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TRAMADOL ALLOWS REDUCTION OF NAPROXEN DOSE AMONG PATIENTS WITH NAPROXEN-RESPONSIVE OSTEOARTHRITIS PAIN

A Randomized, Double-Blind, Placebo-Controlled Study

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Objective. **To demonstrate that in patients receiving naproxen for the pain of osteoarthritis (OA), the addition of tramadol will allow a reduction in the naproxen dosage without compromising pain relief.**

Methods. **This trial consisted of a 5-week open-label run-in and an 8-week double-blind phase. Patients with at least moderate pain (≥40 mm on a 100-mm visual analog scale) of OA of the knee after a 1-week medication washout were treated with naproxen 500 mg/day for 1 week. Patients whose pain scores were reduced to <20 mm were discontinued. The remaining patients received naproxen 1,000 mg/day for 3 weeks. Tramadol 200 mg/day was added during the third week. Patients were then randomized in a double-blind manner to continue tramadol 200 mg/day or to begin placebo in addition to naproxen. Randomization was stratified based on response to naproxen 1,000 mg/day. During the double-blind phase, the naproxen dose was reduced by 250 mg every 2 weeks. The primary efficacy end point was the minimum effective naproxen dose (MEND). The MEND was defined as 250 mg above the naproxen daily dosage at which pain relief was no longer adequate. Patients discontinuing the double-blind phase of the study for reasons other than lack of efficacy were assigned a MEND equal to the last naproxen dose received. If the effect of treatment between the responder and nonresponder groups was statistically different, the difference in the MEND was assessed separately within the groups.**

Results. **Of 236 patients randomized (mean age 61 years; 147 females), 90 were stratified as naproxen responders and 146 as naproxen nonresponders. There was a significant difference ($P = 0.040$) in the treatment effect between the naproxen responders and nonresponders, thus demonstrating a difference in the way responders and nonresponders react to a decrease in naproxen dosage after the addition of tramadol. Among naproxen responders, the MEND was significantly lower in patients receiving tramadol (n = 36) than in patients receiving placebo (n = 54), 221 mg versus 407 mg, respectively ($P = 0.021$). For the naproxen nonresponders, the mean MEND was 419 mg in the tramadol group and 396 mg in the placebo group ($P = 0.706$).**

Conclusion. **In patients with painful OA of the knee responding to naproxen 1,000 mg/day, the addition of tramadol 200 mg/day allows a significant reduction in the dosage of naproxen without compromising pain relief.**

The goal of analgesic therapy in chronic painful osteoarthritis (OA) is symptomatic relief, thereby allowing the patient to continue routine activities of daily living (1,2). Acetaminophen is commonly recommended as the initial analgesic therapy (1,2). If adequate pain relief is not achieved, nonsteroidal antiinflammatory drugs (NSAIDs) are prescribed. Many patients who are prescribed NSAIDs enjoy pain relief and experience no intolerable adverse events. However, long-term use of NSAIDs has been associated with a variety of potentially serious adverse events, including gastrointestinal hemorrhage and kidney dysfunction. Limiting the dosage of an NSAID may decrease the incidence of these adverse events (3–6).

Tramadol, a centrally acting analgesic, is indi-

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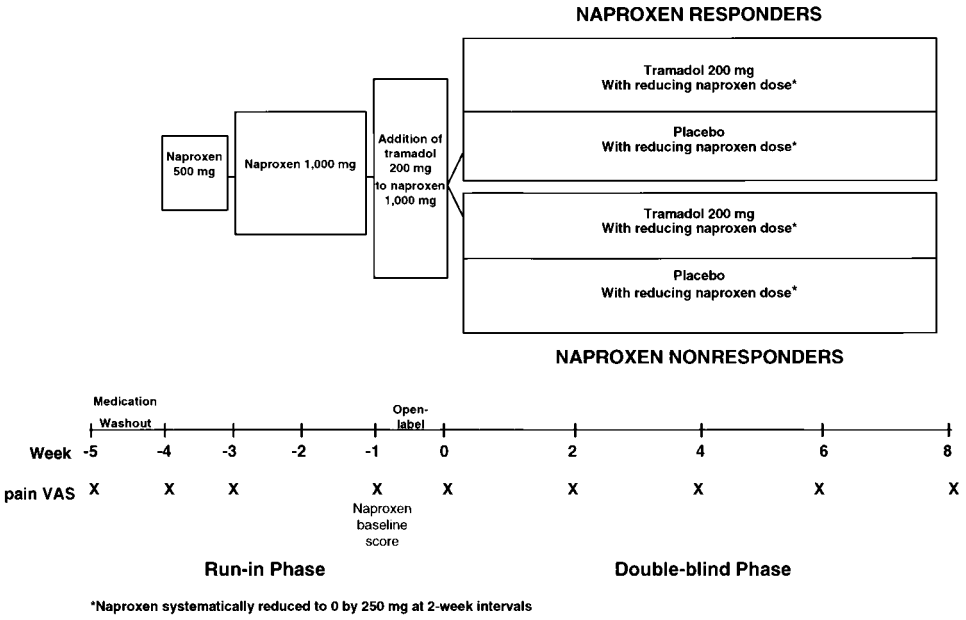

Figure 1. Study design. VAS = visual analog scale.

cated for the treatment of moderate-to-moderately severe pain. Tramadol has at least 2 modes of action that may contribute to its efficacy: binding to mu-opioid receptors and inhibition of norepinephrine and serotonin reuptake (3). Tramadol does not inhibit the synthesis of prostaglandins, and therefore does not cause the serious adverse events generally associated with NSAIDs. Tramadol has been shown to be useful for the flare of OA and is as effective as ibuprofen in the treatment of the pain of OA (8,9).

Although the current American College of Rheumatology guidelines for the treatment of OA of the knee suggest that mu-opioid agonists be prescribed for short-term use only, the data regarding the low rate of abuse of tramadol suggests that it can be used for the long-term treatment of chronic painful conditions. The rate of abuse associated with tramadol since initial marketing in the United States is ~1.5 cases per 100,000 patients exposed (10). This indicates that tramadol may be used in place of an NSAID for patients with OA pain who do not achieve adequate pain relief with acetaminophen.

The objective of this study was to determine if in patients requiring higher doses of naproxen for treatment of chronic knee pain due to OA, tramadol can provide sufficient pain relief to allow a significant reduction in naproxen dosages without compromising pain relief.

PATIENTS AND METHODS

Study design. This was a randomized, double-blind placebo-controlled study performed at 20 investigational sites (Appendix A). There were 2 phases: a 5-week run-in phase and an 8-week double-blind phase (Figure 1). Patients were required to have a visual analog scale (VAS) score for pain of <80 mm (on a 100-mm scale) to enter the study. At the end of a 1-week medication washout phase, or sooner if the pain became intolerable, patients with a pain assessment of ≥40 mm, which was at least 20 mm higher than their prewashout score, were eligible to continue the run-in phase.

During the next week, patients received naproxen 250 mg twice a day. At the end of that week, patients whose VAS score was <20 mm were discontinued from the study. The remaining patients received naproxen 500 mg twice a day. A VAS score was obtained 2 weeks after starting the 1,000 mg/day dosage of naproxen and represented the naproxen baseline VAS score for further efficacy assessments. During the final week of the run-in phase, all patients received tramadol 200 mg/day in addition to naproxen 1,000 mg/day.

Patients who completed the entire run-in phase and were willing to continue participating in the study were eligible for entry into the double-blind phase. Within each center, patients were randomized to either continue tramadol 200 mg/day or begin placebo along with naproxen. The randomization was stratified based on the patient's baseline VAS score (score at end of second week of treatment with naproxen 1,000 mg/day). Those patients with a VAS score <40 mm *and* at least 20 mm lower than the end-of-washout VAS score, were stratified as naproxen responders. All other patients were stratified as naproxen nonresponders.

During the 8-week double-blind phase, the initial dosage of naproxen in the double-blind phase was 750 mg/day. This dosage was reduced by 250 mg every 2 weeks. The naproxen dosage reduction was accomplished in a single-blind manner (i.e., the patients did not know what dosage of naproxen they were receiving). The dosage of tramadol or placebo remained constant during the double-blind phase.

Study visits were scheduled every 2 weeks following randomization. The protocol was approved by each site's investigational review board, and informed consent was obtained from all patients.

Patient selection criteria. Patients ages 45 years or older were eligible for inclusion in the study if they had symptomatic (painful) OA of the knee for at least 1 year and if they were taking a stable dosage (daily dosage ± 25%) of any NSAID for the last 30 days. The diagnosis of OA was confirmed by demonstration of osteophytes on knee radiographs.

Patients were excluded from the study if they had any of the following conditions: rheumatoid arthritis (RA), fibromyalgia, ankylosing spondylitis, or gout; intraarticular injections of corticosteroids in the target knee; or major trauma, infection, or apparent avascular necrosis of the target knee. Patients with a known contraindication to tramadol or NSAIDs, a serum creatinine value >1.5 mg/dl, those taking warfarin, lithium, methotrexate, monoamine oxidase inhibitors, or sedative hypnotics on an as-needed basis, or patients with a known history of substance abuse were also excluded.

Drug administration. During the run-in phase, patients were treated with open-label naproxen 250 mg twice a day for 1 week, followed by naproxen 500 mg twice a day for 3 weeks. Open-label tramadol, titrated in 50 mg/day increments to 200 mg/day, was added during the final week of the run-in phase. During the double-blind phase, patients were randomly assigned to treatment with tramadol 200 mg/day or matching placebo. In the double-blind phase, the initial dosage of naproxen was 750 mg/day. The naproxen dosage was reduced by 250 mg/day every 2 weeks. No pain medication or treatments other than the study medications were allowed.

Efficacy assessment. At each clinic visit, patients were asked to rate on a 100-mm VAS scale the amount of pain experienced in the target knee during the previous 48 hours. Inadequate pain relief during the double-blind period of the trial was defined as 1) a VAS score ≥40 mm and at least a 20-mm increase from the baseline VAS score, or 2) patient report of inadequate pain relief at any time.

The primary efficacy end point was the minimum effective naproxen dose (MEND). The MEND was assigned in 1 of 2 ways. Patients discontinuing the double-blind phase because of inadequate pain relief were assigned a MEND equal to the last naproxen dosage which provided relief (the current naproxen daily dosage plus 250 mg). Patients discontinuing the double-blind phase of the study for reasons other than lack of efficacy were assigned a MEND equal to the last daily naproxen dosage received.

Safety assessment. Safety was assessed primarily by adverse events for all patients exposed to tramadol in the run-in and double-blind phases. Patients were encouraged to spontaneously report any adverse event or to respond to the general question "How has your health been since your last visit?" Vital signs were recorded at each visit.

Table 1. Disposition of patients during the open-label, run-in phase*

	No. of patients
Began medication washout	381
Reasons for discontinuation before naproxen 500 mg/day	
VAS score <40 mm or increased by <20 mm from the prewashout score	2
Inadequate pain relief	3
Adverse event	4
Other	7
Began naproxen 500 mg/day	365
Reasons for discontinuation before naproxen 1,000 mg/day	
VAS score <20 mm at visit 3	9
Inadequate pain relief for previous 24 hours	2
Adverse event	11
Other	15
Began naproxen 1,000 mg/day	328
Reasons for discontinuation before naproxen 1,000 mg/day with tramadol 200 mg/day	
Adverse event	10
Other	7
Began naproxen 1,000 mg with tramadol	311
Reasons for discontinuation before randomization	
Inadequate pain relief for previous 24 hours	2
Adverse event	60
Other	9
Randomized	240

* VAS = visual analog scale.

Statistical analysis. An initial analysis of the interaction between treatment (tramadol or placebo) and responder status using a 3-factor analysis of variance (investigational site, prerandomization response to naproxen, treatment group) was performed. Significance was assessed at the 10% level. If the effect of treatment was significantly different between responders and nonresponders, the difference in the MEND between the tramadol and placebo treatment groups was assessed separately within the responder and nonresponder groups using an F-test at the 5% significance level. The primary analysis was performed using all randomized patients who took the study drug and had at least 1 double-blind efficacy assessment.

Power calculation was based on the assumption that 30% of the placebo-treated patients and 55% of the tramadol-treated patients would be able to discontinue naproxen. Sixty placebo and 60 tramadol patients would provide 80% power to detect this difference at a 2-sided 5% significance level. This estimate was doubled to account for naproxen responders and nonresponders.

RESULTS

Demographic and baseline characteristics. The disposition of patients during the open-label run-in phase is presented in Table 1. Of the 381 patients who entered the washout phase, 365 began naproxen. Nine patients achieved adequate pain control (VAS <20 mm) at the end of 1 week of naproxen 500 mg/day and did not

Table 2. Demographics of the study patients

	Naproxen responders*		Naproxen nonresponders†	
	Tramadol (n = 36)	Placebo (n = 54)	Tramadol (n = 78)	Placebo (n = 68)
Sex, no. (%)				
Male	16 (44.4)	23 (41.6)	30 (38.5)	20 (29.4)
Female	20 (55.6)	31 (57.4)	48 (61.5)	48 (70.6)
Race, no. (%)				
White	31 (86.1)	44 (81.5)	63 (80.8)	56 (82.4)
Black	5 (13.9)	9 (16.7)	12 (15.4)	10 (14.7)
Other	0 (0.0)	1 (1.9)	3 (3.8)	2 (2.9)
Age, mean ± SD years	62.1 ± 10.1	60.9 ± 9.4	63.4 ± 10.2	59.3 ± 9.2
Time from diagnosis of osteoarthritis, mean ± SD years	9.9 ± 6.9	10.2 ± 10.1	7.3 ± 7.0	9.7 ± 9.2

* Randomized patients with naproxen 1,000 mg/day baseline pain visual analog scale (VAS) score <40 mm and at least 20 mm less than end of washout VAS score stratified as naproxen responders at time of randomization.
† Randomized patients with naproxen 1,000 mg/day baseline pain VAS score ≥40 mm or a decrease <20 mm than end of washout VAS score stratified as naproxen nonresponders at time of randomization.

continue. Eleven patients taking naproxen 500 mg/day and 10 patients taking naproxen 1,000 mg/day discontinued because of adverse events. Sixty of the 311 patients taking naproxen 1,000 mg/day with tramadol 200 mg/day discontinued due to adverse events during the last week of the run-in phase.

Two hundred forty patients completed the run-in phase and were randomized either to continue tramadol (n = 117) or to begin placebo (n = 123). Four patients (3 taking tramadol, 1 taking placebo) were randomized but were not included in the efficacy analysis because they did not have an efficacy assessment or they did not take the study medication. A total of 236 patients were evaluated. The distribution of demographic and baseline characteristics of the patients was similar between the tramadol and placebo treatment groups (Table 2).

Ninety patients (36 taking tramadol, 54 taking placebo) were stratified as naproxen responders and 146 (78 taking tramadol, 68 taking placebo) as naproxen nonresponders. Patients randomized to receive tramadol or placebo within the naproxen responder and nonresponder groups had similar levels of pain at the end of the washout and at baseline (after 2 weeks of treatment with naproxen 1,000 mg/day).

Efficacy in the open-label phase. Among patients who were eventually randomized as naproxen responders, the mean ± SD VAS score was 72.2 ± 14.2 mm at the end of washout. The mean VAS score decreased by 69%, to 22.1 ± 10.9 mm, after 2 weeks of naproxen at 1,000 mg/day (Table 3). Among patients who were eventually randomized as naproxen nonresponders, the mean VAS score was 79.7 ± 13.9 mm at the end of

Table 3. Open-label, run-in VAS scores

	Naproxen responders, mean ± SD*		Naproxen nonresponders, mean ± SD†	
	Tramadol (n = 36)	Placebo (n = 54)	Tramadol (n = 78)	Placebo (n = 68)
End of washout	72.1 ± 13.4	72.3 ± 14.9	81.2 ± 11.9	78.0 ± 15.8
Baseline‡	23.5 ± 10.5	21.2 ± 11.2	64.7 ± 16.4	63.8 ± 16.1
Entry into double-blind phase§	18.6 ± 15.1	15.6 ± 15.0	45.7 ± 21.3	42.2 ± 22.1

* Randomized patients with naproxen 1,000 mg/day baseline pain visual analog scale (VAS) score <40 mm and at least 20 mm less than end of washout VAS score stratified as naproxen responders at time of randomization.
† Randomized patients with naproxen 1,000 mg/day baseline pain VAS score ≥40 mm or a decrease <20 mm than end of washout VAS score stratified as naproxen nonresponders at time of randomization.
‡ Measured after naproxen 1,000 mg/day for 2 weeks.
§ Measured after naproxen 1,000 mg/day and tramadol for 1 week.

Table 4. Analysis of mean minimum effective naproxen dose

	Minimum effective naproxen dose (mg)*	*P*	
		Treatment difference within prerandomization response stratum	Treatment by prerandomization response
Naproxen responders†			
Tramadol	221	0.021	0.040
Placebo	407		
Naproxen nonresponders‡			
Tramadol	419	0.706	
Placebo	396		

* Adjusted mean is the least-squares mean.
† Randomized patients with naproxen 1,000 mg/day baseline pain visual analog scale (VAS) score <40 mm and at least 20 mm less than end of washout VAS score stratified as naproxen responders at time of randomization.
‡ Randomized patients with naproxen 1,000 mg/day baseline pain VAS score ≥40 mm or a decrease <20 mm than end of washout VAS score stratified as naproxen nonresponders at time of randomization.

washout and decreased by 19%, to 64.3 ± 16.2 mm, after 2 weeks of naproxen 1,000 mg/day. The addition of tramadol 200 mg/day for 1 week provided clinically significant reduction in pain intensity among naproxen nonresponders (reduction in mean VAS score 19 mm) but interestingly not in the naproxen responders (reduction in mean VAS score 5 mm).

Efficacy in the double-blind phase. *MEND.* The difference in MEND between tramadol and placebo was statistically significantly different among responders and nonresponders ($P = 0.040$). This demonstrated that responders react differently than nonresponders to the decrease in naproxen after randomization to tramadol or placebo. Because of this result, the MEND was analyzed separately within the responder and nonresponder groups.

Among naproxen responders, the MEND was significantly lower in patients receiving tramadol than in patients receiving placebo: 221 mg versus 407 mg, respectively ($P = 0.021$) (Table 4). For the naproxen nonresponders, the mean MEND was 419 mg in the tramadol group and 396 mg in the placebo group ($P = 0.706$).

Figure 2 summarizes the percentages of patients with adequate pain control at each visit according to prerandomization response. Among naproxen responders, more patients in the tramadol group (58%) than in the placebo group (39%) were able to discontinue naproxen. However, among naproxen nonresponders, only 37% of tramadol patients and 40% of placebo patients were able to discontinue naproxen.

Safety. Of the 311 patients exposed to tramadol and naproxen in the run-in phase, 60 (19.3%) discontinued due to an adverse event. Twenty-two percent of tramadol patients and 13% of placebo patients discontinued due to an adverse event during the double-blind phase. The most common adverse events leading to discontinuation in the open-label and double-blind phases were nausea, dizziness, vomiting, and somnolence.

Adverse events experienced by at least 10% of the patients who were exposed to tramadol along with naproxen during the open-label and double-blind phases included nausea (27.3%), dizziness (20.6%), constipation (16.7%), somnolence (15.1%), headache (12.9%), and vomiting (11.9%). Three patients experienced serious adverse events (abdominal pain and gastric ulcers; nervousness, headache, and left-sided weakness; and gastroenteritis) while taking tramadol and naproxen. Two patients taking placebo and naproxen experienced serious adverse events (cellulitis and leg ulcers following a motor vehicle accident and cardiac-related chest pain).

DISCUSSION

This study demonstrated that tramadol decreased the amount of naproxen needed to maintain adequate pain relief in naproxen-responsive patients with painful OA of the knee. The addition of tramadol 200 mg/day allowed for a mean reduction of 78% in the daily dosage

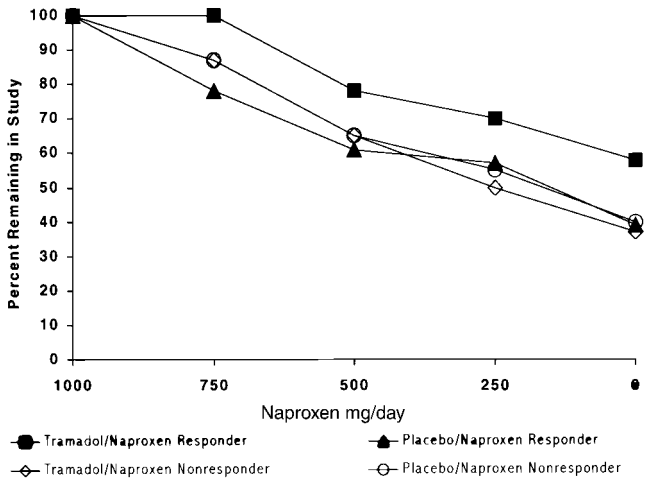

Figure 2. Percentages of patients remaining in the study while taking tramadol 200 mg/day or placebo with decreasing doses of naproxen, by naproxen response status.

of naproxen without compromising pain relief. Fifty-eight percent of naproxen-responsive patients were able to discontinue naproxen with the addition of tramadol.

Higher NSAID dosages is a known risk factor for serious NSAID-induced adverse events. A meta-analysis by Henry et al (11) determined that the relative risk for developing drug-induced peptic ulcer disease requiring hospitalization was 3.7 (95% confidence interval 1.7–7.7) for low-dose (≤750 mg/day) naproxen and 6.0 (95% confidence interval 3.0–2.2) for high-dose (1,000 mg/day) naproxen. A similar dose relationship was also found for ibuprofen and indomethacin, 2 other drugs for which data were available (11). In addition, the incidence rate for hospitalizations due to acute renal failure is twice as high as among patients using high-dose NSAIDs (19 per 100,000 patient-years) than among those taking lower doses (8 per 100,000 patient-years) (12). In patients requiring NSAID therapy, the incidence of serious adverse events may be decreased if the NSAID can be used at the lowest effective dose. The results of this study suggest that patients responding to higher doses of naproxen or potentially any NSAID may be able to reduce their risk of serious NSAID-induced adverse events by adding tramadol.

A unique design was developed for this study to ensure selection of patients who required higher-dose NSAID therapy to control pain. This was accomplished by incorporating precise criteria at specific time points during the run-in phase. Upon study entry, a pain VAS score of <80 mm was required to allow patients to demonstrate a clinically significant increase in VAS score (≥20 mm) during the washout and remain on the 100-point scale. Patients were then eligible to continue the run-in phase if, after washout of existing NSAID therapy, they had a VAS score of ≥40 mm with an increase of at least 20 mm from the prewashout score, thereby selecting patients with at least moderate, NSAID-sensitive pain. To establish the need for a higher NSAID dose to control pain, patients with VAS scores <20 mm after 1 week of receiving naproxen 500 mg/day were considered to have sufficient pain control and were discontinued.

Another unique design feature of this study included exposing patients to tramadol for 1 week prior to randomization in order to decrease the number of patients discontinuing the study due to adverse events during the double-blind period. Therefore, the results from the double-blind phase were not obscured by an extremely high dropout rate due to adverse events, and a more meaningful assessment of the NSAID-sparing effect could be made. This may be seen as incorporating bias toward tramadol, since patients randomized to receive placebo after receiving tramadol for 1 week may recognize that they are no longer taking an active drug. However, during the first 2 weeks of the double-blind phase, 75% of patients in the responder group who discontinued because of insufficient pain relief did so only in accordance with the more objective efficacy failure criteria of increased VAS score at a regularly scheduled visit. This suggests a true decrease in pain relief due to the decrease in naproxen dose rather than an unblinding effect.

In the double-blind phase of this trial, 20% of patients taking the tramadol with naproxen dropped out due to adverse events, compared with 13% of patients taking the placebo and naproxen. The side effects that led to withdrawal (nausea, vomiting, and dizziness) are similar to those experienced in other studies of tramadol and may be related to the drug's central mechanism. As with other centrally acting agents, clinical experience has found that a slower introduction of tramadol reduces the incidence and intensity of side effects (13,14). These experiences were validated in a recent study that showed the initiation of tramadol using a slow titration decreases the number of patients discontinuing therapy due to adverse events, especially dizziness and vertigo (15). In that study, 1.5% of patients initiating tramadol therapy over 10 days dropped out because of dizziness and/or vertigo, compared with 10.1% of patients receiving tramadol 200 mg on the first day.

The concept of NSAID responsiveness and nonresponsiveness in patients with OA or RA has recently been addressed in the rheumatology literature (16,17). Responder status does not appear to be dependent on severity of disease or pharmacokinetic profile within subjects (18–20). Pretreatment measurement of the erythrocyte sedimentation rate and total white blood cell count may be useful in predicting response status in patients with RA, but laboratory values appear to have no value in predicting NSAID responsiveness in patients with OA (21). Recent work by Walker et al (21) showed that in patients with OA, 27% were NSAID responders, 55% were nonresponders, and 18% had questionable response. The results of this study are similar to those of Walker. Assuming that patients receiving naproxen alone responded to naproxen in the same manner as those receiving naproxen with tramadol, 38% of patients evaluated could be classified as naproxen responders.

Naproxen responders and nonresponders were stratified prior to randomization because we postulated that the 2 groups would behave differently as their naproxen dosage was reduced. As was postulated, when

tramadol was added to the treatment in patients responding well to 1,000 mg/day of naproxen, the dosage of naproxen could be reduced by >75% without compromising pain relief.

The nonresponder group behaved differently. Patients continuing to experience at least moderate pain (VAS score >40 mm) while receiving naproxen 1,000 mg/day did have a significant benefit when tramadol 200 mg/day was added as open-label therapy; the VAS score was reduced by an average of 19 points. However, during the double-blind portion of the study, both the placebo and tramadol nonresponder groups failed at about the same rate. One possible explanation is that the naproxen nonresponders have a degree of pain that requires constant exposure to 2 drugs at these dosages to maintain pain relief; therefore, withdrawing one or both analgesics, as was done in the double-blind phase, had the same effect. Another possibility is that these patients may require either a higher dosage of naproxen or a higher dosage of tramadol than were used in this study to allow a differentiation from placebo. In a previous study of the treatment of chronic painful conditions, an average daily dosage of 250 mg of tramadol was used (22).

This study demonstrated that by adding tramadol 200 mg/day to the regimen of patients with OA knee pain responsive to naproxen 1,000 mg/day, a significant reduction in the naproxen dosage could be achieved. Fifty-eight percent of patients could discontinue naproxen completely without compromising pain relief. Adding tramadol to the treatment regimen of patients with OA receiving higher doses of NSAIDs may ultimately allow a reduction in NSAID-related adverse events. Longer-term observations would be necessary to confirm this benefit.

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APPENDIX A: THE TRAMADOL PRODUCT SUPPORT–NSAID PROTOCOL STUDY GROUP

These studies were performed by the following investigators, who comprise the Tramadol Product Support–NSAID Protocol Study Group: Roy D. Altman, MD, University of Miami, Miami, FL; Charles A. Birbara, MD, Clinical Pharmacology Study Group, Worcester, MA; Kenneth D. Brandt, MD, Indiana University School of Medicine, Indianapolis, IN; Stephen D'Aimco, MD, Tennessee Clinical Trials, Inc., Nash-

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