Nonsteroidal Antiinflammatory Drugs or Acetaminophen for Osteoarthritis of the Hip or Knee? A Systematic Review of Evidence and Guidelines

ANKE WEGMAN, DANIËLLE van der WINDT, MAURITS van TULDER, WIM STALMAN, and THEO de VRIES

ABSTRACT. ***Objective.*** The interpretation of available evidence on the relative efficacy of nonsteroidal antiinflammatory drugs (NSAID) and acetaminophen in osteoarthritis (OA) has recently been debated. This systematic review summarizes the available evidence on the efficacy of NSAID compared to acetaminophen, and compares the quality and content of clinical guidelines regarding the pharmacological treatment of OA.

Methods. Published reports of randomized controlled trials (RCT) and clinical guidelines were identified by a systematic search of bibliographic databases and relevant websites. The quality of RCT was assessed by 2 reviewers independently using a standardized checklist. Data from these RCT were used to calculate pooled differences between groups for pain and disability. The methodology of identified guidelines was appraised using the AGREE (Appraisal of Guidelines for Research and Evaluation) instrument.

Results. The search strategy resulted in the identification of 5 RCT. Statistical pooling of data from 3 trials with adequate methods and sufficient data presentation resulted in a pooled standardized mean difference for general pain of 0.33 (95% CI 0.15 to 0.51), indicating a small effect in favor of NSAID. Pooled estimates for other outcome measures were smaller. Three of the 9 identified guidelines satisfied more AGREE criteria than others, particularly regarding rigor of development. Stakeholder involvement, applicability, and editorial independence were poorly described in most guidelines. The content of recommendations regarding the use of NSAID or acetaminophen was fairly consistent.

Conclusion. Acetaminophen is often effective in OA and is associated with fewer adverse reactions than NSAID. Available evidence supports the recommendations of recent guidelines to use acetaminophen as initial therapy for OA in addition to nonpharmacological interventions. Further research is needed to establish the efficacy of NSAID or acetaminophen in relevant subgroups of patients. We agree with guidelines that it is important that treatment is tailored to individual patients taking into account the severity of symptoms, previous use of acetaminophen, and the patient's knowledge, expectations, and preferences. (J Rheumatol 2004;31:344–54)

Key Indexing Terms:
METAANALYSIS PRACTICE GUIDELINES OSTEOARTHRITIS
ACETAMINOPHEN NONSTEROIDAL ANTIINFLAMMATORY AGENTS

Osteoarthritis (OA) is a major cause of pain, disability, and health care use in the middle-aged and elderly population. Estimates of its prevalence depend on variations in definition, but OA is thought to affect more than 10 to 12% of the population[1,2]. With the increasing number of elderly, the prevalence and impact of OA is expected to increase over the next decades. Pain relief and improvement of functional disability is the primary goal of treatment, which often needs to be continued for long periods of time[3,4].

Most patients with symptoms of OA are treated by primary care physicians. Nonpharmacological interventions, such as patient education, exercise, or occupational therapy, are the mainstay of treatment, but oral medication is often an important element of therapy[3-5]. In primary care, nonsteroidal antiinflammatory drugs (NSAID) are prescribed in 35 to 78% of patients with OA[6-9]. Given the relatively high risk of gastrointestinal (GI) complications, NSAID should not be prescribed for long periods of time, and only reluctantly in patients with increased risk of serious side effects[10-12]. A simple analgesic, such as acetaminophen, has been reported to be well tolerated with few

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common side effects. Use of acetaminophen has been associated with chronic renal failure. However, causal relations have not been established between acetaminophen and chronic renal failure. Fored, *et al* discuss the fact that symptoms of diseases that predispose patients to renal failure may lead to an increased use of analgesics, thus possibly introducing a protopathic (reverse causality) bias[13]. Hepatic toxicity occurs rarely in doses below 4 g/day, but patients with excessive alcohol consumption may be at increased risk for this adverse event[14,15]. Finally, acetaminophen does not affect platelet function, but can interact with warfarin, and may influence anticoagulation[16].

Given the relatively low risk of side effects, the majority of early clinical guidelines for OA recommend acetaminophen as first-line therapy[3,4,17-19]. These recommendations were strengthened by the results of 2 randomized clinical trials (RCT) demonstrating no significant benefit of NSAID over acetaminophen[20,21]. Recently additional evidence has appeared, and guidelines have been updated[22] or newly developed[5,23,24]. However, the validity and interpretation of available evidence and the quality and content of guidelines for the pharmacological management of OA have been debated[25-31]. Criticisms include the completeness of the literature search, interpretation of available evidence, differentiation between opinion and evidence, and the presence of unbalanced or biased recommendations.

Given the often prolonged pharmacotherapy, with associated side effects and costs, it is important to obtain good insight into the available evidence and recommendations regarding pharmacotherapy. We systematically evaluated the available evidence from RCT on the short and longterm efficacy of NSAID compared to acetaminophen for OA of the hip or knee. We also critically appraised the quality of guidelines on the management of OA, and compared the content of recommendations in these guidelines regarding treatment of OA with either NSAID or acetaminophen.

MATERIALS AND METHODS

Search strategies. Publications on RCT were retrieved by a computerized search of Medline, Embase, and the Cochrane Database (until December 2001). For the identification of RCT the first 2 stages of the search strategy of the UK Cochrane Centre were used[32]. This strategy was combined with a search for OA, hip, knee, nonsteroidal antiinflammatory drugs, acetaminophen, and analgesics. For the identification of guidelines a systematic search in Medline (until December 2001) was conducted using the search terms osteoarthritis, hip, knee, and guidelines. Further, several sites on the Internet were screened for publications on guidelines. Finally, the references of all retrieved articles, including systematic reviews, were screened for potentially relevant publications.

Selection of available evidence (RCT) and guidelines. Citations from computerized databases were blinded for authors, affiliation, and source. For the review of available evidence on the efficacy of NSAID compared to acetaminophen, we included publications that met the following conditions: (1) comparison of NSAID with acetaminophen; (2) patients with pain and/or disability related to OA of the hip or knee; (3) at least one of the following outcome measures: overall change, pain, or disability; (4) random allocation of interventions; and (5) publication as a full report (letters and abstracts were excluded). Language restrictions were not used.

For the review of guidelines on the pharmacological management of OA, the following selection criteria were used: (1) development of the guideline by a working group of experts (representatives of a professional group, not individual authors); and (2) recommendations are given on the pharmacological management of hip or knee OA. Systematic reviews or narrative reviews were not included. Language restrictions were not used.

Quality assessment of available evidence. Two reviewers (DvdW and MvT) independently scored the methodological quality of each trial using the internal validity criteria of the Amsterdam-Maastricht Consensus List for Quality Assessment[33]. In this checklist much emphasis is put on an adequate randomization procedure and sufficient blinding (5 out of 11 criteria). Other criteria in the checklist refer to prognostic similarity of intervention groups at baseline, control for co-interventions, compliance, length of followup, dropout rate, and intention-to-treat analysis. Disagreements between the reviewers were identified and discussed during a consensus meeting. A total score for methodological quality was calculated by summing the total number of positively scored criteria (maximum score 11 points).

Data extraction and analysis of available evidence. Details on characteristics of study population, interventions, outcome measures, followup, side effects, and results were extracted for each randomized trial. For outcomes on a dichotomous scale the differences in proportions between study groups were computed (risk difference), together with the 95% confidence intervals (CI). Subsequently, the number needed to treat (NNT) was calculated[34]. For outcomes evaluated on a continuous or interval scale, standardized mean differences (SMD) were computed as the difference between the mean change in outcome since baseline in the compared groups, divided by the pooled standard deviation of change scores. A SMD of 0.2 can be considered to be a small effect, 0.5 moderate, and > 0.8 a large effect[35]. A positive NNT or SMD indicated superior effects of NSAID, a negative NNT or SMD superior effects of acetaminophen.

Statistical pooling of results was considered if there was sufficient clinical homogeneity regarding study populations, interventions, and outcome measures. A chi-square test was used to detect statistical heterogeneity of trial results. In case of statistical heterogeneity ($p < 0.10$), potential sources of heterogeneity were explored, including differences among trials in type and dosage of NSAID, dosage of acetaminophen, severity of OA, or aspects of validity (dropout rate, intention-to-treat analysis, and use of escape medication). Pooled estimates of outcome (random effects model) were computed for homogeneous subgroups of trials[36,37].

Quality assessment of guidelines. The AGREE (Appraisal of Guidelines for Research and Evaluation) instrument was used to critically assess the design of guidelines on the pharmacological management of OA[38]. This checklist includes items on the scope and purpose of the guideline, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence (Table 1). Each item was scored by 2 reviewers independently (AW and DvdW), and then consensus was obtained on the final score. The scoring system of the AGREE instrument (4-point ordinal scale) was collapsed into a 2-point scale (+ = agree; – = disagree), and a category was added that could be used to indicate absence of sufficient information on a specific item (? = unclear).

The following details were extracted and compared across guidelines: year of publication, country, target population, number of RCT available at the time of guideline development, evidence used for recommendations, methods used to formulate recommendations, and content of recommendations.

RESULTS

Search results. The search for RCT yielded over 1500 citations from Medline, Embase, the Cochrane Controlled Trials Register, and reference checking. Nearly all publications were excluded after assessment of titles and abstracts, as

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Table 1. Criteria for appraising the quality of clinical guidelines (AGREE criteria)[38]. Each item was scored + (agree), – (disagree), or ? (insufficient information).

Scope and purpose
1. The overall objective of the guideline is specifically described.
2. The clinical question covered by the guideline is specifically described.
3. The patients to whom the guideline is meant are specifically described.
Stakeholder involvement
4. The guideline development group includes individuals from all relevant professional groups.
5. The patient's view and preferences have been sought.
6. The target users of the guideline are clearly defined.
7. The guideline has been piloted among end users.
Rigor of development
8. Systematic methods were used to search for evidence.
9. The criteria for selecting the evidence are clearly described.
10. The methods used for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.
Clarity and presentation
15. The recommendations are specific and unambiguous.
16. The different options for management of the condition are clearly presented.
17. Key recommendations are easily identifiable.
18. The guideline is supported with tools for application.
Applicability
19. The potential organizational barriers in applying the recommendations have been discussed.
20. The potential cost implications of applying the recommendations have been considered.
21. The guideline presents key review criteria for monitoring and/or audit purposes.
Editorial independence
22. The guideline is editorially independent from the funding body.
23. Conflicts of interest of guideline developement members have been recorded.

most concerned nonrandomized studies or trials comparing 2 different types of NSAID. For 14 citations the full publications were retrieved. Seven of these 14 publications were excluded as they compared acetaminophen with placebo[39] or another analgesic[40-42], used acetaminophen in combination with another drug[43], used a mixed patient population without separate presentation of results for OA[44], or was only available as an abstract[45]. Seven publications, describing the results of 5 different RCT, were finally included in the review and subjected to quality assessment and data extraction[20,21,46-50].

The search for guidelines resulted in 211 citations from Medline and 6 from the Internet. Nine guidelines (10 publications) were included in the review[3-5,17-19,22-24,51]. Excluded publications often concerned narrative or systematic reviews or did not specifically concern the pharmacological management of OA.

Available evidence on the efficacy of NSAID compared to acetaminophen. Table 2 presents details of the selected trials with respect to quality score, study population, interventions, and results. The quality score varied between 5 and 8 points out of a maximum score of 11. Methodological shortcomings often concerned inadequate control for co-interventions or insufficient length of followup (< 3 months). A longer followup period was only carried out by Williams, *et al*[20]. Although procedures for randomization and blinding were considered adequate in the trials by Solomon and Abrams[49] and Wojtulewski, *et al*[50], the publications refer to small crossover trials (42 and 24 participants, respectively) with inadequate analysis and presentation of results. The 3 other trials included larger patient populations (ranging between 178 and 227 participants), and provided detailed information on measures of pain, disability, and overall change.

Pincus, *et al*[46] reported statistically significant differences in favor of diclofenac (150 mg plus misoprostol) compared to acetaminophen (4 g) for overall change, general pain (Health Assessment Questionnaire), and disability [Western Ontario and McMaster University (WOMAC) OA Index target joint score]. These differences were further reinforced in the crossover period. SMD ranged between 0.28 and 0.30. The trial by Bradley, *et al*[21] showed statistically significant benefits only for measures of pain, with SMD ranging between 0.37 and 0.39. The trial by Williams, *et al*[20] demonstrated statistically significant differences in favor of naproxen for pain at rest only (SMD = 0.35). The results of longterm followup are difficult to interpret due to considerable dropout after 2 years.

Additional subgroup analyses by Pincus, *et al*[46] revealed that greater improvements with NSAID (compared to aceta-

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Table 2. Details of RCT comparing NSAID and acetaminophen (ACT): quality score, study population, interventions, and results (including SMD and 95% CI).

Study	Quality Score	Study Population	Interventions (n)	Followup	Overall Change (95% CI)	Pain on Motion (95% CI)	Pain at Rest/ General Pain (95% CI)	Disability (95% CI)
Pincus[46]	8	OA hip or knee (n = 227, 71% women). Mean age 62 yrs, duration of symptoms unclear. Washout 3 to 7 days before both treatment periods, increase of pain during washout	i: diclofenac 2 x 75 mg + 200 µg misoprostol daily (112) ii: ACT 8 x 500 mg daily (115) (6 weeks, crossover)	At 6 weeks (12 weeks, after cross-over)	Investigator estimate (0–100), mean change (SD): i: –9.3 (18.5) ii: –3.6 (19.0) SMD = 0.30 (0.04, 0.57)	—	HAQ-VAS (0–100): mean change (SD) i: –20.8 (25.7) ii: –13.1 (28.6) SMD = 0.28 (0.01, 0.55)	WOMAC joint (0–100): Mean change (SD) i: –12.2 (21.6) ii: –6.6 (18.0) SMD = 0.28 (0.01, 0.55) HAQ-ADL (0–3) Mean change (SD) i: –0.16 (0.31) ii: –0.08 (0.32) SMD = 0.25 (–0.01, 0.52)
Williams[20]	7	OA knee (n = 178, 75% women). Median duration of symptoms 39 (i) and 71 (ii) months, mean age 59 yrs. No NSAID in preceding 3 mo. No washout preceding trial	i: naproxen: 2 x 375 mg daily (90) ii: ACT 4 x 650 mg daily (88) Duration: 2 yrs	Every 6 weeks until withdrawal (2 yrs)	Physician assessment (1–5): mean change (SD) at 6 weeks: i: 0.338 (0.647) ii: 0.274 (0.672) SMD = 0.11 (–0.22, 0.43) At 2 years (n = 62): i: 0.2 (0.60) ii: 0.3 (0.90) SMD –0.13 (–0.64, 0.37)	Pain on motion (0–10): mean change (SD) at 6 weeks i: 1.027 (2.481) ii: 0.703 (2.062) SMD = 0.14 (–0.18, 0.47) At 2 years (n = 62): i: 2 (3.2), ii: 1 (2.9) SMD = 0.32 (–0.18, 0.83)	Pain at rest (0-10): mean change (SD) at 6 weeks i: 0.909 (2.2721) ii: 0.100 (2.386) SMD = 0.35 (0.02, 0.67) At 2 years (n = 62): i: 2 (2.7), ii: 1 (2.6) SMD = 0.37 (–0.13, 0.88)	50 ft walk time (s) mean change (SD): at 6 weeks i: 1.081 (3.884) ii: 0.443 (3.940) SMD = 0.16 (–0.16, 0.49) At 2 years (n = 62): i: 3 (3.2), ii: 0 (3.3) SMD = 0.91 (0.38, 1.44)
Bradley[21,47,48]	6	OA knee (n = 184 patients, 74% women). Mean duration of symptoms 9 yrs, mean age 56 yrs. Washout 3 to 7 days, all had pain after washout	i: ibuprofen 4 x 600 mg daily (64) ii: ibuprofen 4 x 300 mg daily (65) iii: ACT 4 x 1000 mg daily (66) Duration: 4 weeks	At 4 weeks	Improved according to physician, % (95% CI): i: 38% (26 to 50) ii: 44% (32 to 57) iii: 37% (24 to 49) i vs iii: 1% (–16 to 18) NNT = 100 ii vs iii: 7% (–9 to 25); NNT = 14	Walking pain (0–3) mean change (SD): i: 0.45 (0.96) ii: 0.31 (0.81) iii: 0.13 (0.75) SMD i vs iii = 0.37 (0.01, 0.73) SMD ii vs iii = 0.23 (–0.13, 0.59)	Pain at rest (0–3) Mean change (SD): i: 0.40 (1.04) ii: 0.33 (0.68) iii: 0.06 (0.71) SMD i vs iii = 0.38 (0.02, 0.74) SMD ii vs iii = 0.39 (0.03, 0.75)	50 ft walk time (s) mean change (SD): i: 0.7 (3.4) ii: 0.5 (3.8) iii: 0.5 (2.0) SMD i vs iii = 0.07 (–0.29, 0.43) SMD ii vs iii = 0.00 (–0.36, 0.36)
Solomon & Abrams[49]	6	OA knee (n = 42). Patient characteristics (age, sex, duration OA) unknown. Washout 7 days before trial	i: ketoprofen 200 mg daily ii: ACT 6000 mg daily Duration: 7 days (crossover)	At 2 weeks (after cross-over)	Patient preference: ketoprofen: 25 (59%) PCM: 12 (29%) No preference: 5 (12%)	Not presented		Not presented
Wojtulewski[50]	5	OA hip or knee (n = 24). Patient characteristics are not described. Washout not described	i: fenoprofen 600 mg ii: ACT 990 mg iii: placebo Single dose (crossover)	At 6 hrs	Not presented	Pain relief (0–3) mean: i: 1.4, ii: 1.2, iii: 1.0		Not presented

NNT: number needed to treat, SMD: standardized mean difference, HAQ: Health Assessment Questionnaire, VAS: visual analog scale. ACM: acetaminophen.

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minophen) were only found for patients with at least moderate pain or disability. These results were not confirmed by secondary, post hoc analyses of the trial by Bradley, *et al*[21], in which no association between level of pain and response to NSAID was found[48].

Table 3 shows the results of pooled analyses of the 3 trials that were of adequate methodological quality, and provided sufficient data to enable metaanalysis[20,21,46]. All analyses showed sufficient clinical homogeneity to allow statistical pooling. Pooled estimates of differences between NSAID and acetaminophen were statistically significant, yet small, in favor of NSAID (high or low dose) for general pain or pain at rest (SMD = 0.33, 95% CI 0.15–0.51). These results are presented in more detail in Figure 1. For the other outcome measures the differences were smaller. The size of pooled estimates for differences in pain on motion, functional disability, and overall change (physician assessment) ranged between 0.18 and 0.24 (Table 3).

Appraisal of guidelines. Table 4 presents the results of the appraisal of the 9 selected guidelines using the AGREE criteria. Three guidelines satisfied more criteria than others, particularly regarding rigor of development[5,19,24,51]. The other guidelines did not sufficiently describe the methods used for searching and selecting evidence (item 8 and 9), nor did they define the methods used for formulating recommendations (item 10). Scope and purpose were adequately described in nearly all guidelines, but stakeholder involvement seemed to be limited in most guidelines: the patient's

Table 3. Pooled differences between NSAID and acetaminophen for OA of the hip or knee (4 to 6 weeks followup).

Outcome Measure	Included Trials	Test for Statistical Homogeneity (chi-square)	Pooled SMD (95% CI) (random effects model)
Overall change (physician assessment)	2[20, 46 †]	0.85, p = 0.36	0.22 (0.02, 0.43)
Pain on motion*			
Comparison with high dose ibuprofen	2[20, 21]	0.83, p = 0.36	0.24 (0.00, 0.48)
Comparison with low dose ibuprofen		0.12, p = 0.73	0.18 (–0.06, 0.42)
Pain at rest/ general pain*			
Comparison with high dose ibuprofen	3[20, 21, 46 †]	0.20, p = 0.90	0.33 (0.15, 0.50)
Comparison with low dose ibuprofen		0.23, p = 0.89	0.33 (0.15, 0.51)
Functional disability*			
Comparison with high dose ibuprofen	3[20, 21, 46 †]	0.90, p = 0.64	0.19 (0.01, 0.37)
Comparison with low dose ibuprofen		1.54, p = 0.46	0.18 (0.00, 0.35)

* The trial by Bradley, *et al* [21] includes 3 intervention groups; acetaminophen is compared to high dose ibuprofen (2400 mg daily) and low dose ibuprofen (1200 mg daily). † For the trial by Pincus, *et al*[46] the results at 6 weeks (before crossover) are introduced in the analysis. SMD: standardized mean difference, CI: confidence interval.

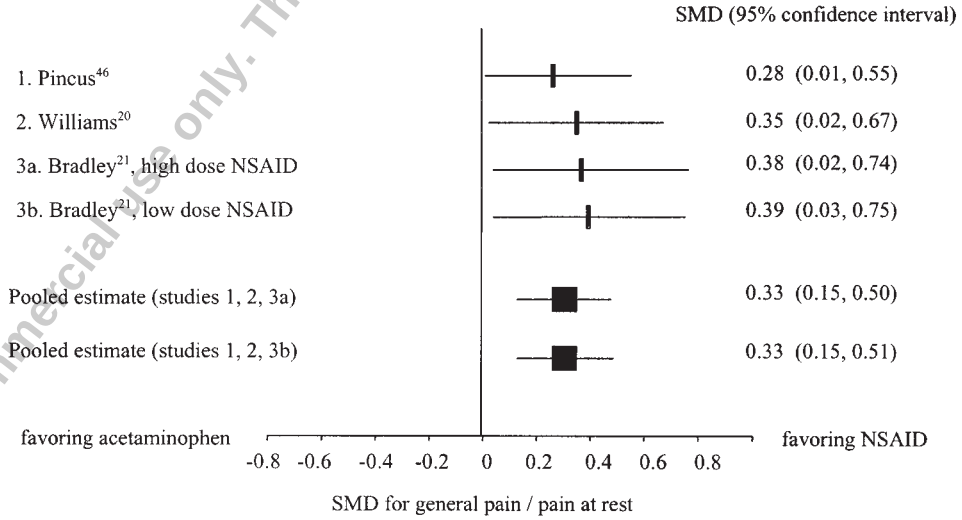

Figure 1. Differences between NSAID and acetaminophen for pain at rest or general pain: results of individual studies and pooled standardized mean difference (SMD) at 4 to 6 weeks' followup (random effects model, SMD, and 95% CI).

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Table 4. Results of the appraisal of guidelines for the management of OA, using the AGREE criteria[34].

	BSR 1993[17]	ACR Hip 1995[3]	ACR Knee 1995[4]	Netherlands 1998[18]	North of England 1998[19]	ACR Update 2000[22]	Canada 2000[5]	EULAR 2000[24]	Germany 2000[23]	Positive Scores per Item (%)
Scope and purpose										
1	+	+	+	+	+	+	+	+	+	9 (100)
2	+	–	–	+	+	+	+	+	+	7 (78)
3	+	+	+	+	+	+	+	+	+	9 (100)
Stakeholder involvement										
4	+	?	?	–	+	?	+	+	+	5 (56)
5	–	–	–	–	–	+	+	–	–	2 (22)
6	?	–	–	+	+	–	+	–	+	4 (44)
7	?	?	?	+	+	?	+	–	?	3 (33)
Rigor of development										
8	–	?	?	?	+	?	+	+	–	3 (33)
9	–	–	–	–	+	–	–	+	–	2 (22)
10	–	–	–	?	+	?	+	+	–	3 (33)
11	+	+	+	+	+	+	+	+	+	9 (100)
12	–	–	–	–	+	?	+	+	–	3 (33)
13	?	?	?	+	+	?	+	?	?	3 (33)
14	–	–	–	+	+	–	–	+	+	4 (44)
Clarity and presentation										
15	+	+	+	+	+	+	+	+	–	8 (89)
16	+	+	+	–	+	+	+	+	+	8 (89)
17	–	+	+	–	+	–	+	+	–	5 (56)
18	?	?	?	+	?	?	?	?	?	1 (11)
Applicability										
19	+	–	–	–	–	–	–	–	–	1 (11)
20	–	+	–	–	+	+	+	+	–	5 (56)
21	+	–	–	–	–	–	–	–	–	1 (11)
Editorial independence										
22	?	?	?	?	+	+	+	?	?	3 (33)
23	?	?	?	?	?	?	?	?	?	– (0)
Positive items (%)	9 (39)	7 (30)	6 (26)	10 (43)	18 (78)	9 (39)	17 (74)	14 (61)	8 (35)	

BSR = British Society for Rheumatology, ACR = American College of Rheumatology, EULAR = European League Against Rheumatism

view and preferences (item 5), for example, were apparently only sought by the developers of the Canadian guideline[5] and the American College of Rheumatology (ACR) update[22], although the European League Against Rheumatism (EULAR) committee indicated the intent to do so[24]. A pilot among end-users (item 7) was only described for the Dutch, Canadian, and North England guidelines[5,18,19]. Most guidelines did not present information on potential organizational barriers to application of the recommendations (item 19), nor criteria for monitoring and auditing (item 21). Finally, editorial independence of the guideline committee (item 22) or conflicts of interest of individual members of guidelines committees (item 23) could not be established for the majority of the guidelines.

In Table 5 we summarize details of the guidelines regarding the target population, evidence base, and recommendations concerning the use of NSAID and acetaminophen in OA. The recommendations of the German guideline were solely based on consensus among committee members[23]. The other guidelines mainly used results from RCT, and included most of the evidence available at the time of development. However, none of the guidelines referred to the early crossover trials by Solomon and Abrams[49] and Wojtulewski, *et al*[50] identified by our search. These 2 studies may have been missed, or perhaps were not considered to be of sufficient relevance or quality. Systematic reviews and metaanalyses were used[18,22] or carried out[5,19,24] by 5 guidelines. The ACR update also referred to patient preference studies, and in addition used evidence that had only been presented in abstracts or as a conference presentation[22].

The actual content of recommendations regarding the use of NSAID or acetaminophen was fairly consistent across most guidelines. The 3 guidelines that received relatively good scores for rigor of development all recommend acetaminophen (maximum 4 g/day) as first-line therapy in OA[5,19,24]. NSAID are recommended for patients with moderate to severe symptoms, and for those who are unresponsive to acetaminophen. The North England guideline

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Table 5. Details of guidelines on the management of OA, including recommendations reguarding prescription of NSAID or acetaminophen.

Guideline	Target Population	Evidence Base	Evidence Used	Recommendation
BSR 1993[17]	OA hip and knee clinical criteria, radiography not always needed	No systematic evaluation of the literature. No explicit link between evidence and recommendations	RCT[21]	1. Analgesics (acetaminophen) 2. NSAID are considered if adequate doses of acetaminophen are ineffective: small dose, regularly reassess need for NSAID therapy
ACR hip 1995[3]	OA hip, clinical criteria and radiography	No clear presentation of a systematic evaluation of the literature. No explicit link between evidence and recommendations	RCT: none available for hip OA. References for knee OA[20, 21, 39]*	1. Acetamenophen (max 4 g daily) 2. If inadequate, low dose ibuprofen (< 1600 mg daily) or nonacetylated salicylates 3. If inadequate, full-dose NSAID
ACR knee 1995[4]	OA knee, clinical criteria and/or radiography	No clear presentation of a systematic evaluation of the literature. No explicit link between evidence and recommendations	RCT[20,21,39]*	1. Acetaminophen (max 4 g daily) 2. If inadequate, low dose ibuprofen (< 1600 mg daily) or nonacetylated salicylates 3. If inadequate, full-dose NSAID
Netherlands 1998[18]	OA knee, clinical criteria	Systematic review of the literature mentioned, but not clearly presented. No explicit link between evidence and recommendations	RCT[20, 21, 47]± plus systematic review	1. Acetamenophen, 3-4 g daily
North of England 1998[19]	Joint pain believed to be caused by degenerative arthritis	Systematic review and metaanalysis, search strategies are available. Explicit link between evidence and recommendations, using a grading system	RCT[20, 21, 43]*	1. Acetaminophen (max 4 g daily) 2. If inadequate, low dose ibuprofen (1200 mg Daily) 3. If inadequate, add acetaminophen (max 4 g daily) or high dose ibuprofen (2400 mg daily) 4. If inadequate, alternative drugs (diclofenac, naproxen or other NSAID, or co-codamol)
ACR update 2000[22]	OA hip and knee, ACR criteria	Use of systemic reviews. Strong weight given to results of systematic reviews and RCT	RCT[20, 21] Abstracts[45]*, [46] plus systematic reviews plus patient preference studies	1. Acetaminophen (max 4 g daily) 2. If inadequate: evaluation of risk factors for serious upper GI and renal toxicity, then COX-2-specific inhibitor or NSAID (plus misoprostol) 3. NSAID for patients with moderate to severe pain or signs of inflammation
Canada 2000[5]	OA, clinical criteria radiography rarely needed	Extensive literature review, but search strategy not presented. Explicit link between evidence and recommendations, using a grading system	RCT[20, 21, 39]*	1. Acetaminophen (max 4 g daily) for mild to moderate OA 2. NSAID may be used for moderate to severe OA, and in those whose symptoms are inadequately controled by acetaminophen
EULAR 2000[24]	OA knee, clinical criteria and/or radiography	Systematic review of the literature. Explicit link between evidence and recommendations, using a grading system	RCT[20, 21, 39]*	1. Treatment should be tailored to the individual patient 2. Acetaminophen is the treatment of first choice 3. NSAID should be considered in those unresponsive to acetaminophen (although there is no direct evidence base)
Germany 2000[23]	OA knee, clinical criteria and radiography	No systematic review of the literature. No explicit link between evidence and recommendations: consensus based	None used	1. NSAID are the basis of therapy 2. Low dose NSAID for those at relatively high risk of adverse events. Acetaminophen can be used to reduce use of NSAID

* These RCT were not included in our review, as they did not meet our selection criteria. BSR: British Society for Rheumatology, ACR: American College of Rheumatology, EULAR: European League Against Rheumatism.

proposes a more detailed stepped-care approach for the pharmacological management of OA[19]. The EULAR guideline explicitly emphasizes the need to tailor therapy to the individual patient[24]. Most guidelines recommend avoiding longterm use of NSAID in patients with a relatively high risk of adverse events, and some even present a risk profile[3–5,22]. In addition, 2 guidelines recommend regular reassessment of the need for NSAID therapy in patients who have been taking NSAID for some time[17,22].

NSAID seem to be the mainstay of pharmacological

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treatment only in the German guideline, with acetaminophen as an alternative in patients with a high risk of adverse events[23]. In contrast, the Dutch guideline, which was developed by general practitioners, states a clear preference for acetaminophen. This guideline more strongly emphasizes the increased risk of adverse events associated with NSAID, as well as the limited benefits of NSAID compared to acetaminophen[18].

DISCUSSION

We conducted a systematic review of available evidence on the relative efficacy of NSAID compared to acetaminophen for OA of the hip or knee, which showed consistent, yet modest, differences on pain in favor of NSAID (pooled SMD 0.33). The evidence base was relatively small. The search identified a large number of trials evaluating the efficacy of NSAID, but only a few included a comparison with acetaminophen. Our search strategy identified trials published until December 2001. Two relevant additional RCT have been published since that time. Geba, *et al*[52] showed that the selective cyclooxygenase-2 inhibitor rofecoxib provides advantages over celecoxib and acetaminopen in patients with knee OA. In a small study, Case, *et al*[53] reported larger clinical improvements in patients treated with diclofenac compared to acetaminophen. However, differences in improvements between intervention groups were not statistically significant, possibly due to insufficient statistical power.

The important question is whether the magnitude of the differences between NSAID and acetaminophen merits the initial use of NSAID. In the 2 most frequently cited trials, the differences between NSAID and acetaminophen at 4–6 weeks' followup were statistically significant only for pain at rest[20,21]. With the publication of the trial by Pincus, *et al*[46], the beneficial effects of NSAID seemed to be more strongly emphasized[22,29].

Statistical significance should not dominate the discussion. It is more important to decide on the clinical relevance of the reported differences. This is difficult and certainly arbitrary, as it will depend on several factors, including the severity of the condition, potential side effects, inconvenience of therapy, treatment preferences, and costs[54]. For 50-foot walk time the difference in improvement between NSAID and acetaminophen was less than 0.7 second[20,21], a difference that will be considered relevant by few. For general pain or pain at rest the difference in improvement was roughly 8 points on a visual analog scale (range 0 to 100)[46], 0.8 point on a numeric rating scale (0–10)[20], or 0.3 point on an ordinal 4-point scale[21]. Taking the mean baseline score into account the average difference in response was 17 to 27% in favor of NSAID. This seems to be a relevant treatment effect; research in patients with OA has shown that a difference of about 15% on pain or 30% on function is associated with other predefined definitions of clinically important change[55,56]. The question remains whether this difference is large enough to recommend the use of NSAID, despite the higher risk of adverse reactions.

There appears to be wide variation among patients in the response to NSAID. Scott-Lennox, *et al*[57] suggested that the washout period that often precedes randomization in clinical trials may affect the response to therapy. In their study, patients with higher intensity flares during washout were more likely to report substantial improvement of symptoms, regardless of treatment (active or placebo). Most trials selected for our review included a washout period before baseline assessment. Little information is available about the course of symptoms during washout (flare intensity), but in 2 of the larger trials pain scores increased during washout[21,46]. Secondary, post hoc analyses of the trial by Bradley, *et al*[21] seem to confirm the assumption of Scott-Lennox, *et al*: a larger improvement of pain was found for patients with higher pain levels after washout, with no significant differences between intervention groups[48]. On the other hand, subgroup analyses by Pincus, *et al*[46] showed that patients with higher pain scores after washout seemed to profit more from NSAID compared to acetaminophen.

The ACR update[22] recommend NSAID as initial therapy for patients with more severe pain, and also for those with signs of inflammation. Secondary analyses[47] of the trial by Bradley, *et al*[21] did not provide evidence for a stronger effect of NSAID in patients with signs of inflammation, such as joint tenderness or swelling. Additional research is needed to explore and confirm relevant subgroup differences. This requires randomized trials in sufficiently large populations using prestratification based on baseline severity of pain, function, or other indicators of disease severity. Such research may facilitate the early identification of patients for whom acetaminophen will suffice, and those who benefit more from NSAID.

In addition to treatment efficacy, drug preferences are the result of several factors, including subjective benefit, side effects (actual or potential), ease of administration (e.g., the larger number of tablets per day when using acetaminophen may be perceived as bothersome), doctor or patient beliefs and interactions, and severity of disease[25,58]. Preferences of patients for either NSAID or acetaminophen have been assessed in a large survey[25] and in a few randomized trials[46,49]. About 60% of patients in these studies preferred NSAID to acetaminophen. However, this also means that acetaminophen may be satisfactory to a considerable proportion of patients. In the trial by Pincus, *et al*, 42% of subjects and care providers, while still blinded to treatment allocation, rated acetaminophen as better than or equally effective compared to NSAID[46]. Therefore, considering the higher risk of adverse reactions to NSAID, it seems worthwhile to recommend continued use of acetaminophen in these patients as long as symptoms do not greatly interfere with daily activities. Acetaminophen may also be recom-

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mended in patients who report previous use of acetaminophen, but have not tried adequate doses.

The appraisal of guidelines showed that the methods for developing the guideline were often unclear. Additional information on the development process was not available for all guidelines. The addition of a category for scoring absence of information facilitated the appraisal, and may have prevented overly negative scores for some guidelines. Nonetheless, guideline development often appeared to be inadequate, particularly regarding methods for selecting evidence and formulating recommendations. Clear instructions for developing guidelines have become available[59,60], and some of the recent guidelines clearly meet these higher standards[5,19,24]. Further improvements can be made in the description of stakeholder involvement, applicability, and editorial independence. The fact that most guidelines do not clearly state that there was no conflict of interest for individual members of the guideline committee was surprising. We argue that editorial independence is of utmost importance, particularly for guidelines in which the pharmaceutical industry may have a strong interest.

In the EULAR guidelines, the authors indicate that there was often discordance between research evidence and the opinion of experts[24]. In this international guideline, variation across countries regarding health care delivery systems and attitudes toward OA contributed to this discordance. A Delphi system was used to obtain consensus on difficult issues. Despite variation in the design of the guidelines in our review, the actual content of recommendations regarding the use of NSAID or acetaminophen in OA was fairly consistent, with most guidelines recommending acetaminophen (maximum 4 g/day) as the first-line therapy in OA. The results of a nested case-control study[61] and a recent retrospective cohort study[62] indicate that patients who take high dose acetaminophen may be more likely to experience GI events compared with those taking low dose acetaminophen, and that these risks may be similar to high dose NSAID. Both studies controlled for known risk factors of confounding by indication, i.e., the risk that patients who are more likely to suffer GI complications are more likely to be prescribed acetaminophen than NSAID. However, in observational research it is almost impossible to completely avoid or adjust for confounding by indication[61]. RCT with longterm followup are warranted to prospectively compare the benefits and risks of high dose acetaminophen with high dose NSAID.

Guidelines are designed to assist clinicians in making decisions about appropriate health care in specific situations. Guidelines generally deal with the "average" patient, and may not always be appropriate for individual patients, each of whom may have different needs and expectations. Several factors need to be taken into account that may vary considerably across patients, such as comorbidity, comedication, daily activity requirements, patient preferences, and the patient's perceptions and knowledge of OA[63]. The need to tailor management to individual patients was explicitly stated in the EULAR guidelines[24]. In an editorial, Dieppe argued that guidelines are too constrained to be useful in the management of a chronic heterogeneous condition such as OA. A better alternative may be to lay out the options available, with information on the advantages and disadvantages of each option that can be understood by both patients and health care providers[64]. This can be a welcome addition to current guidelines, particularly in patients for whom the expected benefits of NSAID may be limited (e.g., patients with mild symptoms), and may also facilitate processes of shared decision-making between patient and physician[65,66]. Further, N-of-1 trials may be helpful to resolve the question for individual patients whether acetaminophen is equally as effective as NSAID in the management of pain and disability[67,68].

In conclusion, evidence from RCT shows that the benefits of NSAID on pain are significantly greater than those of acetaminophen, but the difference was small and may be of limited value to a large proportion of patients with OA. This supports the recommendations of recent guidelines to use acetaminophen as initial therapy for OA (in addition to nonpharmacological interventions). Further research is needed to establish the efficacy of NSAID or acetaminophen in relevant subgroups of patients. Nevertheless, we agree with recently developed guidelines that it is important that treatment is tailored to individual patients, taking into account the severity of symptoms, risk of side effects, previous use of acetaminophen, and the patient's expectations and preferences.

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