic reviews, 266 randomised controlled trials (RCTs) and 21 new economic evaluations (EEs) were published between 2006 and 2009. Of 51 treatment modalities, new data on efficacy have been published for more than half (26/39, 67%) of those for which research evidence was available in 2006. Among non-pharmacological therapies, ES for pain relief was unchanged for self-management, education, exercise and acupuncture. However, with new evidence the ES for pain relief for weight reduction reached statistical significance, increasing from 0.13 [95% confidence interval (CI) −0.12, 0.36] in 2006 to 0.20 (95% CI 0.00, 0.39) in 2009. By contrast, the ES for electromagnetic therapy which was large in 2006 (ES = 0.77, 95% CI 0.36, 1.17) was no longer significant (ES = 0.16, 95% CI −0.08, 0.39). Among pharmacological therapies, the cumulative evidence for the benefits and harms of oral and topical non-steroidal anti-inflammatory drugs, diacerhein and intra-articular (IA) corticosteroid was not greatly changed. The ES for pain relief with acetaminophen diminished numerically, but not significantly, from 0.21 (0.02, 0.41) to 0.14 (0.05, 0.22) and was no longer significant when analysis was restricted to high quality trials (ES = 0.10, 95% CI −0.0, 0.23). New evidence for increased risks of hospitalisation due to perforation, peptic ulceration and bleeding with acetaminophen >3 g/day have been published (HR = 1.20, 95% CI 1.03, 1.40). ES for pain relief from IA hyaluronic acid, glucosamine sulphate, chondroitin sulphate and avocado soybean unsponifiables also diminished and there was greater heterogeneity of outcomes and more evidence of publication bias. Among surgical treatments further negative RCTs of lavage/debridement were published and the pooled results demonstrated that benefits from this modality of therapy were no greater than those obtained from placebo.
Conclusion: Publication of a large amount of new research evidence has resulted in changes in the calculated risk–benefit ratio for some treatments for OA. Regular updating of research evidence can help to guide best clinical practice.

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Introduction

Osteoarthritis (OA) of the hip and knee are major causes of pain and locomotor disability worldwide. The OA Research Society International (OARSI) has recently published global, evidence-based, consensus recommendations for the treatment of OA of the hip and knee[1] following a critical appraisal of existing guidelines and a systematic review (SR) of the evidence for relevant therapies from 2002 until January 2006[2]. A considerable number of new studies have been published in the past 3 years. As an aid to assessing whether current OARSI recommendations should be modified in the light of this recent evidence, this paper updates the published evidence for available therapies from 31 January 2006 to 31 January 2009.

Methods

Systematic literature search

A systematic literature search was undertaken for SRs or meta-analyses (MAs), randomised controlled trials (RCTs), observational studies and economic evaluations (EEs) for the management of hip and/or knee OA published in any language between January 2006 and January 2009. Search strategies and electronic databases used previously were repeated[2].

Study selection

To update research evidence, studies for the treatment of hip and knee published between 31 January 2006 and 31 January 2009 were included. SRs/MAs were selected if available and supplemented by RCTs published subsequently. RCTs were selected if there were no published SRs/MAs. If there was more than one SR for the same treatment, the latest SR containing most studies and having the best quality characteristics was used and others were cross-checked to ensure that all RCTs were included in the database. Information concerning side effects was obtained from both RCTs and observational studies. While the efficacy of each therapeutic intervention was assessed separately for hip and knee OA, side effects were evaluated for each intervention regardless of the target joint. For determination of cost-effectiveness, only cost-utility analyses were included[2].

To examine change between 2006 and 2009, primary studies for the treatment of hip and knee OA were identified through published SRs/MAs. New primary studies published after the SRs/MAs were added. Multiple SRs/MAs were cross-checked to ensure that all published primary studies were included. Authors were contacted to validate data if necessary.

Quality and content assessment

Data were extracted using six customised extraction forms according to study design (SR, RCT, cohort, case–control, cross-sectional studies and EE). On each form for each study demographic data, quality scores and outcomes were recorded. The quality of SRs/MAs was assessed using the Oxman and Guyatt checklist[3] and the quality of RCTs was evaluated using the Jadad method[4]. All quality scores were converted into percentages of the maximum score attainable. For each modality of treatment the studies with the highest level of evidence (LoE)[5], and the highest quality of study (QoS) were used to represent the best evidence for efficacy (Table I). Quality assessments were not undertaken for other types of study design, such as cohort or case–control studies. For each EE, the study perspective, comparator, time horizon, discounting, modelling and uncertainty were evaluated.

Data analyses

Effect sizes (ESs) and number needed to treat (NNT) were used for efficacy, whereas relative risks (RRs), hazard ratios (HRs) and odds ratios (ORs) were estimated for side effects. Whenever possible, these outcome measures were extracted/calculated for each study. Publication bias was examined using funnel plots and an Egger's test[6]. Heterogeneity was examined using Forest plots and Q tests, and the degree of heterogeneity was calculated and presented as the I^2 – the percentage of the variance across studies that cannot be attributed to chance[7]. Reasons for heterogeneity were explored using sub-group analysis, and overall pooling of data was undertaken as appropriate. Sensitivity analyses were undertaken to examine changes from 2006 and 2009 and differences between analyses obtained from pooling all studies and from pooling only higher quality studies with a Jadad score of 5. Cumulative MA was used to assess changes in treatment ES year by year in order to document any significant trends associated with accruing evidence. Cost-effectiveness was estimated by calculation of cost per quality-adjusted life year (QALY) gained[2]. A glossary of terms and abbreviations is listed in Appendix I.

Results

SR of the scientific literature published between January 2006 and January 2009 identified 64 SRs, 266 RCTs and 21 EEs, which met the inclusion criteria. Of the 51 modalities of treatment addressed in the OARSI recommendations, 35 have now been systematically reviewed with 16 new or updated SRs in the last 3 years.

The best available evidence for ES with 95% confidence intervals (CIs) for relief of pain and stiffness and improvement in function for non-pharmacological, pharmacological and surgical treatments for OA of the hip and knee in January 2009 is summarised in Table I together with the LoE and the quality of studies on which these numbers are based. Table I also shows the NNT for each therapy where these can be calculated.

Non-pharmacological treatments

Self-management, education and information

Self-management, education and provision of information about OA and its treatment are widely promulgated as core recommendations for the treatment of OA hip and knee in recent guidelines from National Institute of Health and Clinical Excellence (NICE)[8] and the American Academy of Orthopaedic Surgeons (AAOS)[9] as well as in the OARSI guidelines[1] and in many previously published guidelines[2].

A new RCT undertaken in a UK primary care setting compared outcomes following a self-management course including an educational booklet, with administration of the educational booklet alone[10]. The results showed no significant differences between the two groups for reduction in Western Ontario and McMaster Universities OA index (WOMAC) scores for pain and stiffness, or improvement in physical function at 4 months and 12 months. ESs were 0.02 (95% CI −0.11, 0.16) for reduction in pain, 0.01 (−0.12, 0.15) for reduction in stiffness and 0.06 (−0.08, 0.20) for functional improvement at 4 months. When combined with the results of trials included in the previous MA[11], the overall ES for reduction in pain and improvement in function remained extremely small (0.06, 95% CI 0.02, 0.10) but statistically significant (Tables I and II).

In another RCT performed in a primary care setting in France, standardised consultations which included education about OA, advice about physical exercise and weight reduction were compared with usual care[12]. At 4 months the standardised intervention was followed by an average weight reduction of 1.11 (SD 2.49) kg, compared with only 0.37 kg (SD 2.39) ($P = 0.007$) in the group receiving usual care. However, these differences in weight

Table I
Best evidence for efficacy for various modalities of therapy for hip and knee OA available 31 January 2009

Modality	Joint	QoS (%)	LoE	Best evidence until 31 January 2009			
				ES_{pain} (95% CI)	$ES_{function}$ (95% CI)	$ES_{stiffness}$ (95% CI)	NNT (95% CI)
Non-pharmacological							
Self-management	Both	100	Ia	0.06 (0.02, 0.10)[10,11,*]	0.06 (0.02, 0.10)[10,11,*]	0.01 (−0.12, 0.15)[10,*]	
Telephone	Both	100	Ia	0.12 (0.00, 0.24)[154]	0.07 (0.00, 0.15)[154]		
Education	Both	100	Ia	0.06 (0.03, 0.10)[11,12,*]	0.06 (0.02, 0.10)[11]		
Strengthening	Knee	100	Ia	0.32 (0.23, 0.42)[20]	0.32 (0.23, 0.41)[20]		
	Hip*	100*	Ia*	0.38 (0.08, 0.68)[15,*]			
Aerobic	Knee	100	Ia	0.52 (0.34, 0.70)[20]	0.46 (0.25, 0.67)[20]		
Water-based exercise	Both	100*	Ia*	0.19 (0.04, 0.35)[13,*]	0.26 (0.11, 0.42)[13,*]	0.17 (−0.05, 0.39)[155]	
Balneotherapy	Knee	75	Ia				NS[156]
Spa/sauna	Both	75	Ib	0.46 (0.17, 0.75)[157]			NS
Weight reduction	Knee	100*	Ia*	0.20 (0.00, 0.39)[21,*]	0.23 (0.04, 0.42)[21,*]	0.36 (−0.08, 0.80)[158]	3 (2, 9)[158]
TENS	Both	75	Ia				2 (1, 5)[159]
Laser	Both	100	Ia				4 (2,17)[160]
Ultrasound	Both	50	Ia	0.06 (−0.39, 0.52)[161]			
Radiotherapy	Both	50	IIb	Similar effects between OA and RA from an MA of uncontrolled trial[162]			
Heat/ice	Knee	75	Ia	0.69 (−0.07, 1.45)[163]	1.03 (0.44, 1.62)[163] for quads strength; 1.13 (0.54, 1.73)[163] for flexion	0.83(−0.03, 1.69)[163] for swelling	
Massage	Knee	40	Ib	0.10 (−0.23, 0.43)[164]			
Acupuncture	Knee	100*	Ia*	0.35 (0.15, 0.55)[23,*]	0.35 (0.14, 0.56)[23,*]	0.41 (0.13, 0.69)[30]	4 (3, 9)[30]
Insoles	Knee	100	Ia	No different between type of insoles, no placebo/usual care comparisons[165]			
Joint protection (braces)	Knee	100	Ia	More benefits with a knee brace than a neoprene sleeve[165]			
Electrotherapy/EMG	Knee	100*	Ia*	0.16 (−0.08, 0.39)[31,*]	0.33 (0.07, 0.59)[31,*]		
Pharmacological							
Acetaminophen	Both	100	Ia	0.14 (0.05, 0.23)[32,34*]	0.09 (−0.03, 0.22)[34,166,167,*]	0.16 (−0.05, 0.37)[166,168,*]	3 (2, 52)[34–36,*]
NSAIDs	Both	100	Ia	0.29 (0.22, 0.35)[44,*]			
NSAIDs + PPIs	OA/RA	100	Ia				
NSAIDs + H2-blockers	OA/RA	100	Ia				
NSAIDs + misoprostol	OA/RA	100	Ia				
Cox-2 inhibitors	Both	100	Ia	0.44 (0.33, 0.55)[169] (exc Deek's for OA/RA)			
Topical NSAIDs	Knee	100	Ia	0.44 (0.27, 0.62)[48–51,*]	0.36 (0.24, 0.48)[48]	0.49 (0.17, 0.80)[48]	3 (2, 4)[48]
Topical capsaicin	Knee	75	Ia				4 (3, 5)[170]
Opioids	Any*	100*	Ia*	0.78 (0.59, 0.98)[58,*]	0.31 (0.24, 0.39)[58,*]		
IA corticosteroid	Knee	100	Ia	0.58 (0.34, 0.75)[44,*]	0.20 (−0.14, 0.53)[61,*]	0.25 (−0.23, 0.74)[61,*]	5 (3, 38)[61,*]
IAHA	Knee	100	Ia	0.60 (0.37, 0.83)[65,*]	0.61 (0.35, 0.87)[65,*]	0.54 (−0.17, 1.26)[65,*]	7 (3, 119)[65,*]
GS	Both	100	Ia	0.58 (0.30, 0.87)[34,80,82,*]	0.07 (−0.08, 0.21)[84]	0.06 (−0.11, 0.23)[84]	5 (4, 7)[96]
GH*	Knee*	–	Ib*	−0.02 (−0.15, 0.11)[81,171,172,*]			
CS	Knee	100	Ia	0.75 (0.50, 1.01)[95,*]			5 (4, 7)[96]
Diacerhein	Both	–	Ib	0.24 (0.08, 0.39)[112–115,119,120,*]	0.14 (0.03, 0.25)[112–115,119,120,*]		
ASU	Both*	100*	Ia*	0.38 (0.01, 0.76)[99,*]	0.45 (0.21, 0.70)[99,*]		6 (4, 21)[99,*]
Rosehip*	Both*	100*	Ia*	0.37 (0.13, 0.60)[108,*]			6 (4, 13)[108,*]
SAM-e	Knee	100	Ia	0.22 (−0.25, 0.69)[106]	0.31 (0.10, 0.52)[106]		
Surgical							
Lavage/debridement*	Knee*	–	Ib*	0.21 (−0.12, 0.54)[130,132,133,135,173,*]	0.11 (−0.11, 0.33)[130,132,133,135,173,*]	0.05 (−0.34, 0.44)[130,132,173,*]	
Patellar resurfacing	Knee	100	Ib				9 (5, 25)[174]
Osteotomy	Knee	100*	Ia*	Head to head comparisons, no placebo or conservative therapy controlled trials. HTO improves pain and function[137,*]			
Unicompartment knee arthroplasty*	Knee*	75*	SR cohort*	Similar function improvement as TKR or HTO, but less complications and revision than HTO[139,*]			
TJR	Both	100	III	TJR is effective to improve QoL, more beneficial for hip OA from an SR of cohort studies[175]			

Abbreviations: TENS: trans cutaneous electrical nerve stimulation; ES = 0.2 is considered small, ES = 0.5 is moderate, and ES > 0.8 is large; NNT for symptom relief, unless otherwise specified; NS: not significant; TJR: total joint replacement.
Ia: MA of RCTs; Ib: RCT; IIa controlled study without randomisation; IIb: quasi-experimental study (e.g., uncontrolled trial, one arm dose–response trial, etc.); III: observational studies (e.g., case–control, cohort, cross-sectional studies); IV: expert opinion.
QoS was assessed using validated scales, e.g., the Oxman and Guyatt scale for SR and the Jadad's scale for clinical trials. The percentage score was calculated for each study. The best available evidence was presented, i.e., SR with the highest quality, RCT with highest quality followed by uncontrolled or quasi experiment, cohort and case–control study.
* Updated since 2006[2].

reduction were only associated with insignificant pain reduction in the two groups (ES = 0.19, 95% CI −0.02, 0.41), and this did not alter the overall estimate of the effect of educational intervention on symptomatic outcomes in OA significantly (Table II).

Exercise

Seven new SRs of exercise therapy in OA hip and knee have been undertaken in the past 3 years[13–19]. In addition to confirming the conclusion from the earlier MA that both strengthening and aerobic exercise are associated with relief of pain in knee OA[20], one SR found that exercise, particularly strengthening exercise, was also associated with reduction in pain in hip OA (ES = 0.38, 95% CI 0.08, 0.68)[15], and another showed that water-based exercise resulted in relief of pain (ES = 0.19, 95% CI 0.04, 0.35), and improvement in function (0.26, 95% CI 0.11, 0.42) in both knee and hip OA[13] (Table I). The reported costs per QALY were very variable depending on the type of exercise, the comparator used, the country where the study was undertaken and the perspective from which the EE was undertaken (Table V). Within study direct comparisons suggest that class-based exercise may be more economically efficient than home-based exercise, indirect comparisons between studies suggest that water-based exercise may not necessarily be more cost-effective than land based exercise (Table V).

Weight reduction

Two relevant SRs have been published since 2006. One reviewed studies of physical therapy interventions which included weight reduction[16] while the other focussed on studies specifically designed to look at outcomes in patients with knee OA as a result of therapeutic weight reduction[21]. There are now four published RCTs which have examined symptomatic outcomes following weight reduction. The pooled ESs (95% CI) for improvement in pain and physical function were 0.20 (0.00, 0.39) and 0.23 (0.04, 0.42) following an average reduction in weight of 6.1 kg (4.7, 7.6)[21]. As indicated in the OARSI recommendations[1] this SR[21] provided evidence for small improvements in pain and physical function in patients with knee OA following weight reduction which was not available in 2006. However, the recommendation that patients with hip OA should be encouraged to lose weight and maintain their weight at a lower level is still only based on expert opinion unsupported by research evidence (LoE IV).

Table II
Comparison of ESs and LoE for pain relief with different modalities of therapy in 2006 and 2009

	31 January 2006 ES (95% CI), LoE	31 January 2009 ES (95% CI), LoE
Self-management	0.06 (0.02, 0.10), Ia	0.06 (0.02, 0.10), Ia
Education/information	0.06 (0.02, 0.10), Ia	0.06 (0.03, 0.10), Ia
Exercise for knee OA		
Strengthening	0.32 (0.23, 0.42), Ia	0.32 (0.23, 0.42), Ia
Aerobic	0.52 (0.34, 0.70), Ia	0.52 (0.34, 0.70), Ia
Exercise for hip OA	NA	0.38 (0.08, 0.68), Ia
Exercise in water for knee & hip OA	0.25 (0.02, 0.47), Ib	0.19 (0.04, 0.35), Ia
Weight reduction	0.13 (−0.12, 0.36), Ib	0.20 (0.00, 0.39), Ia
Acupuncture	0.51 (0.23, 0.79), Ib	0.35 (0.15, 0.55), Ia
Electromagnetic therapy	0.77 (0.36, 1.17), Ia	0.16 (−0.08, 0.39), Ia
Acetaminophen	0.21 (0.02, 0.41), Ia	0.14 (0.05, 0.22), Ia
NSAIDs	0.32 (0.24, 0.39), Ia	0.29 (0.22, 0.35), Ia
Topical NSAIDs	0.41 (0.22, 0.59), Ia	0.44 (0.27, 0.62), Ia
Opioids	NA	0.78 (0.59, 0.98), Ia
IA corticosteroid	0.72 (0.42, 1.02), Ia	0.58 (0.34, 0.75), Ia
IAHA	0.32 (0.17, 0.47), Ia	0.60 (0.37, 0.83), Ia
GS	0.61 (0.28, 0.95), Ia	0.58 (0.30, 0.87), Ia
GH	NA	−0.02 (−0.15, 0.11), Ib
CS	0.52 (0.37, 0.67), Ia	0.75 (0.50, 1.01), Ia
Diacerein	0.22 (0.01, 0.42), Ib	0.24 (0.08, 0.39), Ib
ASU	NA	0.38 (0.01, 0.76), Ia
Rosehip	NA	0.37 (0.13, 0.60), Ia
Lavage/debridement	0.09 (−0.27, 0.44), Ib	0.21 (−0.12, 0.54), Ib

NA: not available.
The sources of the data for each modality of therapy are shown in Table I and Ref. 2.

Acupuncture

Nine SRs of the use of acupuncture for the treatment of OA published between 2006 and 2009[16,22–29] have confirmed that this non-pharmacological modality of treatment does have some efficacy for relief of pain. The latest MA included results from 11 RCTs[23]. Acupuncture was compared with sham acupuncture, usual care or waiting list controls. Overall, acupuncture was superior to controls with a pooled ES of 0.58 (0.38, 0.78) for pain relief. However, the ES was lower in blinded trials with sham acupuncture controls (ES = 0.35, 95% CI 0.15, 0.55). The ES for relief of pain also diminished with time and was 0.13 (0.01, 0.24) 6 months after treatment[23]. Similar findings were observed for improvement in function (Table I). The cost per QALY of acupuncture in comparisons with sham acupuncture was about $30,519[30] (Table V).

Electromagnetic therapy

Treatment of OA knee or hip with electromagnetic therapy was not recommended in the OARSI guidelines[1] despite evidence from a 2002 Cochrane review suggesting that it might be associated with relatively large improvements in pain in patients with knee OA (ES = 0.77, 95% CI 0.36, 1.17). A subsequent SR published in 2006[31], immediately after the closing date of the literature search available to the OARSI treatment guidelines development group, included five placebo-controlled RCTs of pulsed electromagnetic field therapy published between 1996 and 2005. The cumulative data showed that improvement in function was small (ES = 0.33, 95% CI 0.07, 0.59), and there was no significant efficacy for reduction in pain (ES = 0.16, 95% CI −0.08, 0.39)[31]; very different from the results in the earlier review[2].

Pharmacological treatments

Acetaminophen (paracetamol)

The Cochrane review of acetaminophen was updated in 2006[32]. The update, which included seven placebo-controlled RCTs, demonstrated a statistically non-significant reduction in the ES for pain reduction (ES = 0.13, 95% CI 0.04, 0.22), compared with that previously estimated in an MA of trials in 2004 (ES = 0.21, 95% CI 0.02, 0.41)[33]. Acetaminophen was subsequently shown to have no significant effect in reducing pain in knee OA in the Glucosamine Unum In Die (once a day) Efficacy (GUIDE) RCT (ES = 0.16, 95% CI −0.11, 0.43) which was published in 2007 after completion of the Cochrane update[34]. A funnel plot of the five trials that measured pain outcomes does not suggest significant publication bias (Fig. 1). The trials were homogenous with a pooled ES for pain relief of 0.14 (0.05, 0.23) (Fig. 2). Cumulative MA suggests that though the ES for pain relief is small, it is now stable and unlikely to diminish further, given that there is homogeneity within the published trials and nothing to suggest publication bias (Fig. 3). However, currently available evidence suggests that acetaminophen has no significant effect on stiffness (ES = 0.16, 95% CI −0.05, 0.37) or physical function (ES = 0.09, 95% CI −0.03, 0.22) in patients with symptomatic knee OA (Table I).

The NNT to obtain relief of pain was calculated from the results of one cross-over and the two parallel design trials[34–36]. Although the pooled NNT was only 3 (95% CI 2, 52), there was significant heterogeneity and the NNT ranged from 2 to 8 in the three RCTs. This wide range was largely attributable to the exceptionally small

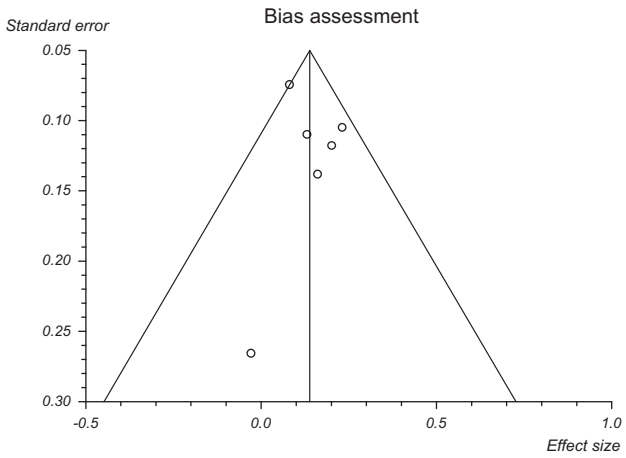

Fig. 1. Funnel plot of trials of analgesic efficacy of acetaminophen in OA.

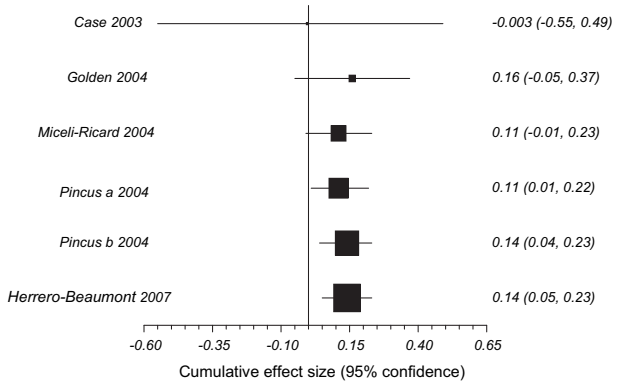

Fig. 3. Cumulative MA of RCTs of analgesic efficacy of acetaminophen in OA.

NNT in the cross-over trial (NNT = 2, 95% CI 1, 2)[35]. Without this trial the NNT was 7 (4, 23).

More evidence has accumulated to suggest that acetaminophen may have upper gastrointestinal (GI) side effects. A population-based cohort study ($n = 644{,}183$) showed that treatment with high dose (>3 g/day) acetaminophen was associated with a greater risk of hospitalisation as a result of GI perforation, ulceration or bleedings (PUBs) than treatment with low dose acetaminophen (≤3 g/day) with an HR of 1.20 (1.03, 1.40)[37]. There is also some evidence for mild loss of renal function in women following long-term consumption of such doses (OR = 2.04, 95% CI 1.28, 3.24) for decline in glomerular filtration rate (GFR) > 30 ml/min[38] and evidence from prospective cohort studies for increases in incident hypertension in women taking > 500 mg acetaminophen daily[39] and in men taking daily acetaminophen when compared with non-users (RR = 1.34, 95% CI 1.00, 1.79)[40].

Acetaminophen, in doses of up to 4 g/day, is currently a core recommendation for use as an analgesic in the OARSI guidelines[1], the recently published NICE[8] and AAOS[9] guidelines as well as other guidelines for the management of hip or knee OA available in 2006[2]. European League Against Rheumatism (EULAR) recommendations for the management of hip[41] and knee[42] OA suggested that doses of up to 4 g/day should be the oral analgesic of first choice for mild-moderate pain because of its relative safety and efficacy and, if successful, should be used as the preferred long-term oral analgesic. The strength of recommendation (SOR) for the use of acetaminophen in doses up to 4 g/day for the initial treatment of mild to moderate pain in patients with knee or hip OA in the OARSI recommendations was high (SOR = 92, 95% CI 88, 99) despite uncertainties about the long-term efficacy and safety of such doses of the drug at the time of publication[1]. Because of additional concerns about acetaminophen's narrow therapeutic margin for hepatotoxicity, an advisory committee of the US Food

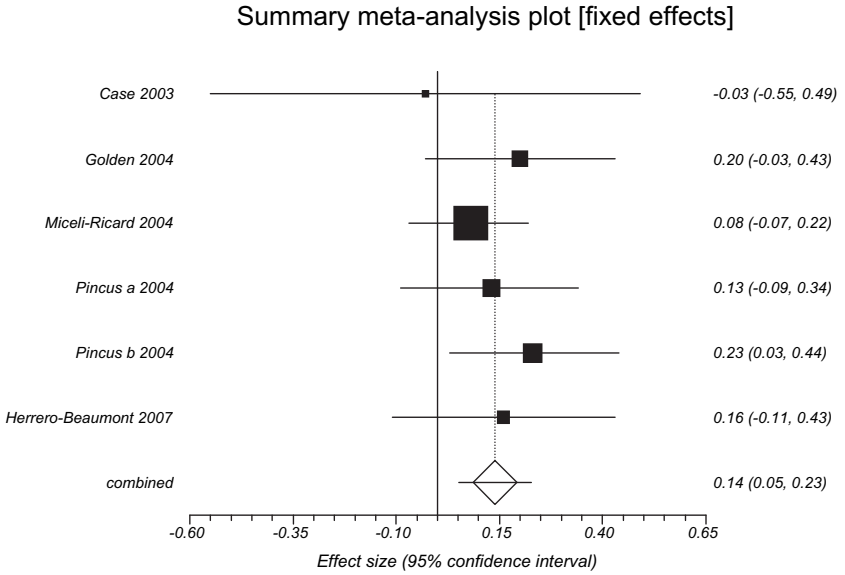

Fig. 2. Forest plot of RCTs for analgesic efficacy of acetaminophen in OA.

and Drug Administration (FDA) recently recommended that the maximum adult daily dose of acetaminophen should be less than 4 g/day and that the acetaminophen content in single doses of over the counter (OTC) analgesic preparations should be limited to 650 mg[43].

Non-steroidal anti-inflammatory drugs (NSAIDs)

A new SR of therapy with oral NSAIDs published in 2007[44] included data from 27 placebo-controlled RCTs ($n = 14,523$). The pooled, updated, ES for pain relief was little reduced (ES = 0.29, 95% CI 0.22, 0.35) (Table II). Although this is in the small to moderate range it is two-fold greater than the ES for relief of pain with acetaminophen (ES = 0.14, 95% CI 0.05, 0.23)[32] (Tables I and II).

Evidence that NSAIDs are superior to acetaminophen for the relief of pain is supported by an SR of head to head comparisons between NSAIDs and acetaminophen (ES = 0.20, 95% CI 0.10, 0.30)[33]. The clinical response rate was higher (RR = 1.24, 95% CI 0.10, 1.41) and the number of patients preferring NSAIDs to acetaminophen was consistently greater (RR = 2.46, 95% CI 1.50, 4.12)[33].

The incidence of serious GI side effects associated with the use of oral NSAIDs was also assessed in the large population-based cohort study of elderly patients in Canada[37]. The HR for GI hospitalisation from PUBs was higher in patients receiving oral NSAIDs (1.63, 95% CI 1.44, 1.85) than in patients being treated with high dose acetaminophen (1.20, 95% CI 1.03, 1.40). However, the HR was markedly greater (2.55, 95% CI 1.98, 3.28) in patients treated with NSAIDs plus high dose acetaminophen[37]. Using a Cox regression model with time-dependent exposure to determine the association between drug exposure and GI hospitalisation these investigators also confirm that the HR for GI hospitalisation in patients receiving non-selective NSAIDs was twice as high as that in patients given the cyclooxygenase (Cox)-2 selective agent celecoxib (2.18, 95% CI 1.82, 2.61), or non-selective NSAIDs together with a proton pump inhibitor (PPI) (2.21, 95% CI 1.51, 3.24)[37]. A recent RCT showed that while treatment with celecoxib alone was associated with a 9% risk of recurrent GI bleeding in very high risk patients with previous history of a GI bleed, this could be abolished by co-prescription of a PPI with celecoxib[45]. This was supported by the data from the population-based retrospective cohort study, in which co-prescription of a PPI was associated with a reduction in hospital admissions for GI bleeds of about 30% in people over the age of 75 years when compared with treatment with celecoxib without additional gastroprotection (HR = 0.69, 95% CI 0.52, 0.93)[46]. A recent cost-utility analysis (CUA) suggested that co-prescription of a PPI with both traditional NSAIDs and Cox-2 selective agents is cost-effective at 3 months in a UK National Health Service setting[47].

Topical NSAIDs

Topical NSAIDs were recommended therapies for the treatment of symptomatic knee OA in 7/9 of the existing guidelines reviewed in 2006[2] and are recommended in the more recent guidelines from NICE[8] and OARSI[1] as alternative or adjunctive therapy. A total of 14 placebo-controlled RCTs have been reported, including 11 that were included in a 2004 MA[48] and three that have been subsequently published[49–51]. The pooled ES for relief of pain is now 0.44 (95% CI 0.27, 0.62) but there is heterogeneity of efficacy between products ($I^2 = 69\%$) as well as significant asymmetry in a funnel plot, also noted in an earlier MA[48], suggesting publication bias with under reporting of negative studies leading to possible overestimation of the efficacy of topical NSAIDs. The earlier studies which suggested that topical NSAIDs were as effective as, and possibly safer than, oral NSAIDs[52–54] are largely supported by a recent RCT and preference study comparing topical ibuprofen and oral ibuprofen for the treatment of chronic knee pain in elderly subjects in a primary care setting[55]. However, cost-utility analyses showed that in the second year of the 2-year RCT, oral ibuprofen was more effective, but more costly, than topical ibuprofen. The cost per QALY of oral ibuprofen compared with topical ibuprofen was £27,130 (equivalent to US $49,448 in 2009)[56,57] (Table V).

Opioids

As previously reported in the OARSI guidelines[1], an MA of 18 placebo-controlled RCTs of opioid analgesics in 3244 patients with OA published in 2007, which was not available at the time of the 2006 OARSI review, showed a moderate to large ES for reduction in pain intensity (0.78, 95% CI 0.59, 0.98) and a small to moderate ES for improvement in physical function (0.31, 95% CI 0.24, 0.39)[58] (Table I). There was, however, substantial heterogeneity in outcomes between studies which did not appear to be related to the particular opioid used or to the methodological quality of the RCTs[58]. Benefits associated with the use of opioids were limited by frequent side effects, including nausea (30%), constipation (23%), dizziness (20%), somnolence (18%) and vomiting (13%)[58] (Table IV). Overall, 25% of patients treated with opioids withdrew from studies compared with 7% of placebo-treated patients with a number needed to harm (NNH) of 5. The withdrawal rate was higher (31%, NNH 4) for strong opioids (oxymorphone, oxycodone, oxytrex, fentanyl, morphine sulphate) than for the weaker opioids (tramadol, tramadol/paracetamol, codeine and propoxyphene) (19%, NNH 9)[58]. An MA of six placebo-controlled RCTs of opioids (tramadol, morphine, codeine, oxycodone and oxymorphone) in 1057 patients with knee OA associated with moderately severe pain (mean of 64.3 mm on a visual analogue pain scale) only showed a small improvement in pain (10.5 mm, 95% CI 7.4, 13.7) compared with placebo which was maximal at 2–4 weeks[44]. This was only just above the minimal perceptible threshold[59] and the authors also suggested that even this apparent efficacy of opioids may be inflated because of the high withdrawal rates and a tendency to report 'best case' scenarios when undertaking intention to treat (ITT) analyses[44]. Another MA of 41 RCTs for chronic non-cancer pain involving 6019 patients, 80% of whom had OA, back pain or rheumatoid arthritis, found that only strong opioids were significantly more effective than acetaminophen or NSAIDs (ES = 0.34, 95% CI 0.01, 0.67)[60].

Intra-articular (IA) corticosteroids

Two SRs have been published since 2006[44,61]. The pooled ES for pain reduction, irrespective of the number of doses administered or the time after injection was 0.58 (0.34, 0.82), corresponding to an NNT of 5 (3, 38)[44]. The ES for relief of pain following single injections of IA corticosteroid was relatively large; 0.72 (0.42, 1.01) 1 week following injection, with an NNT of only 3 (2, 5)[61]. However, this fell to 0.28 (−0.17, 0.73) after 4 weeks and 0.21 (−0.17, 0.59)

Table III
Relationship between ES for pain relief and quality of randomized controlled trial

	All trials ES (95% CI)	High quality trials (Jaded = 5), ES (95% CI)
Acupuncture	0.35 (0.15, 0.55)	0.22 (0.01, 0.44)
Acetaminophen	0.14 (0.05, 0.23)	0.10 (−0.03, 0.23)
NSAIDs	0.29 (0.22, 0.35)	0.39 (0.24, 0.55)
Topical NSAIDs	0.44 (0.27, 0.62)	0.42 (0.19, 0.65)
IAHA	0.60 (0.37, 0.83)	0.22 (−0.11, 0.54)
GS	0.58 (0.30, 0.87)	0.29 (0.003, 0.57)
CS	0.75 (0.50, 1.01)	0.005 (−0.11, 0.12)
ASU	0.38 (0.01, 0.76)	0.22 (−0.06, 0.51)
Lavage/debridement	0.21 (−0.12, 0.54)	−0.11 (−0.30, 0.08)

The source of the data for each treatment is shown in Table I.

Table IV
Side effects associated with pharmacological therapies

Intervention*	Adverse events	RR/OR (95% CI)	Evidence (references)
Acetaminophen (paracetamol)	GI discomfort	0.80 (0.27, 2.37)	Meta-RCTs[33]
	GI perforation/bleed	3.60 (2.60, 5.10)	CC[176]
	GI bleeding	1.20 (0.80, 1.70)	Meta-CCs[177]
	GI hospitalisation†	1.20 (1.03, 1.40)†	CS[37],†
	Renal failure	0.83 (0.50, 1.39)	CS[178]
	Renal failure	2.50 (1.70, 3.60)	CC[179]
NSAIDs	GI perforation/ulcer/bleed	5.36 (1.79, 16.10)	Meta-RCTs[180]
	GI perforation/ulcer/bleed	2.70 (2.10, 3.50)	Meta-CSs[180]
	GI perforation/ulcer/bleed	3.00 (2.50, 3.70)	Meta-CCs[180]
	GI hospitalisation†	1.63 (1.44, 1.85)†	CS[37],†
	Myocardial infarction	1.09 (1.02, 1.15)	Meta-CSs[181]
Topical NSAIDs	GI events	0.81 (0.43, 1.56)	Meta-RCTs[48]
	GI bleed/perforation	1.45 (0.84, 2.50)	Case–control[53]
NSAID + H2-blocker vs NSAID	Serious GI complications	0.33 (0.01, 8.14)	Meta-RCTs[182]
	Symptomatic ulcers	1.46 (0.06, 35.53)	Meta-RCTs[182]
	Serious CV or renal events	0.53 (0.08, 3.46)	Meta-RCTs[182]
NSAID + PPI vs NSAID	Serious GI complications	0.46 (0.07, 2.92)	Meta-RCTs[182]
	Symptomatic ulcers	0.09 (0.02, 0.47)	Meta-RCTs[182]
	Serious CV or renal events	0.78 (0.10, 6.26)	Meta-RCTs[182]
Cox-2 inhibitors + PPI vs Cox-2 inhibitors†	Recurrent ulcer bleeding†	8.9% vs 0%†	RCT[45],†
	GI hospitalisation†	0.69 (0.52, 0.93)†	CS[46],†
NSAID + misoprostol vs NSAID	Serous GI complications	0.57 (0.36, 0.91)	Meta-RCTs[182]
	Symptomatic ulcers	0.36 (0.20, 0.67)	Meta-RCTs[182]
	Serious CV or renal events	1.78 (0.26, 12.07)	Meta-RCTs[182]
	Diarrhea	1.81 (1.52, 2.61)	Meta-RCTs[183]
Cox-2 inhibitors			
Coxibs vs NSAID	Serious GI complications	0.55 (0.38, 0.80)	Meta-RCTs[182]
	Symptomatic ulcers	0.49 (0.38, 0.62)	Meta-RCTs[182]
	Serious CV or renal events	1.19 (0.80, 1.75)	Meta-RCTs[182]
Celecoxib	Myocardial infarction	2.26 (1.00, 5.10)	Meta-RCTs[184]
	Myocardial infarction	0.97 (0.86, 1.08)	Meta-CSs/CCs[181]
Rofecoxib	Myocardial infarction	2.24 (1.24, 4.02)	Meta-RCTs[149]
	Myocardial infarction	1.27 (1.12, 1.44)	Meta-CSs/CCs[181]
Valdecoxib	CV events	2.30 (1.10, 4.70)	Meta-RCTs[185]
Opioids	Any	1.40 (1.30, 1.60)	Meta-RCTs[186]
	Constipation†	4.08 (3.30, 5.05)†	Meta-RCTs[58],†
	Nausea†	3.15 (2.68, 3.72)†	Meta-RCTs[58],†
	Vomiting†	5.99 (4.20, 8.54)†	Meta-RCTs[58],†
	Dizziness†	3.74 (3.00, 4.66)†	Meta-RCTs[58],†
	Somnolence†	4.78 (3.65, 6.26)	Meta-RCTs[58],†
Glucosamine	Any	0.97 (0.88, 1.08)	Meta-RCTs84
Chondroitin sulphate	Any	0.99 (0.76, 1.31)	Meta-RCTs[95],†
Diacerhein	Diarrhoea	3.51 (2.55, 4.83)†	Meta-RCTs[112–115,119,120],†
IAHA	Local adverse events†	1.49 (1.21, 1.83)†	Meta-RCTs[65],†
IA high molecular HA (Hylan)	Flares of pain and swelling†	2.04 (1.18, 3.53)†	Meta-RCTs[74],†

CC: case–control study; CS: cohort study.
H_2-blockers: histamine type 2 receptor antagonists; CV: cardiovascular.
* Compared with placebo/non-exposure unless otherwise stated.
† Updated since 2006[2].

after 6 weeks[61]. While this suggests that treatment may need to be repeated at frequent intervals to maintain efficacy, a long-term trial of IA corticosteroid injections every 3 months for 2 years showed that while there was efficacy for relief of pain after 1 year (ES = 0.67, 95% CI 0.18, 1.17), this was not demonstrable after 2 years (ES = 0.25, 95% CI −0.23, 0.74)[61]. IA steroid injections had no significant effect on physical function (ES = 0.20, 95% CI −0.14, 0.53) or stiffness (ES = 0.25, 95% CI −0.23, 0.74)[61].

IA hyaluronic acid (IAHA)

No less than 17 SRs and MAs have been undertaken to assess the therapeutic effects of IAHA in OA, and the majority of these

Table V
Cost per QALY in 2009

Intervention	Comparator	OA	Perspective*	Time horizon	Discounting	Year published	Country	Cost per QALY	
								Original	Converted ($)†
Education + class-based exercise	Usual care	Hip/knee	Societal	65 weeks	No	2007	Netherlands	51,385 euros	92,081[187]
Class-based exercise	Home-based exercise	Knee	NHS	1 year	No	2004	UK	£238	−503 (cost saving)[188]
Water-based exercise	Usual care	Hip/knee	Societal	1 year	No	2005	UK	£5738	11,530[155]
	Usual care	Hip/knee	Societal	Life	3%	2001	US	$205	334[189]
Acupuncture	Sham acupuncture	Hip/knee	Societal	3 months	No	2005	Germany	17,845 euros	30,519[30]
Acetaminophen + oxycodone	Oxycodone	Hip/knee	Societal	4 months	No	2006	UA	149/ −0.01	More expensive & less effective[190]
NSAID + PPI	NSAIDs	OA/RA	NHS	6 months	No	2005	UK	£33,889	64,856[191]
NSAID + misoprostol	NSAIDs	OA/RA	NHS	6 months	No	2005	UK	£8889	17,011[191]
Oral ibuprofen	Topical ibuprofen	Knee pain	Societal	2 years	Yes	2008	UK	£27,130	49,448[57]
Cox-2 specifics	NSAIDs	OA/RA	NHS	6 months	No	2005	UK	£36,923	70,663[191]
Cox-2 selectives	NSAIDs	OA/RA	NHS	6 months	No	2005	UK	£30,000	57,414[191]
IAHA	Standard care	Knee	Societal	1 year	No	2002	Canada	$10,000	13,876[79]
Total hip replacement	Conventional therapy	Hip	Societal	Life	5%	1996	US	$4754	8964[192]
	Pre-operation	Hip	Societal	Life	5%	2007	Finland	6710 euros	12,024[193]
TKR	Pre-operation	Knee	Institutional	2 years	No	1997	US	$5856	11,042[194]
Unicompartment knee arthroplasty	Pre-operation	Knee	Societal	Life	5%	2007	Finland	13,995 euros	25,079[193]
	TKR	Unicompartment knee OA	Societal	Life	3%	2006	US	$250	428[140]

* Perspective = perspective for EE (societal = costs and benefits to whole society; NHS = costs and benefits to the National Health Service; Institutional = costs and benefits to other payers e.g., insurance company).
† The original cost per QALY was converted into US$ with an inflation rate of 5% pa from the date of the study to the current value on 8 May 2009.

have been in patients with knee OA[61–77]. The largest and most comprehensive SR is the 2006 Cochrane review[65]. This reviewed 76 trials; including 40 vs placebo, 10 vs IA corticosteroid, six vs NSAIDs, five vs physical/exercise therapy, two vs arthroscopy, two vs conventional therapy and 15 in which different HA products were used as comparators. A number of different HA products have been examined, and in most studies they have been administered at weekly intervals for 3–5 weeks. Treatment effects were assessed at 1–4 weeks, 5–13 weeks, 14–26 weeks and 45–52 weeks. The pooled ES vs placebo at 1–4 weeks was 0.60 (95% CI 0.37, 0.83) for reduction in pain, 0.61 (0.35, 0.87) for improvement in physical function and 0.54 (−0.17, 1.26) for reduction in stiffness, with an NNT of 7 (3, 119) for the patients' global assessment of a positive clinical response (Table I) but an asymmetric funnel plot and positive Egger test suggested the possibility of publication bias. There was also very considerable heterogeneity of outcomes between trials. When analysis is restricted to high quality studies with a Jadad score of 5, there is no evidence for significant relief of pain (Table III). Inconclusive data from an earlier MA suggested that the heterogeneity between trials might be due to the higher molecular weight products having greater efficacy[70]. A more recent MA[74] of 13 RCTs compared outcomes following IA injections of high molecular weight Hylan with IA injections of standard HA products in a total of 2085 patients with knee OA. The pooled ES showed that IA Hylan was not significantly more effective in relieving pain (0.27, 95% CI −0.01, 0.55) but there was a high degree of heterogeneity between trials with an I^2 of 88%. The pooled ES was close to zero when only trials with blinded patients, adequate concealment of allocation and ITT analysis were included. Reduction in pain diminished with time, and was no longer significant after 14 weeks. In 10 trials comparing IAHA injections with IA corticosteroids there were no significant differences 4 weeks after injection but IAHA was shown to be more effective 5–13 weeks post injection[65].

This is further supported by a recent MA of seven RCTs in patients with knee OA in which IAHA was compared directly with IA corticosteroid[78]. Pain relief was greater following IA corticosteroids at 2 weeks (ES = 0.39, 95% CI 0.12, 0.65), but not at 4 weeks (ES = 0.01, 95% CI −0.21, 0.23). IAHA was followed by superior reduction in pain at 8 weeks (ES = 0.22, 95% CI −0.5, 0.49) and the difference in symptomatic benefit favouring IAHA became statistically significant at 12 weeks (ES = 0.35, 95% CI 0.03, 0.66) and 26 weeks (ES = 0.39, 95% CI 0.18, 0.59).

Analyses of the results for other outcomes such as reduction in stiffness and improvement in function following IAHA were similar. No major safety issues were detected, apart from some local adverse events such as transient pain and swelling at the injection site (RR = 1.49, 95% CI 1.21, 1.83)[65]. MA for adverse events showed that IA injections of high molecular weight Hylan were followed by a greater frequency of flares of pain and swelling compared to the standard IAHA (RR = 2.04, 95% CI 1.18, 3.53)[74]. The cost per QALY for IAHA compared with standard therapy was $13,876[79] (Table V).

Glucosamine

One SR[80] and three new RCTs[34,81,82], which examined evidence for symptomatic efficacy of glucosamine preparations in OA, have been published since 2006. There are now 20 published placebo-controlled RCTs of glucosamine in OA, of which 19 provided data for further analysis, including 16 in which glucosamine sulphate (GS) preparations (13 oral, two intra-muscular and one IA) have been used and three in which glucosamine hydrochloride (GH) was given. Pharmacological effects of GS and GH should not differ as both dissociate in the acid milieu of the stomach to release an identical amino sugar, glucosamine[83]. The calculation of ES for pain

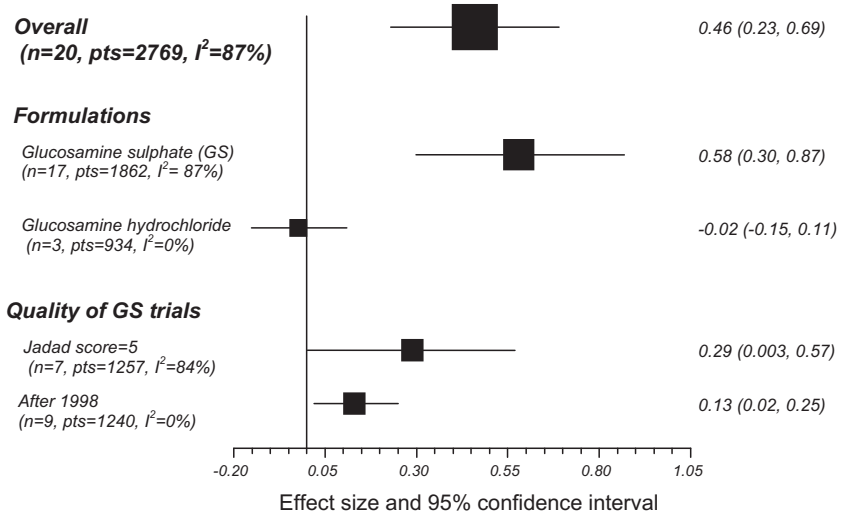

Fig. 4. Analgesic efficacy of glucosamine in OA: analysis of RCTs according to formulations employed and quality of trials.

relief which was used to support the OARSI recommendations for glucosamine products was based on the 2005 Cochrane review[84] where outcomes of RCTs were pooled regardless of the formulations employed (0.61, 95% CI 0.28, 0.95)[2]. MA of RCTs, including those published after 2006, in which GS or GH has been given shows moderate symptomatic efficacy, ES = 0.46 (95% CI 0.23, 0.69) but there is significant heterogeneity of outcomes ($I^2 = 87\%$, $P < 0.0001$) as well as considerable evidence of publication bias ($P = 0.002$ using the Egger test). The ES for pain reduction was 0.58 (95% CI 0.30, 0.87) for GS but insignificant for GH, ES = −0.02 (95% CI −0.15, 0.11) (Fig. 4). Whilst the outcomes of trials for GH were homogenous ($I^2 = 0\%$), those for GS were very heterogeneous ($I^2 = 87\%$). Egger test analysis of the trials using GS also suggests significant publication bias ($P = 0.009$) but the small number of RCTs in which GH has been utilised ($n = 3$) precludes such analysis. When analysis of trials of GS is limited to high quality RCTs (Jadad = 5) the ES is 0.29 (95% CI 0.003, 0.57) (Fig. 4) and there is no evidence of publication bias ($P = 0.74$ using the Egger test), but heterogeneity of outcomes remains considerable ($I^2 = 84\%$, $P < 0.0001$). When trials with low quality scores (Jadad score < 5) and the one trial with exceptionally large effect (ES = 1.27, 95% CI 0.89, 1.58), are excluded, outcomes of trials with GS become homogeneous ($I^2 = 0\%$) but efficacy is greatly reduced (ES = 0.15, 95% CI 0.03, 0.27) (Table III). Cumulative MA of RCTs of GS from 1981 to 2008 shows a progressive diminution of ES (Fig. 5). Further analysis of the data included in the SR of 15 RCTs published in 2007[80] shows homogeneity ($I^2 = 9\%$) but no efficacy in trials in which allocation concealment was adequate; ES = 0.04 (95% CI

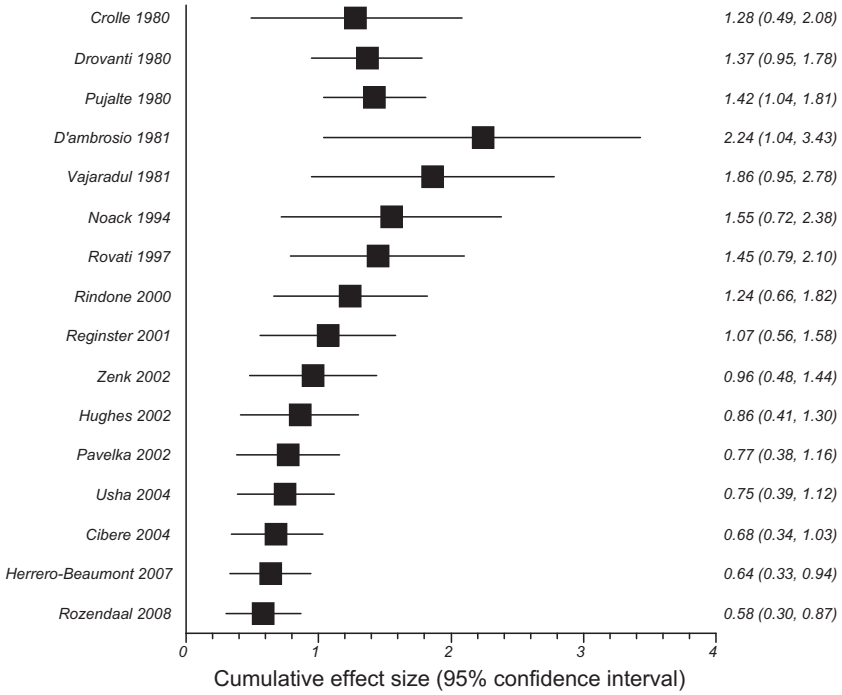

Fig. 5. Cumulative MA of RCTs of analgesic efficacy of GS in OA.

−0.07, 0.14); and heterogeneity ($I^2 = 88\%$) but apparent efficacy with an ES = 0.42 (95% CI 0.19, 0.64) in trials with inadequate allocation concealment. Efficacy in RCTs using ITT analyses was less than in those that did not: ES = 0.23 (95% CI 0.002, 0.46) vs ES = 0.53 (95% CI 0.06, 1.00); and was absent in investigator led RCTs that were not industry funded ES = −0.002 (95% CI −0.11, 0.11) compared with an ES = 0.44 (95% CI 0.18, 0.71) in the industry funded studies.

While the three trials utilising GH were undertaken after publication of the consolidated standards for reporting clinical trial (CONSORT) statement[85], a number of the trials in which GS was used were published before the adoption of consolidated standards for the reporting of clinical trials by the majority of journals in 1998[85]. When analysis is restricted to all RCTs of GS published since 1998 the outcomes are homogenous ($I^2 = 0\%$) and there is no evidence of publication bias ($P = 0.76$ using the Egger test) but efficacy is diminished; ES = 0.13 (95% CI 0.02, 0.25) (Fig. 4).

Evidence for glucosamine products having a possible structure-modifying effect in patients with knee or hip OA remains controversial. Three RCTs of GS 1500 mg daily (two in knee OA and one in hip OA) have been published[82,86,87]. The pooled ES for slowing of joint space loss in the medial compartment of the knee in the two trials in patients with knee OA, which included 414 patients, was small but significant (ES = 0.24 95% CI 0.04, 0.43). However, no significant decrease in joint space narrowing was demonstrable in an RCT involving 221 patients with hip OA after 24 months therapy, either in the whole group (ES = 0.03 95% CI −0.06, 0.12)[82], or in sub-groups pre-defined for severity and whether the OA was localised or generalised[88]. There was also no evidence of significant reduction of joint space narrowing of the medial compartment of the knee over 24 months in a sub-group of 77 patients with knee OA treated with GH 1500 mg/day in the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) (ES = 0.15, 95% CI −0.07, 0.38)[89].

A follow-up observational study of the patients with knee OA that had participated in the RCT of GS showed that the 5-year incidence of total knee replacement (TKR) in patients who had taken GS 1500 mg/day for at least 12 months was less than half of that in those who had taken placebo (6.3 vs 14.5%) ($P = 0.0024$)[90]. The use of joint replacement surgery as a reliable end point for trials of structure-modifying therapies in OA is, however, not yet established[91]. The decision to undertake joint replacement surgery is influenced by many factors; such as the severity of pain and disability, the patients age, gender[92] and co-morbidities, as well as the surgeon's threshold for recommending the procedure and the patient's willingness to undergo surgery.

Chondroitin sulphate (CS)

Five MA have been undertaken[44,93–96]. The most recent 2007 MA of 20 trials involving 3846 patients[95] demonstrated pain relief with a moderate to large ES (ES = 0.75, 95% CI 0.50, 0.99). However, there was evidence of publication bias in favour of trials of CS having positive outcomes (Fig. 6), and the results were extremely heterogeneous (Fig. 7) ($I^2 = 92\%$). Cumulative MA demonstrates a chronological reduction in the ES (Fig. 8). When the analysis is restricted to high quality trials with a Jadad score of 5, there is no evidence for significant relief of pain (ES = 0.005, 95% CI −0.11, 0.12) ($I^2 = 0\%$) (Table III).

Trials which examined whether CS might have structure-modifying effects were systematically reviewed in 2008[97]. Four company-sponsored RCTs in patients with knee OA (three full reports and one abstract) were included in this review. There was no heterogeneity in outcomes between trials and the pooled results demonstrated a small but significant reduction in the rate of decline of joint space narrowing per year in patients treated with CS

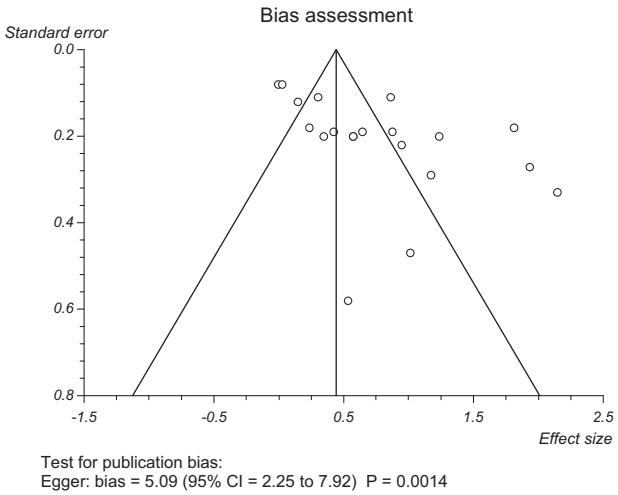

Fig. 6. Funnel plot of trials of analgesic efficacy of CS in OA.

compared with placebo (ES = 0.26, 95% CI 0.16, 0.36). More recently, the full report of one of these trials was published[98]. Loss of minimum joint space width (JSW) over 2 years was significantly lower in the treated patients (−0.07, S.E.M. 0.03) than in those treated with placebo (0.031, S.E.M. 0.04) ($P < 0.0001$)[98].

Avocado soybean unsponifiables (ASU)

Evidence for symptomatic efficacy of ASU (300 mg/day for 3–12 months) was assessed in a recent SR of four industry-sponsored RCTs involving 272 patients with hip OA and 392 patients with OA knee[99]. The overall ES for pain reduction was 0.39 (95% CI 0.01, 0.76) but there was considerable heterogeneity of outcomes ($I^2 = 83\%$). The ES was smaller (0.22, 95% CI −0.06, 0.51) and heterogeneity was reduced ($I^2 = 61\%$) when analysis was limited to high quality trials (Jadad score = 5) (Table III). Treatment with ASU was also associated with moderate improvement in the Lequesne index (ES = 0.45, 95% CI 0.21, 0.70; $I^2 = 61\%$). Twice as many patients responded to ASU when compared with placebo (RR = 2.19, $P = 0.007$) with an NNT of 6 (95% CI 4, 21).

Vitamin E

As part of a wider SR of the efficacy of antioxidant vitamins and selenium in patients with inflammatory joint diseases and OA, six RCTs of vitamin E in patients with OA (four vs placebo, two vs diclofenac) were systematically reviewed[100]. The studies were poor in quality and the results were equivocal. Vitamin E gave better relief of pain than placebo in two small, short-term, studies but was no better than placebo in two larger, longer-term, placebo-controlled RCTs and appeared to give equivalent pain relief to diclofenac in two active control trials. Further high quality trials are needed.

Other nutritional supplements

SRs of trials of the nutritional supplements *Perna Canaliculus* (green-lipped mussel)[101], dimethyl sulfoxide (DMSO) and methylsufonylmethane (MSM)[102,103] for the treatment of OA concluded that definitive evidence for efficacy of green-lipped mussel extracts, DMSO and MSM, was not established because of methodological flaws in the RCTs. The RCTs of MSM in >150 patients with knee OA were, however, more rigorous. In one12-week double blind placebo-controlled trial MSM 500 mg tid resulted in significant improvement in a Likert pain scale and in the Lequesne functional index[104] and in another 12-week double

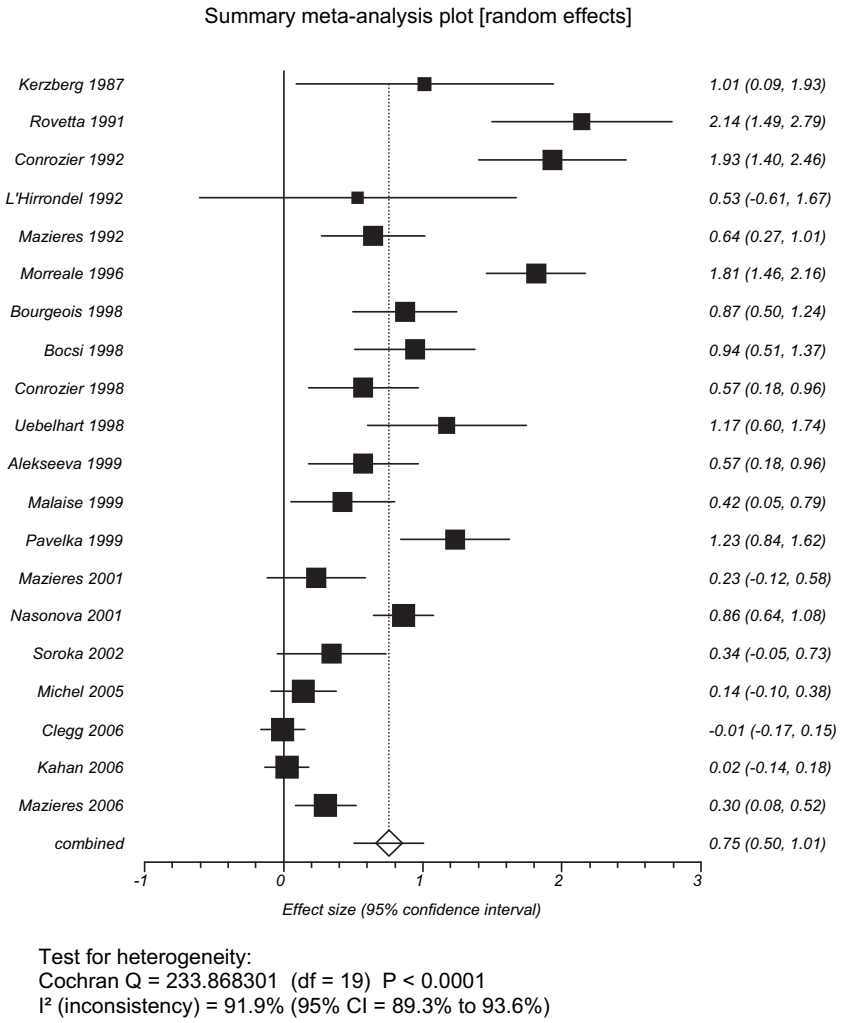

Fig. 7. Forest plot of trials of analgesic efficacy of CS in OA.

blind placebo-controlled RCT MSM 3 g bd was significantly superior to placebo in decreasing WOMAC pain and functional scores[105].

S-Adenosylmethionine (SAM-e) is widely used as a dietary supplement by patients with OA in the USA, despite a 2002 SR which suggested that SAM-e had no significant efficacy in relief of pain in knee OA (ES = 0.22, 95% CI −0.25, 0.69)[106], No new RCTs or SRs of SAM-e in the treatment of hip or knee OA were published between 2006 and 2009 but a single double blind cross-over RCT comparing SAM-e (600 mg bd) with celecoxib (100 mg bd) in 61 patients with knee OA showed that while celecoxib gave better relief of pain after 1 month ($P = 0.024$) there was no significant difference in pain relief between the treatment groups at 2 months[107].

Other herbal remedies

Herbal medicines are very widely used by patients with symptomatic hip and knee OA. In addition to the evidence for efficacy of ASU reviewed above there are now >15 SRs of variable quality of trials of rosehip powder, devil's claw (*Harpagophytum procumbens*), ginger, willow bark extracts, Salai guggal and a number of other herbal preparations. A recent MA of three manufacturer-supported placebo-controlled RCTs of a rosehip powder from *Rosa canina* (the Dog Rose) in 287 patients with OA in various joints found that rosehip powder had a small but significant effect in reducing pain (ES = 0.37, 95% CI 0.13, 0.60)[108]. Outcome was homogeneous between trials ($I^2 = 0\%$) and patients receiving rosehip powder responded twice as frequently as those on placebo (OR 2.19) corresponding to a NNT of 6 (95% CI 4, 13)[108]. A 2006 review of 14 trials of *H. procumbens* in patients with OA included four double blind placebo-controlled RCTs[109]. The better quality placebo-controlled trials with >50 mg harpagoside daily demonstrated some efficacy for relief of pain[101] but evidence for pain relief with ginger, *Boswellia serrata* gum resin, willow bark extract and other herbal preparations is sparse and inconclusive[110].

Diacerhein

Diacerhein is an anthraquinone derivative which has been shown to inhibit IL-1β in *in vitro* studies[111] and to have some slow-acting, and persisting, symptomatic efficacy in patients with OA of the knee[112–114] and hip[115]. The SR of the research evidence for symptomatic efficacy in patients with hip and knee OA from 2002 to 2006 was based on four RCTs[112,114–116]. Efficacy for pain reduction was small (ES = 0.22, 95% CI 0.01, 0.42)[2] with considerable heterogeneity between trials, and diarrhoea was a significant problem (RR = 3.98, 95% CI 2.90, 5.47)[2]. Two MAs were published in 2006[117,118] and one further NSAID-controlled RCT was published in 2007[116]. The updated ES for relief of pain, based on analysis of six

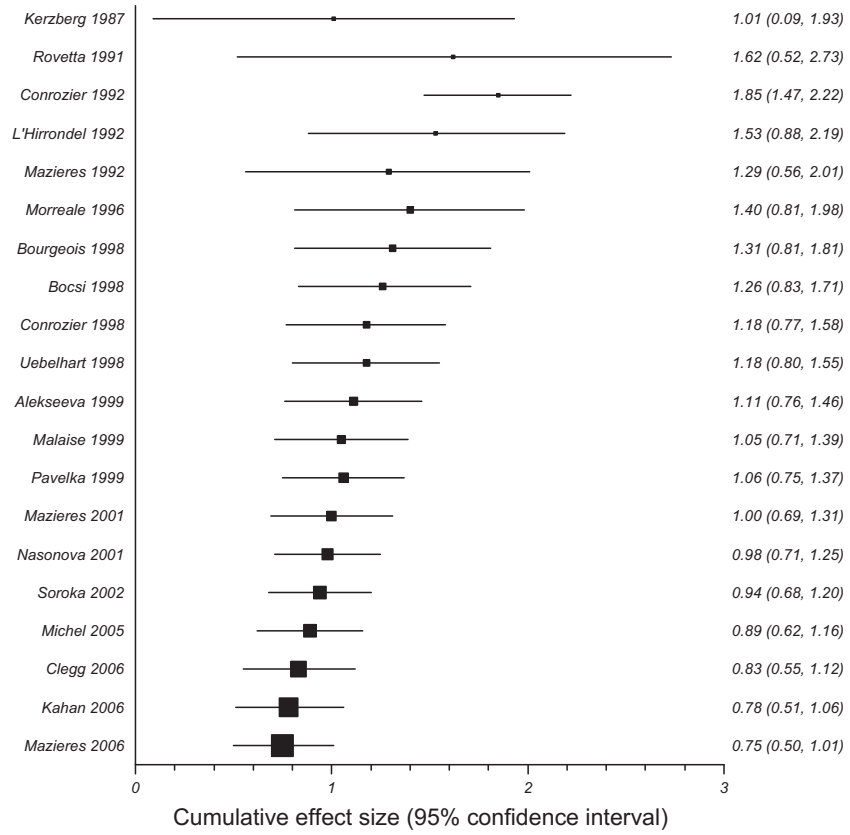

Fig. 8. Cumulative MA of trials of analgesic efficacy of CS in OA.

RCTs[112–115,119,120] is 0.24 (95%CI 0.08, 0.39) (Table I) and RR of diarrhoea compared to placebo is 3.51 (2.55, 4.83) (Table IV).

Anti-resorptive bone-acting agents

Interest in the possibility that drugs which inhibit bone turnover might have potential as structure-modifying agents for the treatment of OA followed the demonstration of chondroprotection in animal models of OA after administration of alendronate, calcitonin or oestrogen[121,122]. Treatment with oestrogens and alendronate have also been associated with significantly less knee OA-related subchondral bone attrition and bone marrow oedema – like lesions in cohorts of elderly women, than in women not taking bone anti-resorptive drugs[123], but RCTs of agents that suppress bone turnover have failed to demonstrate slowing of structural progression in patients with knee OA[124]. Treatment with risedronate 5 mg/day, 15 mg/day, 35 mg/week or 50 mg/week was not associated with symptomatic benefit or slowing of radiographic progression as measured by decreased JSW over 2 years in a large, multinational, placebo-controlled RCT involving 2483 patients with medial compartment knee OA in Europe and North America[124], despite dose-dependent reduction in urinary levels of the C-terminal cross-linking telopeptide of type II collagen (CTX-II), a cartilage degradation biomarker that has been shown to be associated with progression of knee OA[125]. Comparable reduction in CTX-II followed treatment with strontium ranelate[126], oestrogen replacement therapy[127], and treatment with the selective oestrogen-receptor modulator (SERM) levomeloxifene[128]. Levels of CTX-II, type II collagen neoepitope (C2C) and matrix metalloproteinase 13 (MMP 13) were also significantly reduced following administration of oral salmon calcitonin 1 mg/day for 84 days in a preliminary, and much smaller, placebo-controlled RCT in 41 patients with knee OA, and this appeared to be associated with statistically significant improvement in the Lequesne algofunctional index[129].

Surgical treatments

Lavage/debridement

Three RCTs have been published[130–132] following Moseley's landmark study[133] in which 180 patients with knee OA, randomly assigned to arthroscopic debridement, arthroscopic lavage or placebo (sham) surgery with a skin incision and simulated arthroscopy, showed no significant differences between the groups in the primary end point (pain on a self-reported 12-item knee specific pain score), or any of the other secondary outcome measures of pain or function[133]. To date there are no SRs of joint lavage as a treatment for OA knee but a Cochrane review of arthroscopic debridement for knee OA was published in 2008[134]. This concluded that there was 'gold' level evidence (www.cochranemsk.org) that arthroscopic debridement provided no benefit in patients with unselected OA knee (LoE Ib). Seven placebo (sham) or active (e.g., lavage plus exercise vs exercise alone) controlled RCTs have been reported. All included relatively long-term observations ranging from 3 months to 2 years. To allow some comparability with other treatments, the 3-month observation point has been used to estimate the efficacy of this therapy. Investigators employed either closed needle lavage[130,135] or arthroscopic lavage[131,132] but only Moseley's study[133] clearly separated lavage from debridement. The pooled results showed no benefit for lavage and/or debridement over placebo with ESs of 0.21 (95% CI −0.12, 0.54) for pain relief, 0.11 (−0.11, 0.33) for improvement in function and 0.05 (−0.34, 0.44) for reduction in stiffness

(Table I). The ES was further reduced when MA was restricted to the high quality trials (Table III). However, one recent single blind RCT compared tidal irrigation ($n = 71$) with IA corticosteroid injections ($n = 79$). Both treatments were equally effective at 4 weeks and the tidal irrigation was superior to IA steroid injection after 26 weeks[136].

Other surgical therapies

A Cochrane SR of the efficacy and safety of correction osteotomy for the treatment of unicompartment knee OA was updated in 2007[137]. Thirteen studies involving nearly 700 patients were reviewed. All concerned high tibial osteotomy (HTO) for medial compartment knee OA. Six studies compared two techniques of HTO, four studies compared different perioperative or post-operative care and one study compared HTO alone with HTO plus additional treatment. However, no studies have been undertaken to compare HTO with placebo (sham) surgery or conservative treatment alone. Two studies including one with 5 years follow-up compared HTO with unicompartmental joint replacement. The heterogeneity of studies precluded pooling of outcomes but the authors concluded that despite lack of comparisons with placebo or non-operative treatments there was 'silver' level evidence (www.cochranemsk.org) that valgus HTO does have some efficacy in reducing pain and improving function (LoE IIa). An earlier MA published in 2004 found that the overall failure rate for HTO at 10 years was 25% and the average time between HTO and joint replacement surgery was 6 years[138].

Another SR published in 2007, compared the safety and efficacy of unicompartmental knee arthroplasty (UKA) in patients with knee OA, with HTO and total knee arthroplasty (TKA)[139]. Three RCTs, two controlled trials and three cohort studies were reviewed for function (primary efficacy outcome), post-operative pain, complications and revision rate. Similar percentages of patients had improvement in function following UKA and TKA (RR = 1.03, 95% CI 0.97, 1.10) and HTO (1.26, 95% CI 0.95, 1.19), but fewer patients experienced complications such as deep vein thrombosis following UKA (RR = 0.34, 95% CI 0.14, 0.81), and the revision rate was lower following UKA than HTO (RR = 0.51, 95% CI 0.29, 0.89)[139]. When compared with TKA, the cost per QALY for UKA was only $428[140].

Discussion

The OARSI evidence-based, expert consensus recommendations for the treatment of OA of the hip and knee were published in 2008[1] following critical appraisal of existing guidelines and an SR of the evidence for relevant therapies from 2002 until January 2006[2]. This paper updates the published evidence for available therapies from 31 January 2006 to 31 January 2009, as an aid to determining whether any of the current treatment recommendations[1] require modification at this time.

Timing of updates of evidence and recommendations

The value of clinical practice guidelines is diminished if the scientific evidence on which they are based is out of date[141,142] and the National Guideline Clearinghouse (www.guideline.gov) database is limited to guidelines that have been developed, reviewed or revised within the last 5 years. Reassessment of guidelines for validity every 3 years was recommended in 2001 after it was demonstrated that three quarters of guidelines published by the US Agency for Healthcare Research and Quality (AHRQ) were in need of updating[142]. However, setting arbitrary dates for the SR of new evidence and for revision of recommendations may not be appropriate. While some treatment guidelines, in rapidly evolving fields, become outdated very quickly, early revision of recommendations can be both wasteful of time and resources, and unnecessarily confusing for clinicians, in more slowly evolving areas of medicine. There are currently no generally accepted criteria for determining what kind of new evidence should trigger the need to modify existing treatment guidelines[143], or when SRs should be updated[144]. It has been suggested that there are six situations which should trigger an update of clinical practice guidelines[143]:

1. Changes in evidence of existing benefits and harms of available therapies.
2. Changes in outcomes considered to be important.
3. Changes in available treatments.
4. Changes in evidence that current treatment practice is optimal.
5. Changes in social or economic values that individuals or society place on particular outcomes
6. Changes in resources available for health care.

To these one might add:

7. Changes to correct errors identified following publication, feedback and independent review[145].

This paper provides a systematic update of evidence for the benefits and harms of new and existing therapeutic options for the treatment of hip and knee OA published between 31 January 2006 and 31 January 2009. It also examines the potential influence of this new evidence, by placing it in the context of all the available scientific literature, using sensitivity analyses and cumulative MAs.

Methodology

The search strategies, electronic databases and criteria for inclusion and exclusion of studies were identical to those previously employed and only cost-utility analyses were included for determination of cost-effectiveness[2]. For each CUA, the study perspective, comparator, time horizon, discounting, modelling and uncertainty were evaluated. We selected the best available evidence, both in the 2006 SR[2], and in the current systematic update of evidence primarily based on the evidence hierarchy[5]. The quality of individual SRs/MAs has been assessed using the Oxman and Guyatt checklist[3] and the quality of RCTs evaluated using the Jadad method[4]. The Jadad[4], or Oxford quality scoring system, is the best validated and most widely used of more than 20 scales[146] that have been employed to assess the quality of RCTs. It is simple to use and focuses on the assessment of three important components that contribute to the internal validity of RCTs; randomisation, blinding and withdrawals. It can be criticised, however, for being too simplistic[147], for placing too much emphasis on the quality of reporting of trials and not enough on the quality of the methods, and for not including assessments of allocation concealment or ITT analysis[148], both of which can be important sources of bias in RCTs. As analysis of individual components of trial quality can provide information that is not captured in a composite score of trial quality, original studies included in the SRs/MAs were assessed for quality characteristics; including allocation concealment, the distribution of ES, evidence of heterogeneity and the likelihood of publication bias, wherever possible. Sensitivity analyses were used to examine changes in evidence between 2006 and 2009 and changes influenced by the quality of the studies.

Cumulative MAs

Cumulative MA was used to assess changes in treatment ES year by year, in order to detect any significant trends associated with accruing evidence. The value and potential hazards of this technique are well illustrated in the cumulative MA of the ES for pain

relief in RCTs of acetaminophen published between 2004 and 2007 (Fig. 3) and RCTs of GS (Fig. 5) and CS published between 1992 and 2008 (Fig. 8). In the former case the ES for acetaminophen, though very small, had apparently stabilised and remained statistically significant in the context of an absence of evidence of publication bias, suggesting that further RCTs to test analgesic efficacy were not required. It should be noted, however, that acetaminophen had no significant efficacy for relief of pain when only high quality trials were considered (ES = 0.10, 95% CI 0.00, 0.23). In the latter cases cumulative MAs show an impressive chronological reduction in the ES for pain relief in RCTs of GS and CS (Figs. 5 and 8), suggesting an instability of efficacy, which may be attributable, at least in part, to an increase in the quality of studies after the CONSORT statement was published and widely adopted as a standard for conducting RCTs in 1998[85]. When the analyses are restricted to high quality trials with Jadad scores of 5, GS appears to have modest symptomatic efficacy (ES = 0.29, 95% CI 0.003, 0.57) but CS does not (ES = 0.005, 95% CI −0.11, 0.12) ($I^2 = 0\%$) (Table III). However, funnel plots demonstrate significant asymmetric distribution for CS (Fig. 6) and GS (data not shown) suggesting significant publication bias. As positive trials and trials with larger ES are more likely to have been published, it is very probable that the ES will become smaller in the future following publication of further RCTs if publication bias is eliminated.

Cumulative MA can also be used retrospectively to identify when a treatment ES first reached levels that were statistically significant, or when significant adverse effects first became apparent[149]. Although cumulative MA can provide important evidence to suggest that further trials are unnecessary or even unethical[150], great care must be taken to first ensure that potential biases in the RCTs being subjected to MA are sought for and excluded[6,150].

Strengths and limitations

An independent narrative review of the OARSI treatment guidelines[151] drew attention to some dilemmas such as how to weigh conclusions from a flawed MA against the results from a more recent high quality RCT, the results of which had not been included in the most recent MA; or what should be done about pooled ES estimates from high quality MAs, the authors of which had themselves questioned the results because of concerns about methodological flaws in some of the included RCTs. McAlindon also focussed attention on the general dilemma of how best to deal with data from SRs and RCTs published after the closing date of the SR of evidence[151]. In so doing, he threw out a challenge to the OARSI Treatment Guidelines Committee to consider the possibility of exploring alternative methods for guideline development that could facilitate frequent updates, or even real time adjustments to recommendations in a fast moving field.

Many evidence-based treatment guidelines, including the OARSI recommendations for the management of hip and knee OA[1] have used the 'best available evidence', according to a widely accepted evidence hierarchy[5], to guide recommendations. While this has the important advantage that the guideline developers are spared the need to undertake an SR for every treatment modality, it has a number of limitations:

- SRs/MAs may not provide better evidence than individual RCTs in certain instances.
- The results of some important high quality RCTs may have become available after the publication of the latest SR/MA.
- It may be difficult to determine which RCT provides the best evidence for efficacy of a modality of treatment when no SR/MA is available.
- Evidence for certain treatment modalities (e.g., surgical therapies) is often based on uncontrolled observational studies and cohort studies where outcomes have been compared with standard medical care or historical controls. Whereas in the past RCTs were thought to be precluded for surgical treatments for ethical and methodological reasons, recent studies have emphasised that it is both necessary and possible to undertake RCTs of surgery in musculoskeletal diseases[130–133,152,153].

Most importantly:

- It is not always easy to determine which SR/MA provides the best available evidence when several have been undertaken.
- Cross-treatment comparisons may not be possible when SRs/MAs have used differing inclusion/exclusion criteria for RCTs.

For example an MA of all trials for GS showed significant efficacy for pain relief with a moderate ES (ES = 0.61, 95% CI 0.28, 0.95), whereas in a sub-group analysis of trials judged to have adequate allocation concealment efficacy was not apparent (ES = 0.04, 95% CI −0.09, 0.17)[84]. Although there are cogent arguments for using either approach, the OARSI Treatment Guideline Committee favoured pooling of all available trial data for each modality of therapy in order to facilitate comparisons of ES across treatments based on the published MAs. Further comparisons should be made using the same criteria, rather than applying different quality criteria for inclusion of trials in the MAs for different modalities of therapy.

As the publication of new RCTs and SRs/MAs increases progressively it would be very useful to have available a continuously updated, comprehensive, and coherent database of well-characterised trials of all modalities of treatment of OA. Such a database would:

- Allow statistical pooling of data at any time point for a variety of analyses based on different inclusion/exclusion criteria.
- Provide an unconstrained hypothesis-free database of OA therapy that can be used to generate and test new hypotheses.
- Assist clinical decision making for all treatments under consideration.

However, care must be taken to continue to distinguish the processes that lead to formulating treatment guidelines and the strength of expert consensus recommendations, which are based on expert assessment of the 'best evidence' available; from the updated cumulative evidence itself. Following appraisal of the cumulative, updated evidence contained in this paper, and any feedback from stakeholders that may follow publication, the OARSI Treatment Guideline Committee will review the current OARSI recommendations[1] and reach consensus on whether changes should be made in 2010.

Conflict of interest

Full disclosure statements from all members of the OARSI Treatment Guidelines Committee are shown in Appendix II. These were reviewed by the OARSI Ethics Committee. No potential conflict of interest was identified that should preclude any member of the committee participating in this critical appraisal. Corporate members of OARSI are also listed in Appendix II.

Acknowledgements

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This paper is endorsed by the Board of Directors of OARSI but has been developed independently by the OARSI Treatment Guidelines Committee.

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Appendix I. Glossary of terms and abbreviations (in alphabetic order)

AAOS: American Academy of Orthopaedic Surgeons.
AHRQ: Agency for Healthcare Research and Quality.
ASU: avocado soybean unsponifiables.
CI: confidence interval.
CONSORT: consolidated standards for reporting clinical trials.
Cost-effectiveness analysis (CEA): a form of economic evaluation in which the costs and consequences of alternative interventions are expressed as cost per unit of health outcome as measured in physical or natural units. Natural units could range from clinical measures, such as pain reduction, through total joint replacement saved and life-years gained. It is also used as a general term for economic evaluation in the US.
Cost-utility analysis (CUA): a form of economic evaluation in which the costs and consequences of alternative interventions are expressed as cost per quality-adjusted life year (QALY) gained. QALY combines changes in quantity and quality of life (QoL) into one composite measure which is independent of programme or disease. It, therefore, allows cross-programme/disease comparisons and is an outcome very useful for policy making and resource allocation.
Cox-2: cyclooxygenase-2.
CS: chondroitin sulphate.
CTX-II: C-terminal cross-linking telopeptide of type II collagen.
Cumulative meta-analysis: repeated performance of meta-analysis whenever a new trial becomes available for inclusion.
DMSO: dimethyl sulfoxide.
EE: economic evaluation (UK) or cost-effectiveness analysis (US). These are studies which measure both the clinical effectiveness (e.g., pain reduction) and the costs (resource) incurred in achieving the clinical outcome and the treatment of any adverse consequences of the treatment. The incremental cost-effectiveness ratio (ICER) is a way of presenting this composite measure. It is calculated by dividing the difference in costs by the difference in effectiveness of alternative therapies.
Egger test: a regression test used in conjunction with Funnel plots to detect publication bias in meta-analyses.
ES: effect size. This is a standard mean difference between groups (e.g., treatment vs placebo). ES is calculated by dividing the mean difference between treatments by the standard deviation of the difference. It is, therefore, a number without units that can be used for cross-study comparisons. Clinically $ES = 0.2$ is considered small, $ES = 0.5$ is moderate and $ES > 0.8$ is a large effect.
EULAR: European League Against Rheumatism.
FDA: Federal Drug Administration.
Funnel plot: a funnel plot is a scatterplot of treatment effect against a measure of study size or sampling error. It is used primarily as a visual aid to detect bias or systematic heterogeneity. An asymmetric funnel suggests the possibility of either publication bias or a systematic difference between smaller and larger studies. Whatever the cause, an asymmetric funnel plot suggests that simple statistical pooling is inappropriate.
GAIT: Glucosamine/Chondroitin Arthritis Intervention Trial.
GFR: glomerular filtration rate.
GH: glucosamine hydrochloride.
GI: gastrointestinal.
Gold and Silver evidence: Cochrane collaboration musculoskeletal group gradings for levels of evidence. 'Gold' level – one RCT; 'Silver' level – either one randomised trial with head to head comparisons or high quality case–control study.
GS: glucosamine sulphate.
GUIDE: Glucosamine Unum in Die (once a day) Efficacy trial.
H2 *blocker*: histamine H2 receptor antagonist.
HR: hazard ratio is a relative risk measure for time-to-event data. It is specifically useful for survival analysis, where HR gives an estimate of the overall difference between the survival curves. If there is no difference between two groups the value of the $HR = 1$.
HTO: high tibial osteotomy.
I^2: is the degree of heterogeneity in outcomes between studies expressed as a percentage. It is a measure of the variation in outcomes across studies that is not due to chance.
IAHA: intra-articular hyaluronic acid.
ITT: intention to treat analysis.
JSW: joint space width.
LoE: level of evidence. This is based on an *evidence hierarchy* in which studies are ranked according to the quality characteristics of the study design, or information available. In this hierarchy systematic review/meta-analysis of randomised controlled trials (RCTs) are regarded as providing the highest LoE (Ia) for efficacy; followed by a single RCT (Ib), non-RCT (IIa), quasi-experimental study (IIb), comparative observational study (III), and expert opinion (IV).
MA: meta-analysis is a systematic review of research evidence that includes a statistical analysis which examines the

distribution of the outcomes of the included primary studies quantitatively, and combines the results when it is appropriate to do so.
MMP: matrix metalloproteinase.
MSM: methylsufonylmethane.
NA: not available.
NICE: National Institute of Health and Clinical Excellence.
NNT: number needed to treat. This is the number of patients that would need to be treated to achieve a target treatment effect. The smaller the NNT, the better the therapy; the greater the NNT, the less effective is the treatment.
NNH: number needed to harm. This is the number of patients that would need to be treated to have an unwanted effect. The smaller the NNH, the more risk is the treatment; the greater NNH, the less risk is the treatment.
NSAID: non-steroidal anti-inflammatory drug.
OA: osteoarthritis.
OARSI: Osteoarthritis Research Society International.
OR: odds ratio. Provides an estimate of RR in a case–control study.
OTC: over the counter.
PPI: proton pump inhibitor.
PUB: perforation, ulceration or bleeding.
Publication bias: publication bias is a type of selection bias when publishing research results. For example, studies with positive findings are more likely to be published, and outcome measures with positive results are more likely to be reported.
QALY: quality-adjusted life year is a measure of health that encompasses both the *quality* and the *quantity* of life. It is used to compare the overall *value* of different treatments. It is measured by calculating the number of years of life gained as a result of a treatment adjusted to take account of the *quality of life* (QoL). QoL ranges from 0 (worst possible health) to 1 (perfect/best possible health). It is determined by the preferences of patients obtained by *time trade off* or *standard gamble* (methods where patients choose between ill health for longer period and better health for shorter life expectancy), or by using a visual analogue scale stretching from 0 (death) to 100 (perfect health).
QoS: quality of study. This reflects the quality of evidence within each type of study. A number of quality assessment tools (checklists) have been developed, including the AGREE instrument for guidelines, the Oxman and Guyatt checklist for systematic reviews, the Jadad scale for clinical trials.
RCT: randomised controlled trial.
RR: relative risk or rate ratio is a relative risk measure which is used to assess *incident risk* in cohort studies or *prevalent risk* in cross-sectional studies. An $RR = 1$ means that the risk of a disease, or event, is equivalent in two groups.
SAM-e: *S*-adenosylmethionine.
Sensitivity analysis: an analysis to examine the uncertainty in economic evaluation according to different assumptions, or an analysis to determine the changes in meta-analysis with different inclusion criteria.
SERM: selective oestrogen-receptor modulator.
SOR: strength of recommendation
SR: systematic review. A review of the scientific literature relating to a specific question in which explicit methods are employed for the identification, appraisal and summary of research evidence.
TENS: trans cutaneous electrical nerve stimulation.
TKA: total knee arthroplasty.
UKA: unicompartmental knee arthroplasty.
WOMAC: Western Ontario and McMaster Universities OA index.

Appendix II. Committee members' disclosures and corporate members of OARSI

Name	Consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses	Ownership interest	Business relationship	Service with organisation with interests comparable to OARSI	Nothing to declare
W. Zhang	Nil	Nil	Nil	EULAR OA task force	
RW Moskowitz	Adolor Anesiva Bioiberica Bionicare CombinatoRx Cypress Bio Endo Ferring Horizon Therapeutics Merck Novartis Pfizer Rottapharm Sanofi-Aventis	Nil	Nil	Nil	
G. Nuki	NicOxt Savien	Nil	Nil	Nil	
S. Abramson	Amgen GlaxoSmithKline Merck NicOx Novartis Pfizer	Amgen BMS Merck Pfizer Resolvyx	Nil	Nil	

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Appendix II (*continued*)

Name	Consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses	Ownership interest	Business relationship	Service with organisation with interests comparable to OARSI	Nothing to declare
RD Altman	Abbott Anesiva Ferring Kinicure McNeil Negma Novartis Pfizer Proprius Reliant Rottapharm Sanofi-Aventis	Nil	Nil	Nil	
N. Arden	Merck, Sharp & Dohme Novartis Pfizer Proctor & Gamble Q-Med Roche Rottapharm Schering-Plough Servier	Nil	Nil	EULAR OA Task force	
S. Bierma-Zeinstra	Nil	Nil	Nil	EULAR OA Task force	√
KD Brandt	Anesiva Genzyme Novartis Pfizer	Pfizer	Nil	Nil	
P. Croft	Nil	Nil	Nil	Nil	√
M. Doherty	AstraZeneca Glaxo Smith Kline IDEA technology Ipsen Novartis Reckitt	Nil	Nil	EULAR OA task force	
M. Dougados	Abbott AstraZeneca BMS CombinatoRx Merck Negma Novartis Pfizer Pharmasciences Proctor & Gamble Roche Wyeth	Nil	Nil	Nil	
M. Hochberg	Allergan Amgen AstraZeneca Bayer HealthCare Bioiberica Bristol Myers Squibb CaloSyn CombinatoRx Eli Lilly Endo Genzyme GlaxoSmithKline Hoffman-La Roche Merck Merck Serono NiCox Novartis Pharma Pfizer Pozen Roche Sanofi-Aventis UCB Wyeth Zelos	Nil	Nil	Nil	

Appendix II (*continued*)

Name	Consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses	Ownership interest	Business relationship	Service with organisation with interests comparable to OARSI	Nothing to declare
DJ Hunter	Donjoy Genzyme Merck Pfizer Smith & Nephew Stryker Wyeth	Nil	Nil	Nil	
K. Kwoh	AstraZeneca Beveridge Inst Novartis	Cartesia	Nil	Nil	
LS Lohmander	Abbott Boehringer MerckSerono NicOx Pfizer Sanofi-Aventis Tigenix	Nil	Nil	EULAR OA Task Force	
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Eisai Co. Ltd
Kao Corporation
Les Laboratoires Servier
Merck & Company Inc.
NicOx SA
Rottapharm
Seikagaku
Corporation
Zeria Pharmaceuticals

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