Comparison of the Analgesic Efficacy and Safety of Nonprescription Doses of Naproxen Sodium and Ibuprofen in the Treatment of Osteoarthritis of the Knee

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ABSTRACT. ***Objective.*** To compare the analgesic efficacy and safety of nonprescription doses of naproxen sodium, ibuprofen, and placebo in patients with osteoarthritis (OA) of the knee.

Methods. In 2 identical multicenter, randomized, double-blind, placebo-controlled, multidose, parallel-design studies, patients aged ≥ 25 years with OA were randomized to daily doses of naproxen sodium 660 mg, naproxen sodium 440 mg (patients ≥ 65 years), ibuprofen 1200 mg, or placebo, for 7 days.

Results. For investigator and patient assessment of knee joint pain, naproxen sodium (440/660 mg) and ibuprofen were clinically effective at relieving pain compared with placebo (n = 444); both treatments reduced the mean symptom score by 30–45%, compared with a 20–25% reduction with placebo. Naproxen sodium (440/660 mg) significantly improved all 7 symptoms from baseline compared with placebo, while ibuprofen significantly improved 5 of the symptoms. For the subgroup of patients aged ≥ 65 years (n = 183), naproxen sodium 440 mg was significantly superior to placebo in all symptoms except pain on weight-bearing; ibuprofen only significantly reduced day pain. For daily diary evaluations, naproxen sodium and ibuprofen were effective in reducing all 6 symptoms; there was a trend toward higher efficacy for night-time pain with naproxen sodium 440/660 mg compared with ibuprofen. There were no significant differences in adverse event reporting between groups.

Conclusion. Over-the-counter doses of naproxen sodium (440/660 mg) and ibuprofen (1200 mg) effectively relieve pain in patients with mild to moderate OA of the knee. Naproxen sodium provided more effective pain relief for most variables compared with placebo, and for night pain compared with ibuprofen. Efficacy was combined with good safety and tolerability. (J Rheumatol 2004;31:1373–83)

Key Indexing Terms:

ANALGESIA	IBUPROFEN	NAPROXEN
OSTEOARTHRITIS	KNEE	PAIN

Osteoarthritis (OA) is a common chronic musculoskeletal disorder affecting the synovial joints, manifesting as cartilage degeneration, hypertrophy of bone at the margins, and synovial membrane changes[1]. OA ranks fourth in health impact among women and eighth among men[2] in industrial nations.

OA mainly occurs in the elderly, and symptomatic OA, particularly of the knee and hip, is the most common cause of musculoskeletal disability in elderly people[3]. The pain in OA may arise from periosteal elevation, trabecular microfractures, capsular distension, and/or synovial inflammation. As the number of elderly continues to increase, large joint OA, particularly of the knee, is expected to become a greater healthcare challenge[4].

The pattern of joints affected varies depending on sex, men being more prone to OA of the hip[1] and women being more likely to experience more severe and polyarticular disease[5]. The part of the body affected by OA also plays a role in determining the degree of disability[1]. For example, if the patient suffers pain and deformity with the weight-bearing joints (e.g., knee, hip), he or she may be immobilized, potentially reducing quality of life, whereas similar changes in the interphalangeal joints of the hand may cause less change in activities of daily living (ADL)[6].

Pain, especially during the night, is the most common reason patients with OA seek medical help. Since there is no known cure for OA, current treatment strategies for large joint OA aim to educate the patient about OA, alleviate pain, optimize and maintain joint function, and prevent or retard progression of adverse structural change affecting the joint tissues. Encouraging weight loss to reduce stress on weight-bearing joints will benefit the patient by reducing pain and

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increasing mobility. However, the evidence to support the relative efficacy of individual treatments is variable[4,7].

Acetaminophen (paracetamol) is the usual treatment of choice for pain associated with OA and is used at an initial dose of up to 4000 mg/day. If pain control is inadequate with acetaminophen, in patients not at increased risk of upper gastrointestinal (GI) side effects, a nonselective nonsteroidal antiiflammatory drug [NSAID; i.e., not cyclooxygenase (COX-2)-specific], such as naproxen 500 mg/day or ibuprofen 1200 mg/day, can be used instead of, or in combination with, acetaminophen. NSAID are usually prescribed "as required" in contrast to following a fixed daily dose[8], and according to the American College of Rheumatology Subcommittee on Osteoarthritis Guidelines[9], patients should be started on a low dose that should only be increased if there is insufficient symptomatic relief. Although the contribution of inflammation to joint pain and cartilage breakdown remains uncertain, the increasing evidence for the important role of low-grade inflammation in OA indicates that NSAID may be a logical choice for effective analgesia[10]. NSAID have shown efficacy in the management of knee OA in numerous studies[4]; however, the beneficial effects of many NSAID have been counterbalanced by the broader range of GI side effects[11].

Naproxen sodium is a nonselective NSAID composed of smaller particles than naproxen, which significantly increases its absorption rate. It is available over-the-counter (OTC) for treatment of pain, and is available at higher doses on prescription (275 mg and 550 mg). The recommended OTC dosage for naproxen sodium is one 220 mg tablet every 8–12 hours, with a maximum daily dose of 660 mg for up to 7 days of treatment. For patients over 65 years of age, the recommended dosage is one 220 mg tablet every 12 hours, giving a total daily dose of 440 mg[12,13]. Ibuprofen is available OTC at a maximum dose of 1200 mg per day[14].

The efficacy and tolerability of naproxen sodium have been established with prescription doses in approved rheumatologic indications, including OA, and also in dental pain and dysmenorrhea with OTC doses[12,13,15-18]. However, the efficacy and safety of OTC doses have not been extensively studied in the short-term management of OA when treatment is taken "as required."

We compared the analgesic efficacy and safety of nonprescription doses of naproxen sodium with ibuprofen and placebo in the treatment of patients (including the elderly) with OA of the knee, using the results from 2 studies.

MATERIALS AND METHODS

Study design. A secondary analysis was undertaken based on 2 identical multicenter, randomized, double-blind, placebo and active-controlled, multidose, parallel-design studies conducted in the USA (completed May and October 1996), comparing the efficacy and safety of 7 day treatment with naproxen sodium 440/660 mg and ibuprofen 1200 mg in OA of the knee. Identical inclusion and exclusion criteria were applied and each study was undertaken in 5 medical centers (total of 10 centers) in the US. Data from the original case report forms for all patients were combined and subsequently analyzed. Both studies were conducted in compliance with the Helsinki Declaration and were approved by a local Institutional Review Board.

Patients. Subjects enrolled in both trials were in good general health, of both sexes and any race, and were at least 25 years of age. Subjects had received a clinical diagnosis of OA showing at least one of the following radiographic changes: subchrondral sclerosis; joint space narrowing; presence of osteophytes or marginal lipping; or cyst formation in the knee joint typical of OA stage I–III as documented in the previous 3 years. All subjects had episodic flare of OA with at least moderate pain on weight-bearing in the knee as measured on a categoric scale, and had completed the required washout period.

Exclusion criteria included Stage IV OA, moderate to severe chronic lower back pain, inflammatory joint diseases including rheumatoid arthritis, gout, mixed connective tissue disease, seronegative spondyloarthropathy, psoriatic arthritis, and systemic lupus erythematosus. Subjects were excluded if they had been on a daily regimen of prescription NSAID for arthritis pain for the past 3 months; had a recent traumatic injury; or had a history of hypersensitivity or intolerance to any of the study medications. Exclusion criteria also included a history of peptic ulceration within the previous 9 months, GI surgery, GI complaints, or GI dysfunction that could interfere with drug absorption, or any other significant medical conditions. Subjects were prohibited from taking any medication that could interfere with the performance or interpretation of the study pain evaluations. These included antiinflammatory and aspirin-containing medications, or other analgesic medications, antacids, H_2-blockers, prostaglandin analogs, omeprazole, and sucralfate. Subjects who had previously enrolled in or had participated in another investigational drug or device trial during the preceding 4 weeks were excluded. Written informed consent was obtained from the patient before inclusion in each study.

Study protocol. A washout period was required for patients who had taken NSAID within 72 h prior to dosing. The type of NSAID used by the patient determined the length of the washout period: short-acting NSAID (aspirin, naproxen, ibuprofen) required 2 days' washout; long-acting NSAID (piroxicam, nabumetone, oxaprozin) required 4 days' washout.

Patients were randomized in equal numbers, using computer generated blocked randomization, to one of the following: daily doses of naproxen sodium 660 mg (patients < 65 yrs), naproxen sodium 440 mg (patients ≥ 65 yrs), ibuprofen 1200 mg, and placebo. Naproxen sodium 660 mg was administered as one capsule of 220 mg and one placebo capsule TID; and naproxen sodium 440 mg as one capsule of 220 mg and one placebo capsule BID and 2 placebo capsules QD. Ibuprofen was administered as 2 × 400 mg capsules TID, and placebo as 2 capsules TID. All study medications were equal-size capsules packaged in identical blister packs and packaged in boxes containing 3 envelopes for each patient to maintain the blinded conditions.

Patients were treated for 7 days and were observed for a total of 8 days. Data were analyzed for the whole group; subgroup analysis was also performed on the elderly patient population (those ≥ 65 years of age).

Efficacy assessments. Investigator and patient assessment of knee joint pain. Both investigators and patients assessed knee pain at baseline and followup. The degree of pain was rated on a 5 point scale: none = 0, slight = 1, mild = 2, moderate = 3, and severe = 4. Investigators assessed the degree of knee joint pain at rest, on passive motion, and on weight-bearing. Subjects also self-assessed the severity of joint stiffness after rest (in the morning) during the past week, the overall pain severity the day before, and the overall pain severity the previous night. The time it took each patient to walk 50 feet (25 feet in each direction with a turn) was also measured at both visits. Each symptom change (i.e., improvement) from baseline was calculated and compared between treatment groups.

Daily evaluations. Using a patient diary, subjects made daily evaluations of 6 areas. On a scale of 0–4, subjects rated the following: (1) overall arthritis pain (0 = none, 4 = severe); (2) pain control from study medication (0 =

none, 4 = complete); (3) overall pain last night (0 = none, 4 = severe); (4) difficulties experienced in walking one block or climbing one flight of stairs (0 = no difficulty, 4 = extreme difficulty); (5) difficulties experienced in walking several blocks or climbing several flights of stairs (0 = no difficulty, 4 = extreme difficulty); and (6) difficulties experienced in bending, lifting, and stooping (0 = no difficulty, 4 = extreme difficulty). Diaries were to be completed at bedtime, except "overall pain last night," which was to be recorded upon awakening each morning.

Quality of life assessment. Patients also completed a 41 item quality of life questionnaire [a modified version of the Arthritis Impact Measurement Scales 2 (AIMS-2) questionnaire] at baseline and followup, for 9 areas: mobility level, walking and bending, self-care tasks, household tasks, social activity, support from family and friends, work, level of tension and mood were assessed. The subset totals were calculated, from which the total AIMS-2 was determined.

Overall patients' and investigators' evaluation of treatment medication. At the end of the study, patients' and investigators' overall assessments of the study drug were analyzed.

Safety assessments. Patients recorded any adverse events (AE) during the study period. AE were systematically assessed by course, severity, and possible relationship to study drug and outcome, and were classified according to MedDRA 2.4 recommendations. Severity of AE was defined as follows: (1) mild — not affecting normal daily functions; (2) moderate — interfering with normal daily activities; and (3) severe — causing inability to work or to complete normal daily activities. Any possible relationship to study treatment was assessed by the investigators.

Statistical analysis. Patients that received at least one dose of medication were included in the safety population and those with at least one efficacy datum were included in the efficacy population. Patient data for each of the efficacy variables were combined from both studies and analyzed. The Mann–Whitney test was used to test differences between different treatment groups and different studies for patient demographics, and the differences between treatment groups for all efficacy variables. Similarly, the Mann–Whitney test was used to test differences in AE symptoms and organ class frequencies between different treatment groups. The Z test for equality of proportion was used to calculate differences between treatment groups for frequency of patients reporting AE and frequency of AE occurrence.

RESULTS

Patients. A total of 461 patients were enrolled in the 2 studies (Figure 1A). Nine patients either did not take study medication or were lost to followup, leaving 452 patients in the total safety analysis (naproxen sodium 440/660 mg, n = 148; ibuprofen 1200 mg, n = 152; placebo, n = 152). In the efficacy analysis, a further 8 patients were excluded for various reasons including noncompliance with daily study treatment and not meeting inclusion/exclusion criteria, leaving a total of 444 patients in the total efficacy analysis (naproxen sodium 440/660 mg, n = 146; ibuprofen 1200 mg, n = 149; and placebo, n = 149).

A total of 198 (42.2%) enrolled patients were age ≥ 65 years (Figure 1B). Nine patients in this subgroup did not take study medication or were lost to followup and were not included in the safety analysis, and a further 6 patients were not included in the efficacy analysis. Therefore, for this subgroup, 189 patients were included in the safety analysis (naproxen sodium 440 mg, n = 61; ibuprofen 1200 mg, n = 63; placebo, n = 65) and 183 patients were included in the efficacy analysis (naproxen sodium 440 mg, n = 60; ibuprofen 1200 mg, n = 61; placebo, n = 62).

Demographics. The distribution of patients according to age was 7.4%, 13.8%, 17.2%, 26.2%, 29.2%, and 13.7% for age groups < 40, < 45, 45–54, 55–64, 65–74, and ≥ 75 years, respectively. Therefore, 86.1% of patients were at least 45 years of age.

Demographic characteristics of patients are listed in Table 1. In general, there were no statistically significant differences in baseline demographic data between treatment groups. Race proportions were different for patients receiving naproxen sodium compared with patients receiving ibuprofen (p = 0.045). Patients receiving naproxen sodium were also of lower weight compared with patients receiving ibuprofen (p = 0.028). However, outcomes were not influenced by differences in demographic data.

Demographic characteristics for the subgroup of patients aged ≥ 65 years were also similar between treatment groups.

Efficacy assessments. Investigator and patient assessment of knee joint pain. Baseline pain assessments in each of the 7 areas assessed were not significantly different between treatment groups. Overall, both naproxen sodium and ibuprofen at OTC doses were clinically effective at relieving pain compared with placebo. The mean symptom score was reduced by 30–45% from baseline following treatment with either naproxen sodium or ibuprofen, compared with 20–25% following treatment with placebo.

For each of the different symptoms, naproxen sodium (440/660 mg) was significantly superior to placebo at improving symptoms from baseline (Figure 2A). Ibuprofen was superior compared with placebo at improving symptoms from baseline for 5 of the 7 symptoms; however, the improvement in pain at rest and in night pain did not reach statistical significance compared with placebo (p = 0.077 and p = 0.193, respectively). For the symptoms of pain on passive motion, pain on weight-bearing, day pain, and night pain there was a trend toward greater pain relief with naproxen sodium 440/660 mg compared with ibuprofen.

Subgroup analysis for patients aged ≥ 65 years. For the subgroup of elderly patients, naproxen sodium 440 mg was significantly superior to placebo in all symptoms apart from pain on weight-bearing. Although improvement in this symptom did not reach statistical significance (p = 0.064), there was greater improvement following treatment with naproxen sodium compared with placebo and ibuprofen. By contrast, pain assessments following treatment with ibuprofen only reached statistical significance for the symptom of day pain (Figure 2B).

Daily evaluations. On average, patient diaries were completed for each question on each day by more than 95% of patients. Naproxen sodium and ibuprofen were clinically effective in reducing all 6 symptoms recorded in patient diaries; there were no significant differences between the 2 treatment groups for any symptom.

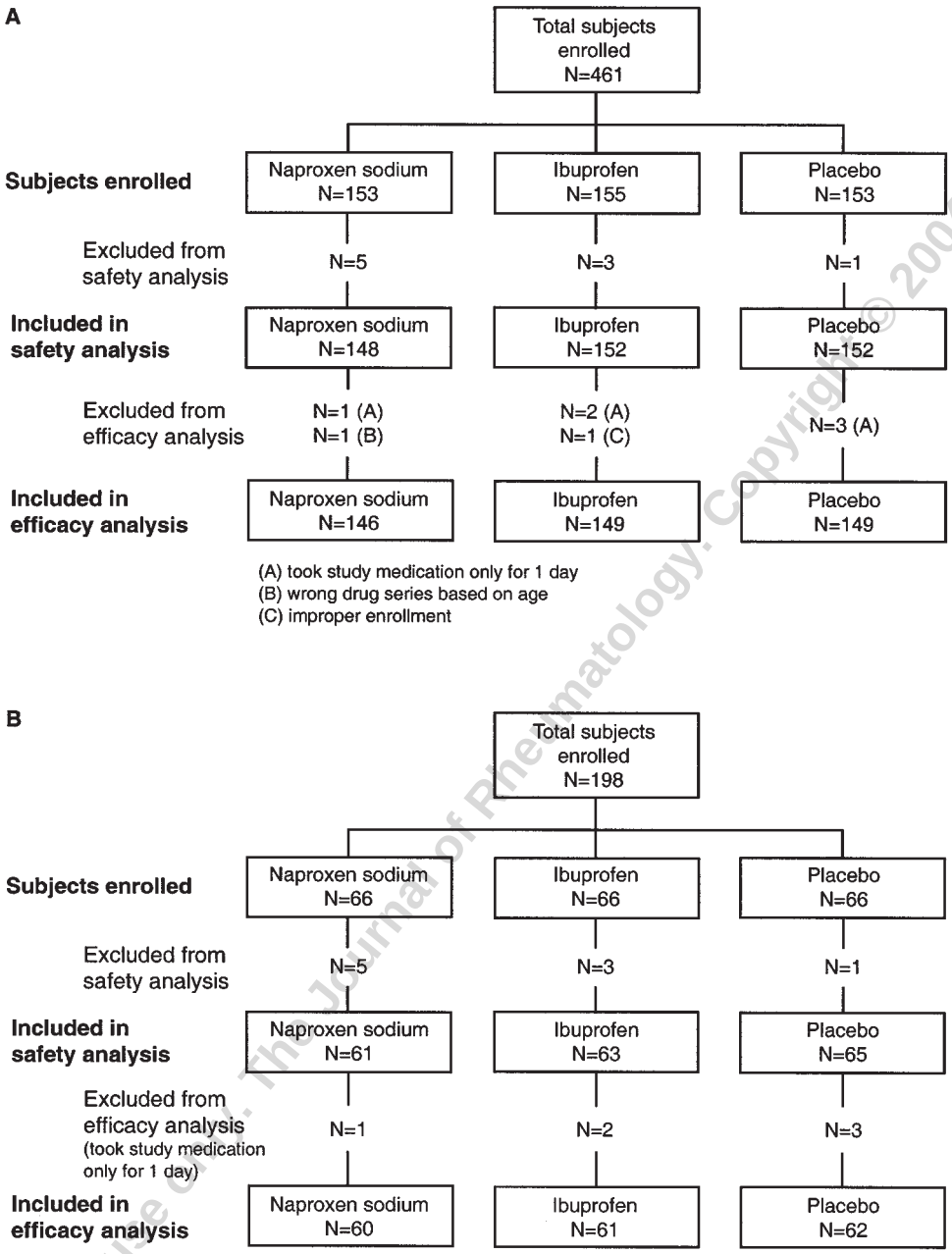

Figure 1. Patients included in the safety and efficacy analyses for (A) the total patient population and (B) the subpopulation aged ≥ 65 years.

For the symptom of arthritis pain, both naproxen sodium 440/660 mg ($p < 0.05$–0.0001) and ibuprofen ($p < 0.05$–0.0001) significantly improved pain compared with placebo throughout the treatment period (Days 1–7). Similarly, for pain control experienced with study medication, both naproxen sodium and ibuprofen significantly improved pain compared with placebo throughout the treatment period (Days 1–7; Figure 3).

For night-time pain, naproxen sodium 440/660 mg showed a tendency toward higher efficacy at reducing pain compared with ibuprofen — naproxen sodium provided significantly greater symptom improvement compared with placebo for Nights 1, 2, 3, and 5 ($p < 0.05$ for Nights 1 and 3; $p < 0.01$ for Nights 2 and 5). By contrast, ibuprofen showed significantly greater symptom improvement compared with placebo only at Nights 1 and 2 ($p < 0.05$) (Figure 4A).

For difficulties in walking one block/climbing one flight of stairs, naproxen sodium 440/660 mg significantly reduced symptoms compared with placebo on Days 2, 3, 6, and 7, while ibuprofen significantly reduced symptoms compared with placebo on all 7 days. Similarly, for difficul-

Table 1. Demographic characteristics for (A) the total patient population and (B) the subpopulation aged ≥ 65 years.

Table A	Naproxen Sodium 440/660 mg, n = 153	Ibuprofen 1200 mg, n = 155	Placebo, n = 153	Total, n = 461
Age, mean ± SD	61.66 ± 12.88	60.07 ± 13.44	59.97 ± 13.72	60.57 ± 13.34
Weight, kg, mean ± SD	80.71 ± 18.86	85.50 ± 19.84	82.55 ± 20.58	82.93 ± 19.83
Height, cm, mean ± SD	167.21 ± 9.61	167.59 ± 9.11	166.63 ± 9.74	167.15 ± 9.48
Sex				
Men, n (%)	50 (32.7)	47 (30.3)	44 (28.8)	141 (30.6)
Women, n (%)	103 (67.3)	108 (69.7)	109 (71.2)	320 (69.4)
Race				
Caucasian, n (%)	143 (93.5)	134 (86.5)	141 (92.2)	418 (90.7)
Black, n (%)	4 (2.6)	12 (7.7)	10 (6.5)	26 (5.6)
Asian, n (%)	2 (1.3)	1 (0.6)	0	3 (0.7)
Hispanic, n (%)	3 (2)	7 (4.5)	2 (1.3)	12 (2.6)
Other, n (%)	1 (0.7)	1 (0.6)	0	2 (0.4)

Table B	Naproxen Sodium 440 mg, n = 66	Ibuprofen 1200 mg, n = 66	Placebo, n = 66	Total, n = 198
Age, mean ± SD	73.42 ± 5.45	72.36 ± 4.99	72.42 ± 5.29	72.74 ± 5.25
Weight, kg, mean ± SD	79.75 ± 16.13	80.94 ± 16.21	77.78 ± 13.33	79.49 ± 15.26
Height, cm, mean ± SD	168.45 ± 10.87	167.60 ± 9.30	165.49 ± 10.43	167.18 ± 10.25
Sex				
Men, n (%)	30 (45.5)	20 (30.3)	25 (37.9)	75 (37.9)
Women, n (%)	36 (54.5)	46 (69.7)	41 (62.1)	123 (62.1)
Race				
Caucasian, n (%)	61 (92.4)	59 (89.4)	61 (92.4)	181 (91.4)
Black, n (%)	3 (4.5)	5 (7.5)	4 (6.1)	12 (6.1)
Asian, n (%)	1 (1.5)	0	0	1 (0.5)
Hispanic, n (%)	1 (1.5)	2 (3.0)	1 (1.5)	4 (2)
Other, n (%)	0	0	0	0

ties in walking several blocks/climbing several flights of stairs, naproxen sodium 440/660 mg significantly reduced symptoms compared with placebo on Days 4, 6, and 7; and for ibuprofen, significant reductions compared with placebo occurred on Days 2, 3, 4, 6, and 7. For bending, lifting, and stooping, naproxen sodium and ibuprofen were very similar, providing effective relief compared with placebo for a total of 5 and 6 days, respectively.

Subgroup analysis for patients aged ≥ 65 years. For elderly patients, naproxen sodium and ibuprofen were clinically effective in reducing all 6 symptoms recorded in patient diaries; there were no significant differences between the 2 treatment groups for any symptoms. However, naproxen sodium 440 mg demonstrated higher efficacy in night pain compared with placebo than ibuprofen compared with placebo — naproxen sodium 440 mg showed significantly greater symptom improvement compared with placebo at Days 1, 2, and 3 of treatment ($p < 0.05$), whereas the reduction in pain intensity with ibuprofen did not reach statistical significance at any timepoint (Figure 4B).

Quality of life assessment. The change from baseline in total quality of life scores showed that naproxen sodium 440/660 mg significantly ($p < 0.05$) improved quality of life compared with ibuprofen 1200 mg. Similarly, for the individual component of work, naproxen sodium significantly ($p < 0.05$) improved quality of life compared with ibuprofen. Naproxen sodium showed a trend toward improvement in total quality of life scores compared with placebo; however, the difference did not reach statistical significance ($p = 0.286$). There was no significant difference between ibuprofen and placebo.

Subgroup analysis for patients aged ≥ 65 years. The change from baseline in the individual components of household tasks and self-care tasks showed that naproxen sodium 440 mg significantly ($p < 0.05$) improved quality of life compared with placebo. Similarly, for mood results, naproxen sodium significantly ($p < 0.05$) improved quality of life compared with ibuprofen. For total quality of life scores, there was no significant difference between naproxen sodium or ibuprofen and placebo.

Overall patients' and investigators' evaluation of treatment medication. Patients rated naproxen sodium and ibuprofen as being significantly better than placebo ($p < 0.0001$ for both) in the overall assessment of study treatment. In addi-

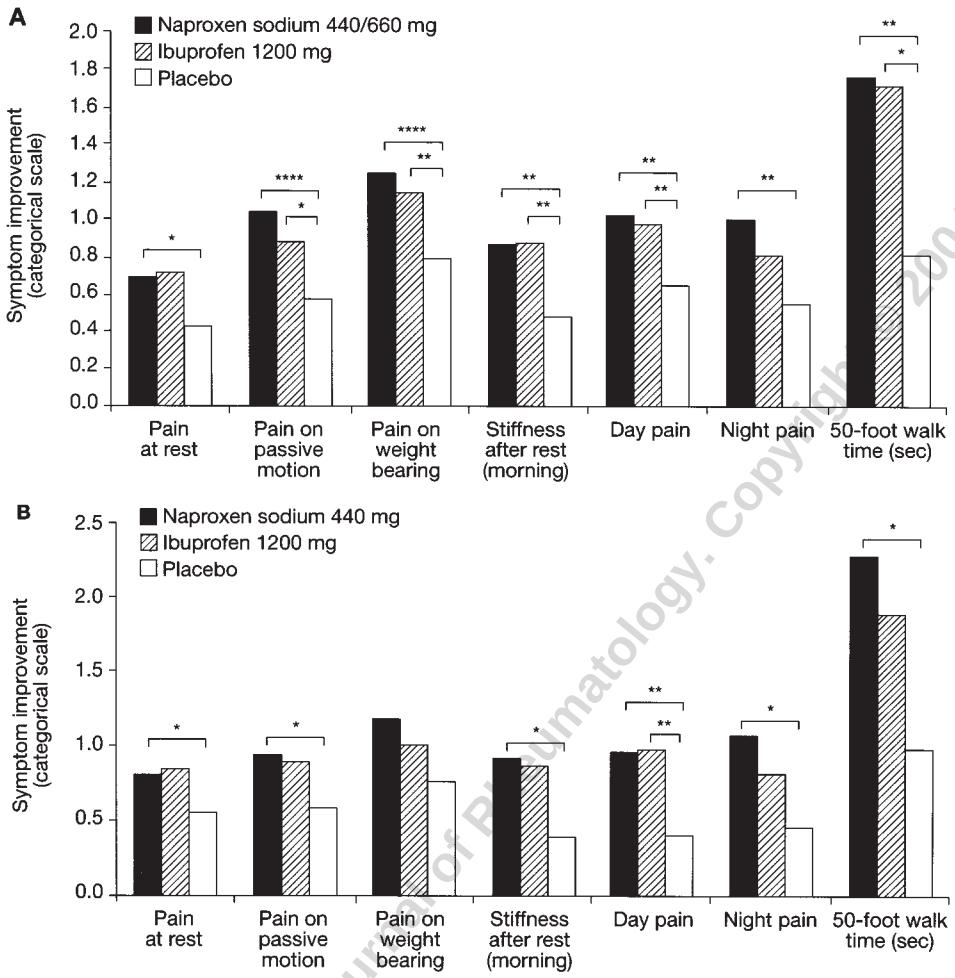

Figure 2. Symptom intensity difference from baseline for each of the 7 pain assessments for (A) the total efficacy population and (B) the efficacy subpopulation aged ≥ 65 years. Comparison with placebo: *p < 0.05; **p < 0.01; ****p < 0.0001.

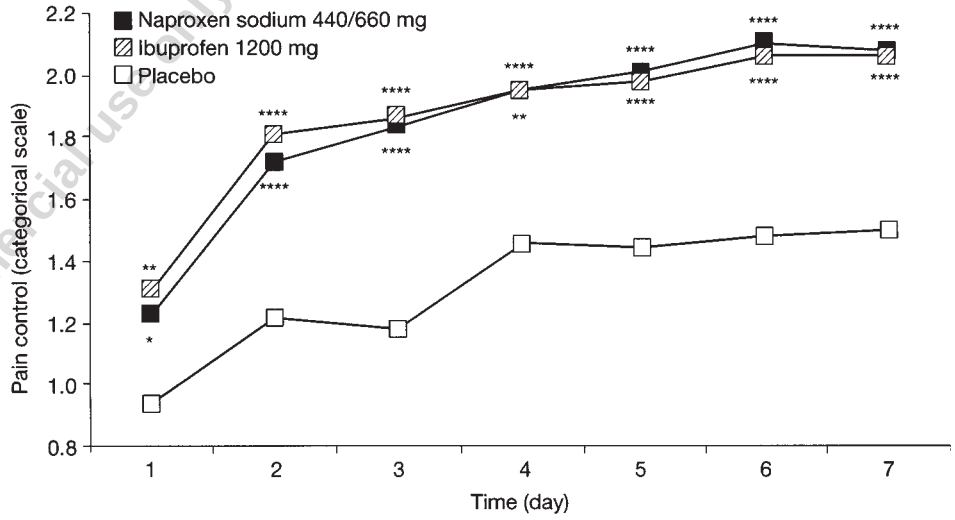

Figure 3. Evaluation of pain control for total efficacy population. Comparison with placebo: *p < 0.05; **p < 0.01; ****p < 0.0001.

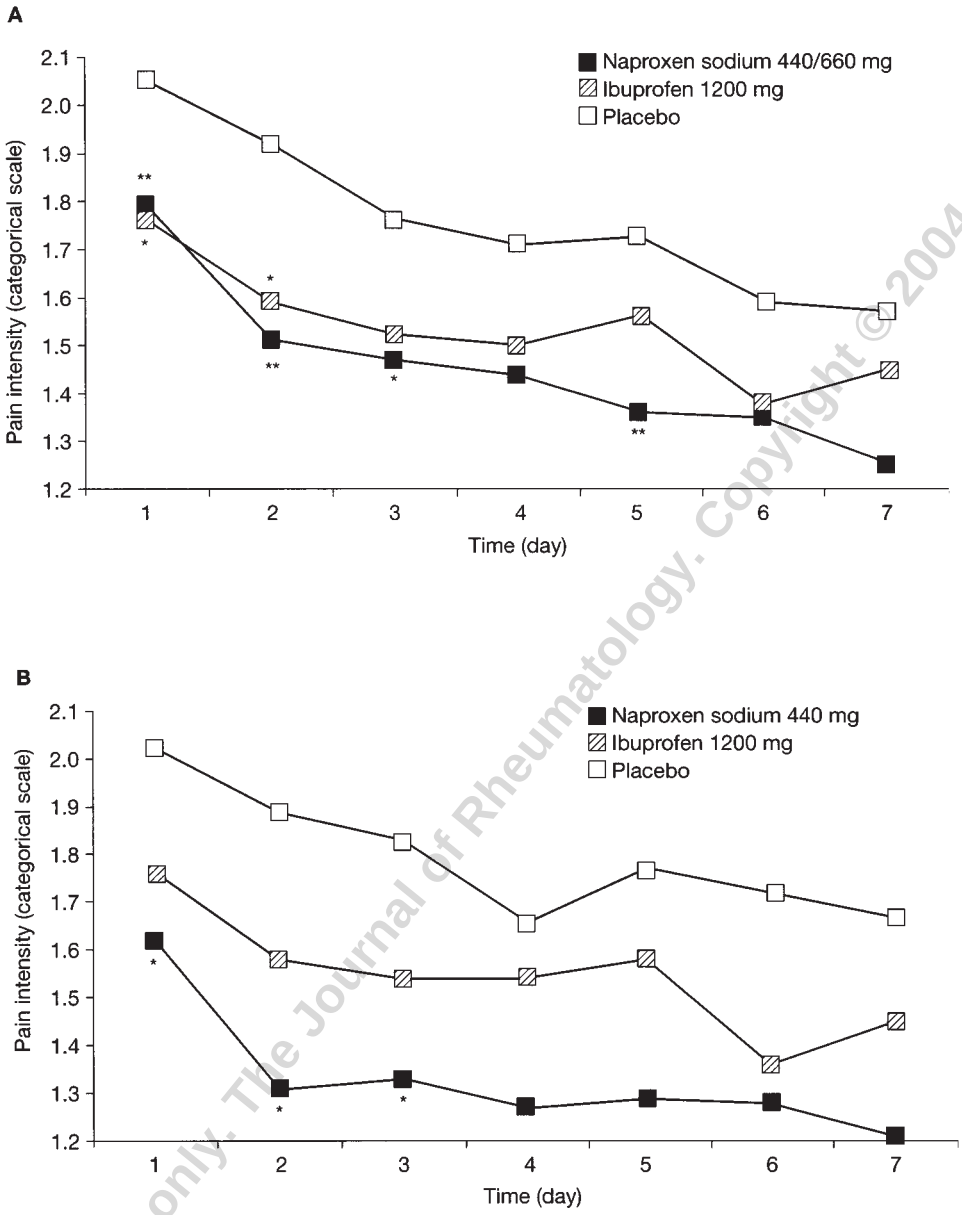

Figure 4. Evaluation of night pain for (A) the total efficacy population and (B) the efficacy subpopulation aged ≥ 65 years. Comparison with placebo: *p < 0.05; **p < 0.01.

tion, investigators' evaluation scores were significantly higher in the naproxen sodium and ibuprofen treatment groups compared with those for placebo ($p < 0.0001$ and $p = 0.001$, respectively). In both patient and investigator evaluations, despite higher scores with naproxen sodium, there were no statistically significant differences in evaluation scores between naproxen sodium and ibuprofen ($p = 0.285$ and $p = 0.131$, respectively). Similar results were obtained in the subgroup of elderly patients.

Safety assessments. There were no significant differences between treatment groups in the number of patients reporting AE, the incidence of AE, and relationship to study medication (Table 2). In the placebo group, 28.95% (44/152) of subjects reported AE compared with 27.70% (41/148) treated with naproxen sodium and 24.34% (37/152) of patients treated with ibuprofen.

The highest number of AE across all treatment groups occurred within the GI disorder system organ class: 13.8% of all patients in the placebo group, 18.9% in the naproxen sodium group, and 12.5% in the ibuprofen group. The most frequent AE was headache (placebo, 7.2%; naproxen sodium, 3.4%; and ibuprofen, 2.6%).

Patients treated with naproxen sodium 440/660 mg had significantly fewer severe AE compared with placebo ($p < 0.01$) and consequently required counteractive therapy less often ($p = 0.001$). There was only one case of lower GI

Table 2. Adverse events occuring in > 2% patients for the total patient population.

	Treatment			
	Naproxen Sodium 440/660 mg	Ibuprofen 1200 mg	Placebo	Total
No. of patients	148	152	152	452
No. of patients reporting AE (%)	41 (27.70)	37 (24.34)	44 (28.95)	122 (26.99)
No. of events reported	69	57	78	204
No. of patients reporting (%)				
No AE	107 (72.30)	115 (75.66)	108 (71.05)	330 (73.01)
1 AE	21 (14.19)	22 (14.47)	20 (13.16)	63 (13.94)
> 1 AE	20 (13.51)	15 (9.87)	24 (15.79)	59 (13.05)
Severity of AE, n (%)				
Mild	41 (59.42)	31 (54.39)	27 (34.62)	99 (48.53)
Moderate	24 (34.78)	18 (31.58)	39 (50.00)	81 (39.71)
Severe	4 (5.80)	8 (14.04)	12 (15.38)	24 (11.76)
Relationship to study drug, n (%)				
Probably yes	31 (44.93)	18 (31.58)	27 (34.62)	76 (37.25)
Probably not	27 (39.13)	25 (43.86)	42 (53.85)	94 (46.08)
Unknown	11 (15.94)	14 (24.56)	9 (11.54)	34 (16.67)
Patients required therapy for AE, (%)				
Yes	10 (14.49)	14 (24.56)	30 (38.46)	54 (26.47)
No	59 (85.51)	43 (75.44)	48 (61.54)	150 (73.53)
Outcome				
Recovered	59 (85.51)	44 (77.19)	62 (79.49)	165 (80.88)
Not recovered	10 (14.49)	13 (22.81)	16 (20.51)	39 (19.12)
GI disorders	28 (18.92)	19 (12.50)	21 (13.82)	68 (15.04)
Abdominal pain	3 (2.03)	0 (0.0)	1 (0.66)	4 (0.88)
Diarrhea	5 (3.38)	2 (1.32)	3 (1.97)	10 (2.21)
Dyspepsia	3 (2.03)	2 (1.32)	7 (4.61)	12 (2.65)
Nausea	5 (3.38)	6 (3.95)	2 (1.32)	13 (2.88)
Abdominal pain, upper	8 (5.41)*	3 (1.97)	2 (1.32)	13 (2.88)
General disorders/administration site conditions	7 (4.73)	5 (3.29)	6 (3.95)	18 (3.98)
Influenza-like illness	3 (2.03)	0 (0.0)	2 (1.32)	5 (1.11)
Edema lower limb	3 (2.03)	2 (1.32)	1 (0.66)	6 (1.33)
Infections	8 (5.41)	3 (1.97)	4 (2.63)	15 (3.32)
Urinary tract infection	3 (2.03)	1 (0.66)	0 (0.00)	4 (0.88)
Investigations	1 (0.68)	4 (2.63)	3 (1.97)	8 (1.77)
Liver function tests abnormal	0 (0.0)†	4 (2.63)	2 (1.32)	6 (1.33)
Musculoskeletal and connective tissue disorders	4 (2.70)	1 (0.66)*	11 (7.24)	16 (3.54)
Arthralgia	1 (0.68)	0 (0.0)*	4 (2.63)	5 (1.11)
Nervous system disorders	10 (6.76)	14 (9.21)	17 (11.18)	41 (9.07)
Dizziness	2 (1.35)	8 (5.26)*	1 (0.66)	11 (2.43)
Headache	5 (3.38)	4 (2.63)	11 (7.24)	20 (4.42)
Psychiatric disorders	4 (2.70)	1 (0.66)	1 (0.66)	6 (1.33)
Respiratory, thoracic, and mediastinal disorders	0 (0.00)*	1 (0.66)	5 (3.29)	6 (1.33)

AE: adverse event. * $p < 0.05$ compared with placebo; † $p < 0.05$ compared with ibuprofen.

bleeding, which was reported in the ibuprofen group. A 47-year-old woman with hypertension receiving beta- and calcium-blockers, as well as hormone replacement therapy (HRT), prematurely terminated the study due to rectal hemorrhage. This AE was rated as mild and "probably related" to study medication by the investigator. After study termination, she recovered without treatment.

Similarly, for the subgroup of patients aged ≥ 65 years, there were no significant differences in the number of patients reporting AE and the incidence of AE reported between treatment groups (Table 3). Patients receiving naproxen sodium in this subgroup had less severe AE compared with placebo ($p < 0.05$) and needed remedial treatment less often compared with patients treated with either ibuprofen or placebo ($p < 0.05$ and $p < 0.01$, respectively).

DISCUSSION

In this pooled analysis, the results of both studies were consistent and both naproxen sodium (440/660 mg) and ibuprofen (1200 mg) demonstrated significantly superior

Table 3. Adverse events occurring in > 2% patients ≥ 65 years old.

	Naproxen Sodium 440 mg	Ibuprofen 1200 mg	Placebo	Total
No. of patients	61	63	65	189
No. of patients reporting AE (%)	14 (22.95)	14 (22.22)	17 (26.15)	45 (23.81)
No. of events reported	24	19	30	73
No. of patients reporting (%)				
No AE	47 (77.05)	49 (77.78)	48 (73.85)	144 (76.19)
1 AE	7 (11.48)	11 (17.46)	8 (12.31)	26 (13.76)
> 1 AE	7 (11.48)	3 (4.76)	9 (13.85)	19 (10.05)
Severity of AE, n (%)				
Mild	14 (58.33)	9 (47.37)	7 (23.33)	30 (41.10)
Moderate	7 (29.17)	6 (31.58)	15 (50.00)	28 (38.36)
Severe	3 (12.50)	4 (21.05)	8 (26.67)	15 (20.55)
Relationship to study drug, n (%)				
Probably yes	14 (58.33)	7 (36.84)	10 (33.33)	31 (42.47)
Probably not	10 (41.67)	9 (47.37)	17 (56.67)	36 (49.32)
Unknown	0 (0.00)	3 (15.79)	3 (10.00)	6 (8.22)
Patients required therapy for AE, (%)				
Yes	2 (8.33)	7 (36.84)	13 (43.33)	22 (30.14)
No	22 (91.67)	12 (63.16)	17 (56.67)	51 (69.86)
Outcome				
Recovered	21 (87.50)	12 (63.16)	23 (76.67)	56 (76.71)
Not recovered	3 (12.50)	7 (36.84)	7 (23.33)	17 (23.29)
GI disorders	11 (18.03)	10 (15.87)	9 (13.85)	30 (15.87)
Abdominal pain	2 (3.28)	0 (0.0)	1 (1.54)	3 (1.59)
Diarrhea	2 (3.28)	1 (1.59)	3 (4.62)	6 (3.17)
Dyspepsia	0 (0.0)*	2 (3.17)	4 (6.15)	6 (3.17)
Nausea	2 (3.28)	3 (4.76)	1 (1.54)	6 (3.17)
Abdominal pain, upper	2 (3.28)	2 (3.17)	0 (0.00)	4 (2.12)
General disorders/administration site conditions	2 (3.28)	2 (3.17)	1 (1.54)	5 (2.65)
Infections	2 (3.28)	2 (3.17)	2 (3.08)	6 (3.17)
Musculoskeletal and connective tissue disorders	2 (3.28)	0 (0.00)	3 (4.62)	5 (2.65)
Swelling	2 (3.28)	0 (0.00)	0 (0.00)	2 (1.06)
Nervous system disorders	3 (4.92)	4 (6.35)	5 (7.69)	12 (6.35)
Dizziness	1 (1.64)	3 (4.76)	0 (0.00)	4 (2.12)
Headache	1 (1.64)	1 (1.59)	4 (6.15)	6 (3.17)
Renal and urinary disorders	1 (1.64)	0 (0.00)	2 (3.08)	3 (1.59)
Respiratory, thoracic, and mediastinal disorders	0 (0.0)	0 (0.0)	2 (3.08)	2 (1.06)

AE: adverse event. * $p < 0.05$ compared with placebo.

pain relief for mild to moderate OA of the knee compared with placebo. This finding is in agreement with results from both the original studies.

For the total patient population, the change from baseline was significantly greater with OTC naproxen sodium compared with placebo for all investigator and patient-assessed symptoms of knee joint pain. The improvement in pain intensity after 7 days of regular treatment was in the magnitude of 30–45%, in contrast to a 30% improvement with prescription doses of NSAID in general[8]. Similarly, pain assessments following treatment with ibuprofen were greater compared with placebo; however, only 5 of the 7 symptoms were significant. These differences in NSAID treatments were even more pronounced when a subgroup analysis was performed on the elderly population. Naproxen sodium was significantly superior compared with placebo for all symptom assessments, apart from pain induced by weight-bearing, whereas the improvements with ibuprofen only reached statistical significance for day pain.

Similar results were obtained for daily evaluation assessments, with both naproxen sodium and ibuprofen reducing all symptoms. For the symptoms of arthritis pain and pain control, both naproxen sodium and ibuprofen significantly improved pain compared with placebo throughout the treatment period. For the evaluation of night-time pain, naproxen sodium showed a tendency to greater improvement compared with ibuprofen, supporting the results of the investigator and patient assessments. One explanation for

these findings is that the pain relief observed with naproxen sodium may be maintained for a longer time period compared with ibuprofen, enabling sustained, optimal pain relief.

Naproxen sodium has previously been reported as having a long duration of action (8–12 hours)[15], providing improved nocturnal analgesia and, in turn, promoting better natural sleep. The reported longer duration of action of naproxen sodium compared with both ibuprofen and acetaminophen[15-18] has important implications for quality of life and day-to-day functioning, and is an important consideration for clinicians in the early therapy of OA, as night pain is one of the first symptoms that OA patients present.

In our study, naproxen sodium 440/660 mg also significantly improved quality of life compared with ibuprofen 1200 mg. However, the difference between naproxen and placebo was not statistically significant. Similarly, there was no significant difference between ibuprofen and placebo. This may be explained by unexpectedly high improvements seen with placebo, due to a large placebo effect. Both naproxen sodium and ibuprofen were rated as being significantly better than placebo in the overall assessment of study treatment by patients and investigators at the end of the study period. Similar results were obtained in the subgroup ≥ 65 years of age.

Previous studies have established the efficacy and tolerability of prescription doses of naproxen sodium in approved rheumatologic indications, including OA. Studies have also shown that the OTC dosage of naproxen sodium has superior efficacy over ibuprofen, acetaminophen, and placebo in relieving postoperative dental pain and dysmenorrhea, and that it is well tolerated[12,13,15-18]. This study also confirms that OTC doses of naproxen sodium are effective and well tolerated in the short-term management of mild to moderate OA of the knee.

In addition, a recent review by Watson, *et al* was performed to determine whether a difference exists in the relative efficacy of individual NSAID for the management of knee OA[19]. The review concluded that no substantial evidence was available at that time to distinguish between equivalent recommended doses of NSAID, one of the main reasons being that appropriate doses of comparator drugs had not been employed. However, our findings using comparative OTC doses show that naproxen sodium provides more effective pain relief compared with ibuprofen for a number of efficacy measures, especially for the symptom of night pain.

A limitation of this study is the relatively short washout times before the administration of the study medication. Patients are usually withdrawn from prior medications 5 half-lives before initiation of study treatment. This presents a potential problem for patients taking naproxen (half-life 14 h; washout period 72 h), oxaprofen (half-life 40–50 h; washout 10 days), and piroxicam (half-life 45 h; washout 10 days) before study initiation, as the washout time for naproxen was 48 hours, and 5 days for both oxaprofen and piroxicam. However, no statistically significant difference was found between the treatment groups at the "baseline" values, and any effect on efficacy variables may be attributed to study medications.

It has been reported that chronic use of prescription-strength NSAID is associated with significant GI, renal, and hepatic effects[4,9]. The good safety profile of nonprescription drugs is especially important as they are used in a wider population than prescription-only drugs. Indeed, recent studies have looked at the safety of ibuprofen in users of nonprescription medicines; evidence of longterm use of ibuprofen was found, confirming the need for pharmacovigilance studies of such drugs[20]. Therefore, a number of studies have examined the safety profile of OTC-strength doses of naproxen sodium; a recent metaanalysis concluded that OTC doses have a safety profile comparable to that of placebo[13].

Our results support this, with the OTC dosage of naproxen sodium having a similar safety profile to that of placebo in the overall study population as well as the elderly subgroup. Ibuprofen also had a similar safety profile to that of placebo; however, it should be noted that one case of rectal hemorrhage rated as mild and "probably related" to study medication was reported in the ibuprofen group; the patient recovered without treatment on withdrawal from the study. The highest number of AE across all treatment groups occurred within the GI disorder system organ class, while the most frequent AE was headache.

In summary, OTC doses of naproxen sodium (440/660 mg) and ibuprofen (1200 mg) effectively relieved pain in patients, including those aged 65 years or older, with mild to moderate OA of the knee. Naproxen sodium provided more effective pain relief compared with placebo for the majority of measures and compared with ibuprofen for the important symptom of night pain. These data indicate that in short-term management of OA of the knee, naproxen sodium 440/660 mg on an as-needed basis provides patients with effective analgesia, potentially enabling them to lead an active life and sleep sufficiently at night. This efficacy is combined with a good safety and tolerability profile.

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